

Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen Detected Abnormalities

APPROVED BY



Australian Government

National Health and Medical Research Council

**National Cervical
Screening Program**
A joint Australian, State and Territory Government Initiative



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APPROVED BY THE NHMRC ON 9 JUNE 2005



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These guidelines were approved by the National Health and Medical Research Council (NHMRC) at its 157th session on 9 June 2005, under section 14A of the *National Health and Medical Research Council Act 1992*. Approval by the NHMRC is granted for a period not exceeding five years, at which date the approval expires. The NHMRC expects that all guidelines will be reviewed no less than once every five years.

Disclaimer

This document is a general guide to appropriate practice, to be followed subject to the clinician's judgment and the patient's preference in each individual case.

These guidelines are designed to provide information to assist decision making and are based on the best evidence available at the time of publication.

The development of these guidelines was facilitated by the NSW Cervical Screening Program on behalf of the National Cervical Screening Program.

These guidelines can be downloaded from the NHMRC website:
www.nhmrc.gov.au/publications.

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Preamble

In approving this document, *Screening to prevent cervical cancer: guidelines for the management of asymptomatic women with screen detected abnormalities*, at its 157th session on 9 June 2005, the National Health and Medical Research Council expressed its support for the National Cervical Screening Program as an important way to maintain the health of all Australian women.

The new guidelines will not only give medical practitioners evidence-based recommendations to better manage patients who have an abnormal Pap smear, but will, through the planned implementation and education programs, raise women's awareness of the usefulness of Pap smears as a tool in preventing deaths from cervical cancer.

The National Health and Medical Research Council, however, recommended that the screening interval in Australia be reviewed as soon as possible to ensure that the National Cervical Screening Program is consistent with international best practice.

National Health and Medical Research Council

9 June 2005

Foreword

About two million Australian women have a Pap test for cervical cancer screening each year. The clinical management of women with abnormal Pap test results involves health professionals across a broad spectrum of disciplines and sectors. These guidelines have been developed to assist women and health professionals to achieve the best outcomes. The target audience includes primary health care providers, general practitioners, cytopathologists, gynaecologists and gynaecological oncologists, as well as public health service administrators.

The previous National Health and Medical Research Council (NHMRC) guidelines *Screening to Prevent Cervical Cancer: Guidelines for the Management of Women with Screen Detected Abnormalities* were developed by an expert group convened by the NHMRC. They were endorsed by the NHMRC in December 1993 and published in 1994. The guidelines were based on the latest available literature at that time and provided effective guidance to practitioners on that basis. However, they were not formulated in line with recent NHMRC standards for clinical practice guidelines.

In 2001, the National Advisory Committee to the National Cervical Screening Program (NCSP) of the Australian Department of Health and Ageing requested that the guidelines be reviewed and updated. The New South Wales Cervical Screening Program funded and managed the review under the direction of the NCSP. The review has been undertaken according to the NHMRC requirements described in *A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines* (NHMRC 1999), and the subsequent handbook series on preparation of clinical practice guidelines (NHMRC 2000abc, 2001, 2002).

These updated guidelines address the current state of cervical cancer in Australia, the natural history of the disease and terminology for cervical cytology; management of squamous abnormalities, glandular abnormalities and special clinical circumstances; and psychosocial, economic and implementation issues. The development of these guidelines has involved widespread consultation with all relevant professional bodies and a wide range of clinicians and consumers. However, while the guidelines are based on good population data, it is important to note that they are only a guide to clinical practice. Clinicians must make individual decisions in consultation with their patients based on individual clinical circumstances.

The guidelines do not address issues related to routine screening interval or frequency, or give detailed information about the treatment of invasive cervical cancer. Furthermore, the guidelines explicitly exclude symptomatic women. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists has issued management guidelines for women with intermenstrual and postcoital bleeding (RANZCOG 2002), which take precedence over these guidelines for such cases.

The updated guidelines are based on revised terminology for cervical cytology reporting in Australia, which will be known as the ***Australian Modified Bethesda System 2004*** (AMBS 2004). The previous NHMRC-endorsed terminology was a uniquely modified version of the The Bethesda System 1991 (TBS 1991), which was developed in the United States. However, its numerical categorisations of abnormalities implied cervical intraepithelial neoplasia (CIN) progression from CIN 1 to CIN 2 to CIN 3 and then cancer. We now know that this is not an accurate reflection of the biology of human

papillomavirus (HPV), cervical cancer and its precursors. During the past decade there has been a greater understanding of the natural history of cervical cancer. The nature of CIN 1 as an infective process rather than a neoplastic one has been demonstrated by recent work in molecular biology and epidemiology. These advances suggest that, rather than an inevitable linear progression towards cancer, most HPV infections acquired by women resolve without medical intervention.

Women with low-grade epithelial abnormalities on cervical cytology are currently the subject of a number of clinical trials investigating their optimal management. However, applying international research to the Australian context has, until now, been extremely difficult because of the structural differences in the terminology system used. The revised terminology system, AMBS 2004, which is presented in this document, reflects a modern understanding of HPV infection, cervical cancer and its precursors and is compatible with terminology systems now used internationally.

The Australian Government Department of Health and Ageing will fund and take responsibility for the dissemination, implementation and monitoring of these guidelines, once they are approved by the NHMRC. A plan for implementing the guidelines is included in Appendix 4 with recommendations for further review. This includes provision for a consumer guide and guides for general practitioners.

These new guidelines are a distillation of the very latest research and data, brought together by some of the leading experts in this field, both internationally and in Australia. I believe they will result in a significant improvement in the care and treatment of asymptomatic women with screen-detected cervical abnormalities in Australia, and I strongly commend them to you.



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Summary of guidelines

Management of women with unsatisfactory Pap smears

GUIDELINE	EVIDENCE
<p>Unsatisfactory Pap test reports</p> <p>A woman with an unsatisfactory Pap test report should have a repeat smear in 6–12 weeks, with correction, when possible, of the problem that caused the unsatisfactory smear.</p>	<p>Consensus</p>

Management of low-grade squamous abnormalities

<p>Human papilloma virus (HPV) testing</p> <p>There is insufficient evidence to support the use of HPV testing in the triage of low-grade squamous intraepithelial lesions.</p>	<p>MSAC 2002</p>
<p>Index Pap test report of low-grade squamous intraepithelial lesions (LSIL)</p> <p>A woman with a Pap test report of LSIL should be managed in the same way irrespective of whether the abnormality is regarded as possible or definite and should be recommended for a repeat Pap test in 12 months.</p>	<p>Australian registry data; Level III-2: three cohort studies of clearance interval (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001)</p>
<p>Index Pap test reports of LSIL in women aged 30+ years</p> <p>A woman aged 30 years or more with a Pap test report of LSIL, without a history of negative smears in the preceding two to three years, should be offered either immediate colposcopy or a repeat Pap smear within six months.</p>	<p>Australian registry data</p>
<p>Twelve-month repeat Pap test after index test results of LSIL</p> <p>If the 12-month repeat Pap test is reported as showing high-grade changes (definite or possible), the woman should be referred for colposcopic assessment.</p> <p>Any woman whose repeat Pap test at 12 months is again reported as showing changes suggestive of LSIL (whether possible or definite), should be referred for colposcopic assessment.</p>	<p>Level IV (Schoolland et al 1998, Sparkes et al 2000, Performance Standards 2003)</p> <p>Level III-2: three cohort studies of clearance interval (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001)</p>

<p>If the 12-month repeat Pap test is reported as normal, the woman should have a further repeat Pap test in 12 months (ie 24 months after the index smear).</p>	<p>Level III-2: three cohort studies of clearance interval (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001)</p>
<p>Fluctuating repeat Pap test results</p> <p>Referral for colposcopy should be considered for a woman if she has two LSIL/possible LSIL reports (at least 12 months apart) within a 3-year timeframe, regardless of intervening normal cytology reports.</p>	<p>Consensus</p>
<p>Colposcopic assessment of women with Pap test reports of LSIL</p> <p>If, at colposcopy, a high-grade lesion is seen or suspected, targeted biopsy should be performed for histological confirmation before definitive therapy.</p> <p>If the colposcopic assessment is normal, the woman should be referred back for annual cytological surveillance until two normal smears are obtained, and then resume routine screening according to the recommendation for the average population.</p> <p>If the colposcopic assessment is satisfactory and a low-grade lesion is suspected, target biopsy can be performed to confirm this diagnosis.</p> <p>Treatment of histologically confirmed low-grade squamous lesions is not recommended, as such lesions are considered to be an expression of a productive HPV infection.</p> <p>Histologically confirmed low-grade squamous abnormalities can be safely managed by repeat cytology at 12 and 24 months. If both smears are negative, it is recommended that the woman return to screenings at the intervals recommended for the average woman.</p> <p>If either repeat smear shows possible or definite LSIL, the woman should be advised to continue having annual smears until at least two are negative, at which time she can return to routine screening.</p> <p>If the colposcopic assessment is unsatisfactory, consideration should be given to repeating the Pap test in 6–12 months. In asymptomatic women and in the absence of any cytologic, colposcopic or histologic suggestion of high-grade disease, further diagnostic procedures, such as cone biopsy or loop excision, are not indicated.</p>	<p>Consensus (RANZCOG 2001)</p> <p>Consensus (RANZCOG 2001)</p> <p>Consensus (RANZCOG 2001)</p> <p>Consensus (RANZCOG 2001)</p> <p>Consensus (RANZCOG 2001)</p> <p>Consensus (RANZCOG 2001)</p>

Management of high-grade squamous abnormalities

<p>Referral of women with Pap test reports of possible high-grade squamous lesions</p> <p>A woman with a Pap test report of possible high-grade squamous lesion should be referred to a gynaecologist for colposcopic assessment and targeted biopsy where indicated.</p>	<p>Level IV (Schoolland et al 1998, Sparkes et al 2000, VCCR 2002)</p>
<p>Referral of women with Pap test reports of high-grade squamous intraepithelial lesions (HSIL)</p> <p>A woman with a Pap test report of HSIL should be referred to a gynaecologist for colposcopic assessment and targeted biopsy where indicated.</p>	<p>Level IV (VCCR 2002, Sparkes et al 2000)</p>
<p>Referral of women with Pap test reports of HSIL with additional features suggestive of an invasive component</p> <p>A woman with a Pap test report of HSIL, with additional features suggestive of an invasive component, should be referred to a gynaecologist with expertise in colposcopic evaluation of suspected gynaecological malignancies or to a gynaecological oncologist, ideally within two weeks.</p>	<p>Consensus</p>
<p>Referral of women with Pap test reports of SCC</p> <p>A woman with a Pap test report of SCC should be referred to a gynaecological oncologist or to a gynaecological oncology unit for urgent evaluation, ideally within two weeks.</p>	<p>Consensus</p>
<p>Histological confirmation</p> <p>Histological confirmation of a high-grade lesion is required before definitive treatment is undertaken.</p> <p>‘See and treat’ is not recommended.</p>	<p>Consensus</p> <p>Consensus</p>
<p>Treatment of a high-grade squamous intraepithelial abnormality</p> <p>Women with a histological diagnosis of CIN 2 or CIN 3 should be treated in order to reduce the risk of developing invasive cervical carcinoma.</p>	<p>Level III-2 (Östör 1993b)</p>
<p>Fertility-sparing treatments</p> <p>Local ablative or excisional treatments should destroy or remove tissue to a depth of at least 7 mm.</p> <p>There is no clearly superior method of fertility-sparing treatment for CIN 2 and 3.</p>	<p>Level IV (Burke 1982, Jordan et al 1985)</p> <p>Level I (Martin-Hirsch et al 2000)</p>

<p>Ablative therapy</p> <p>Ablative therapy may be considered, provided:</p> <ol style="list-style-type: none"> 1. The cervix has been assessed by an experienced colposcopist. 2. A targeted biopsy has confirmed the diagnosis. 3. There is no evidence of an invasive cancer on cytology, colposcopic assessment or biopsy. 4. The entire cervical transformation zone has been visualised. 5. There is no evidence of a glandular lesion on cytology or biopsy. 	<p>Consensus</p>
<p>Cryotherapy for treatment of CIN 3</p> <p>It is advisable that women with CIN 3 are not treated with cryotherapy.</p>	<p>Level IV (Anderson and Husth 1992)</p>
<p>Loop electro-excisional procedure (LEEP)</p> <p>Excess diathermy artefact should be avoided when using LEEPs in order to allow comprehensive pathological examination, including margin status.</p>	<p>Consensus</p>
<p>Cone biopsy</p> <p>Cone biopsy may be necessary to treat women with high-grade squamous lesions and absolute indications that include:</p> <ol style="list-style-type: none"> 1. failure to visualise the upper limit of the cervical transformation zone in a woman with a high-grade squamous abnormality on her referral cervical smear (ie unsatisfactory colposcopy) 2. suspicion of an early invasive cancer on cytology, biopsy or colposcopic assessment 3. the suspected presence of an additional significant glandular abnormality (ie adenocarcinoma in situ) on cytology or biopsy (ie a mixed lesion). <p>Careful attention should be paid to tailoring treatment to the individual woman, taking into account the size, extent, situation and severity of the lesion.</p>	<p>Consensus</p> <p>Consensus</p>

<p>Management of women previously treated for HSIL</p> <p>A woman previously treated for HSIL requires a colposcopy and cervical cytology at 4–6 months after treatment. Cervical cytology and HPV typing should then be carried out at 12 months after treatment and annually thereafter until the woman has tested negative by both tests on two consecutive occasions. The woman should then be screened according to the recommendation for the average population.</p> <p>A woman already undergoing annual cytological review for follow-up of a previously treated HSIL, as advised by the previous NHMRC guidelines (1994), may be offered HPV testing as described above. Once she has tested negative by both cytology and HPV typing on two consecutive occasions, she should be screened according to the recommendation for the average population.</p>	<p>Level IV (Chua and Hjerpe 1997, Bollen et al 1999, Jain et al 2001, Lin et al 2001, Nobbenhuis et al 2001b, Paraskevaidis et al 2001, Bar-Am et al 2003, Zielinski et al 2003, Chao et al 2004)</p> <p>Level IV (Chua and Hjerpe 1997, Bollen et al 1999, Jain et al 2001, Lin et al 2001, Nobbenhuis et al 2001b, Paraskevaidis et al 2001, Bar-Am et al 2003, Zielinski et al 2003, Chao et al 2004)</p>
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Management of cervical glandular abnormalities

<p>Referral of women with Pap test reports of adenocarcinoma</p> <p>A woman with a Pap test report of adenocarcinoma of endometrial origin should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist.</p> <p>A woman with a cytological prediction of adenocarcinoma of either endocervical, extrauterine or unspecified origin should be referred to a gynaecological oncologist or a gynaecological oncology unit.</p>	<p>Level III-3 (Mitchell et al 1993)</p> <p>Consensus</p>
<p>Referral of women with Pap test reports of endocervical adenocarcinoma in situ (AIS)</p> <p>A woman with a Pap test report of endocervical AIS should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist</p>	<p>Australian registry data</p>
<p>Referral of women with Pap test reports of possible high-grade glandular lesions</p> <p>A woman with a Pap test report of possible high-grade glandular lesions should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist.</p>	<p>Australian registry data</p>

<p>Referral of women with Pap test reports of atypical glandular or endocervical cells of undetermined significance</p> <p>A woman with a Pap test report of atypical glandular or endocervical cells of undetermined significance should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies.</p>	<p>Australian registry data</p>
<p>Colposcopic assessment of glandular lesions</p> <p>Colposcopic assessment is mandatory in the presence of a cervical cytology suggesting a glandular lesion.</p>	<p>Consensus</p>
<p>Cone biopsy for the assessment of glandular lesions</p> <p>Cold-knife cone biopsy should be considered the 'gold standard' for the assessment of glandular lesions</p>	<p>Consensus</p>
<p>Referral of women with adenocarcinoma on cone or punch biopsy</p> <p>Women found to have invasive adenocarcinoma on cone or punch biopsy should be referred to a gynaecological oncologist or a gynaecological oncology unit for subsequent management.</p>	<p>Consensus</p>
<p>Management of women with a Pap test report of AIS</p> <p>If invasive carcinoma is not identified at colposcopic assessment, a cone biopsy should be undertaken.</p> <p>Hysterectomy should not be undertaken without prior cone biopsy to exclude invasive carcinoma.</p>	<p>Consensus</p>
<p>Management of women with AIS</p> <p>The management of women diagnosed with AIS on cone biopsy will be dependent upon the age and fertility requirements of the women and the status of excision margins.</p> <p>Hysterectomy is recommended for women who have completed childbearing because of the difficulties of reliable cytological follow-up, a high recurrence rate and the reported multifocality of the disease.</p>	<p>Level IV (Cullimore et al 1992, Hopkins et al 1988, Muntz et al 1992, Im et al 1995, Poynor et al 1995, Denehy et al 1997, Widrich et al 1996, Wolf et al 1996, Azodi et al 1999, Hopkins 2000, Souter et al 2001, Anderson and Nielson 2002, Kennedy and Biscotti 2002, Shin et al 2002)</p>

Special clinical circumstances

<p>Evaluation of an abnormal Pap test during pregnancy</p> <p>Women with low-grade cytologic lesions should be managed in the same way as for women with low-grade squamous abnormalities, with a repeat smear after 12 months.</p> <p>Women with high-grade lesions should be referred for colposcopic evaluation.</p>	<p>Level IV (Coppola et al 1997, Jain et al 1997, Woodrow et al 1998, Nguyen et al 2000)</p> <p>Level IV (Coppola et al 1997, Woodrow et al 1998, Nguyen et al 2000, Palle et al 2000)</p>
<p>Colposcopy during pregnancy</p> <p>The main aim of colposcopy in the pregnant woman is to exclude the presence of invasive cancer and to reassure the woman that her pregnancy will not be affected by the presence of an abnormal Pap test.</p> <p>Biopsy of the cervix is usually unnecessary in pregnancy, unless invasion is suspected colposcopically.</p>	<p>Level IV (Woodrow et al 1998)</p> <p>Level IV (Woodrow et al 1998, Palle et al 2000)</p>
<p>Treatment of a high-grade lesion during pregnancy</p> <p>Definitive treatment of a high-grade lesion, with the exception of invasive cancer, may be deferred safely until after the pregnancy.</p>	<p>Level IV Guerra et al (1998), Economos et al (1993)</p>
<p>Immunosuppressed women</p> <p>If an immunosuppressed woman has a screen-detected abnormality she should be referred for colposcopy, even if the lesion is low-grade, as cytological surveillance alone may be inadequate.</p> <p>Assessment and treatment should be by an experienced colposcopist.</p> <p>The whole of the lower genital tract will need evaluation as the same risk factors apply for cervical, vaginal, and vulval and perianal lesions.</p> <p>Treatment of the cervix should be by excisional methods.</p> <p>Follow-up after treatment should include colposcopy as well as cytology.</p> <p>Follow-up should be annual and indefinite.</p>	<p>Level I/II (Sillman et al 1997, Spitzer 1999)</p> <p>Level III-1 (Petry et al 1994)</p> <p>Level III-1 (Petry et al 1994)</p> <p>Level I/II (Spitzer 1999)</p> <p>Level III-2 (Cordiner et al 1980)</p> <p>Level III-2 (Cordiner et al 1980)</p>

<p>Postmenopausal women with normal endometrial cells</p> <p>Normal endometrial cells occurring in the Pap smear of an asymptomatic postmenopausal woman should not be reported.</p> <p>A symptomatic postmenopausal woman requires investigation irrespective of her Pap test status.</p>	<p>Level III-2 (Gondos and King 1977, Gomez-Fernandez et al 2000, Ashfaq et al 2001, Montz 2001, Chang et al 2001, Brogi et al 2002)</p> <p>Level III-2 (RANZCOG 2002)</p>
<p>Women exposed to diethylstilboestrol (DES) in utero</p> <p>DES-exposed women should be offered annual cytological screening and colposcopic examination of both the cervix and vagina.</p> <p>Screening should begin any time at the woman's request and continue indefinitely. A balanced perspective should be maintained.</p> <p>DES-exposed women who have a screen-detected abnormality should be managed in a specialist centre by an experienced colposcopist.</p>	<p>Level IV (Hacker 2000, RCOG 2002)</p> <p>Level IV (Hacker 2000, RCOG 2002)</p> <p>Level IV (Hacker 2000, RCOG 2002)</p>

1 Guidelines review process

1.1 Introduction

A multidisciplinary guidelines review group was established to review and update the guidelines, including representatives of the Royal Australian and New Zealand College of Obstetricians and Gynaecologists, the Australian College of Rural and Remote Medicine, the Royal Australian College of General Practitioners, the Australian Society of Colposcopy and Cervical Pathology, the Royal College of Pathologists of Australasia, and the Australian Government Department of Health and Ageing. In addition, the review group included representatives with special expertise in cytology, virology, gynaecology, gynaecological oncology, epidemiology, health economics, health communication, Aboriginal and Torres Strait Islander women's health, and consumer concerns.

A three-month public consultation process was undertaken, including an advertisement in *The Australian* newspaper inviting submissions. A website was developed as a vehicle for stakeholder information and consultation. Press releases informing stakeholders of the consultation process and inviting comment were forwarded to all appropriate professional bodies. Presentations were also given at professional meetings of these colleges, and two additional meetings were held for clinicians. Cervical screening programs in each state organised women's consultation sessions. Further consultations about the guidelines were also conducted in November and December 2003 (see Appendix 2).

The recommendations of these guidelines are underpinned by an extensive review of the literature (see Appendixes 2 and 3). However, because of differences in terminology there have been some concerns about the applicability of many overseas studies to the Australian situation. Nevertheless, Australia is very fortunate because extensive case data on Pap tests is held in each state and territory Pap test register. Analysis of these data has been undertaken for the Guidelines Review Group by Dr Heather Mitchell with the assistance of each state and territory Pap test register. This has provided the Guidelines Review Group with a unique source of data upon which to base risk assessment and recommendations for follow-up.

The Guidelines Review Group used the methods outlined in *A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines* (NHMRC 1999) and the accompanying handbooks (NHMRC 2000abc, 2001, 2002) to review the literature and assess the evidence used to support these guidelines.

1.2 Literature review

The Guidelines Review Group developed relevant clinical questions about the natural history of cervical cancer, the prognosis of women with different screen-detected abnormalities and the available options for management of cervical abnormalities and cervical cancer in Australia (see Appendix 3).

Evidence from published studies was predominantly obtained from a thorough search of electronic databases. These included MEDLINE, EMBASE, the specialised trials register maintained by the Cochrane Gynaecological Cancer Group, the Cochrane Database of Systematic Reviews and the Cochrane Library, including the Database of Abstracts of

Reviews of Effectiveness (DARE), Cancerlit, HealthSTAR and CINAHL. Additionally, potential relevant studies were identified from review articles and the references of identified studies, and unpublished studies were sought from the review group members.

General search criteria included all studies published in the English language covering the period from 1966 onward. The exception to this search timeframe was for studies that related to Digene Hybrid Capture II. This test only became available in 1998. Different medical subject headings (MeSH) or search terms were used for different questions, but a general search strategy was used to identify systematic reviews and randomised controlled trials (see Appendix 3).

Studies identified were checked against the clinical questions, and studies that answered the specific questions were included in the development of the guidelines. Articles that did not address the questions were excluded from review process.

1.3 Assessment and classification of evidence

Studies identified from the literature for inclusion in the review and development of the guidelines were initially classified according to the NHMRC levels of evidence (Table 1.1). Where possible, the strength and quality of the evidence was further evaluated using the NHMRC-recommended strategy (NHMRC 2000b; see Table 1.2).

Table 1.1 NHMRC levels of evidence

I	Evidence obtained from a systematic review of all relevant randomised controlled trials.
II	Evidence obtained from at least one properly designed randomised controlled trial.
III-1	Evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).
III-2	Evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case-control studies, or interrupted time series with a control group.
III-3	Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.
IV	Evidence obtained from case series, either post-test or pretest and post-test.

Source: NHMRC 1999

Table 1.2 Dimensions of evidence

Dimension	Definition
Strength of evidence:	
Level	Based on study design used, as an indicator of the degree to which bias has been eliminated by design.
Quality	The methods used by investigators to minimise bias within a study design.
Statistical precision	The p-value or, alternatively, the precision of the estimate of the effect (as indicated by the confidence interval). It reflects the degree of certainty about the existence of true effect.
Size of effect	The distance of the study estimate from the 'null' value and the inclusion of only clinically important effects in the confidence interval.
Relevance	The usefulness of the evidence in clinical practice, particularly the appropriateness of the outcome measures used.

Source: NHMRC 2000b

It is important to note that conducting randomised controlled trials in the area of cervical cancer management is not always practical and in many cases would be unethical. Consequently, there is very little evidence at Level I and II in this document. However, most of the management recommendations have been well tested through current clinical practice and many of the studies reviewed for this document were Level IV (case series). Experts in the field were also contacted to provide evidence based on their experience (whether published or not). Personal communication was also used as a proxy evidence measure.

Although every effort was made to identify and obtain as many published articles as possible, for some questions, no articles or other clinical study information was found. In this situation, the broad agreement of peers on established best practice forms the best available basis for decision making, which can subsequently be evaluated. The Guidelines Review Group has therefore opted to include some recommendations based on a consensus of expert opinion within the review group about current best practice. Where this is the basis for a guideline, it is designated by ‘consensus’ throughout this document.

In addition, many of the clinical questions relevant for these guidelines are questions of prognosis. The National Cervical Screening Program has access to large population datasets through its state and territory Pap test registers. Using these registers, large-scale cohort studies of Australian women with Pap test-detected abnormalities have been conducted to compare outcomes over time from different test results and management options (see Appendixes 7 and 8). These large cohort studies, designated as Level III-2 under the NHMRC scheme (Table 1.1), represent high-quality evidence for answering prognosis questions (NHMRC 2000a) and are therefore a scientifically valid evidence base for many of the guidelines.

Table 1.3 summarises the different categories of evidence used in these guidelines.

Table 1.3 Designation of evidence used in these guidelines

Evidence	Designation in guidelines
Clinical studies (randomised controlled trials, case-control, cohort studies etc)	Levels I, II etc (see Table 1.1) plus further details of strength and quality as appropriate (see Table 1.2)
Expert opinion of current best practice	Consensus
Data from Pap test registries	Australian registry data

2 Cervical cancer in Australia

Australia has the second lowest incidence of cervical cancer in the world among countries with comparable cancer registration systems (GLOBOCAN 2002). This is a remarkable achievement and is largely attributed to the successful implementation of the National Cervical Screening Program (NCSP), an organised approach to cervical screening in Australia implemented by a range of stakeholders, including general practitioners, gynaecologists, gynaecological oncologists, cytologists, women's health nurses, and national and state governments.

Table 2.1 shows the Australian incidence and mortality rates for cervical cancer in comparison with some other countries for the period up to, and including, 2002.

Table 2.1 Incidence of cervical cancer and mortality rate, selected countries, 2002

Country	Incidence per 100,000 women (ASR)	Mortality per 100,000 women (ASR)
New Zealand	10.0	3.2
United Kingdom	8.3	3.1
Sweden	8.2	3.1
United States	7.7	2.3
Canada	7.7	2.5
Australia	6.9	1.7
Finland	4.3	1.8

ASR = age standardised rate (World Standard Population)

Source: GLOBOCAN 2002 <http://www-depdb.iarc.fr/globocan/GLOBOframe.htm>

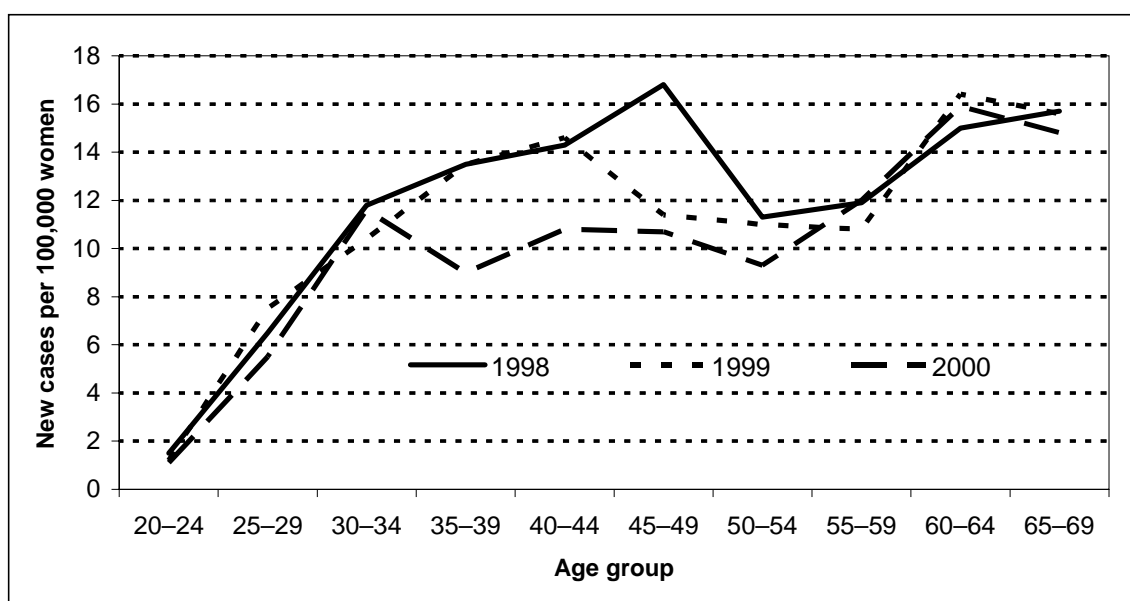
Cervical screening became available for Australian women in the mid-1960s. The approach was opportunistic in that no formal policies were developed, there was no systematic recruitment of women, comprehensive quality control was difficult because of the fragmentation of women's tests across many laboratories, and there was no fail-safe system for treatment of women with abnormal cytology results. While some impact was made on the mortality from cervical cancer, the results were less than optimal.

In 1991, an organised approach, the NCSP, was introduced as a national strategy to achieve further reductions in the incidence of and mortality from cervical cancer. The program has six major components:

- improving communication and education for women and health professionals
- establishing an infrastructure for a systematic approach to screening
- facilitating the regular participation of women in screening programs
- improving the quality control in smear taking and in laboratories processing and reporting cervical cytology
- instituting a fail-safe approach to the follow-up and management of screen-detected abnormalities
- monitoring and evaluating the organised approach.

At around the same time, a two-yearly cervical screening interval was nationally recommended and introduced for the target population aged 20–69 years. State and territory Pap test registries were developed as the infrastructure, and these have now matured into functional units that are integral to the success of the screening program.

In 1987, there were 1092 new cases of cervical cancer in Australia. By 2000, this number had declined to 745 cases and, of these, 578 occurred in the target age group aged 20–69 years (AIHW–AACR 2003a). Overall, cervical cancer incidence and mortality have declined in the target age group by 56.9% and 57.7%, respectively, over the past decade (AIHW–AACR 2003b). Figure 2.1 shows the incidence of cervical cancer in Australia by age in 1998, 1999 and 2000.



Note: Rates are expressed per 100,000 women; age standardised to the 2001 Australian Standard Population
 Source data: National Cancer Statistics Clearing House (AIHW–AACR 2003a, 2003b)

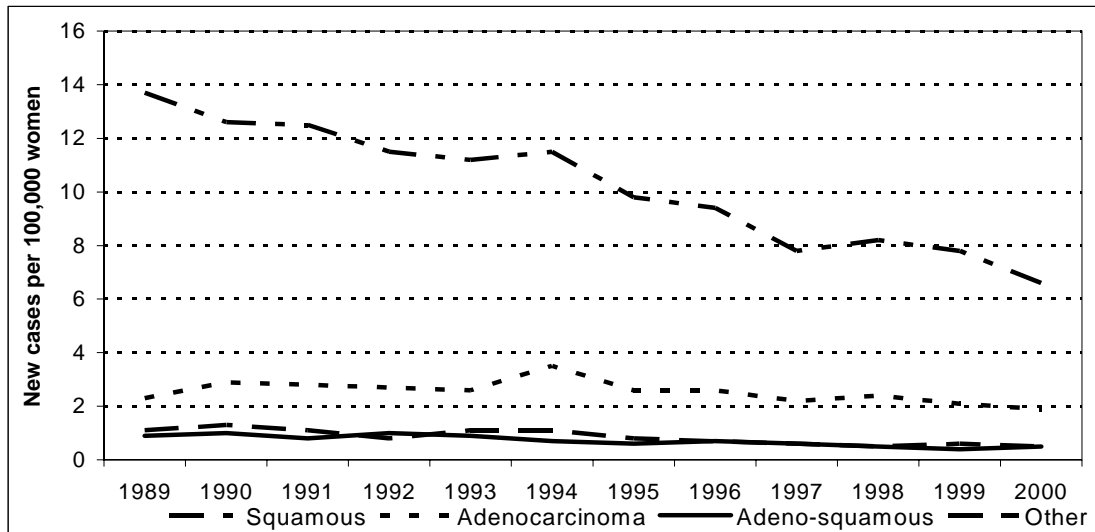
Figure 2.1 Age-specific incidence rates of cervical cancer, Australia, 1998–2000

There is some geographic variation within Australia in both incidence and mortality, but these differences are decreasing. During the period 1997–2000, the age-standardised incidence rate was 14.2 per 100,000 for metropolitan women, 13.6 per 100,000 for rural women and 15.9 per 100,000 for women in remote areas (AIHW–AACR 2003a). During 1998–2001, the mortality rate was 2.1 per 100,000 for metropolitan women, 2.7 per 100,000 for rural women and 3.0 per 100,000 for remote-area women (AIHW–AACR 2003a).

Part of the excess incidence and mortality in remote Australia is attributed to the high disease rates among Indigenous women. Although these rates are decreasing, the risk of dying from cervical cancer for an Indigenous woman is still about six times that of a non-Indigenous woman (AIHW–AACR 2003a).

In 1989, it was estimated that cervical cancer screening was preventing only 46% of squamous malignancies compared with a projected optimal prevention of 90%. By 1998, it was estimated that 70% of squamous cancers were being prevented — again a remarkable testimony to the success of the NCSP (Mitchell 2003).

Figure 2.2 shows time trends between 1989 and 2000 in the incidence of the various histological types of cervical cancer among women aged 20–69 years (AIHW 2004).



Note: Age standardised to the 2001 Australian Standard Population
 Source: National Cancer Statistics Clearing House (AIHW 2004)

Figure 2.2 Age-standardised incidence rates for cervical cancer, by histological type, for women aged 20–69 years, Australia, 1989–2000

Over the period shown in Figure 2.2, the incidence of squamous cervical cancer fell substantially, but the incidence of adenocarcinoma remained essentially unchanged. This is generally attributed to sampling difficulties in obtaining cells from the area where adenocarcinoma arises, problems in pathological interpretation and variations in clinical investigation and treatment.

3 Current concepts of HPV infection and the natural history of cervical neoplasia

3.1 HPV infection causes cancer of the cervix

There is overwhelming evidence that infection with human papillomavirus (HPV) is necessary, though not sufficient, for development of cancer of the cervix. Recent data, using sensitive methods to detect HPV, demonstrate that over 99.7% of cervical cancers test positive for HPV DNA (Bosch 2000). The attributable risk is greater than the risk of lung cancer conferred by smoking. The National Institutes of Health Consensus Conference on Cervical Cancer concluded ‘cervical cancer is unique in that it is the first solid tumour to be shown to be virally induced in essentially every case’ (Braly 1996).

3.2 Cervical cancer is a rare outcome of HPV infection

While persisting infection of the cervix with a high-risk HPV is necessary for the development of cervical cancer, it is certainly not sufficient (Walboomers et al 1999). Worldwide, the estimated prevalence of genital HPV infection is 326 million amongst adult women. This compares with an annual incidence of approximately 450,000 new cases of cervical cancer worldwide (Bosch 2000), indicating that cervical cancer is a rare outcome even of high-risk HPV infection. The modal age at first infection with high-risk genital HPV is between 15 and 25. The point 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.

In contrast, the modal age of diagnosis with cervical cancer in unscreened women varies between 35 and 50, depending on the country. Furthermore, less than 0.2% of cervical cancers occur in women under 25 (Burk et al 1996, Bosch and de Sanjose 2003, Sherman et al 2003a). These data suggest that progression of HPV infection to cancer is slow, and this is confirmed by longitudinal epidemiological studies (Burk et al 1996, Bosch and de Sanjose 2003, Sherman et al 2003a).

The lifetime risk of cervical cancer, given infection with high-risk HPV, varies across geographical regions from 1 in 15 to 1 in 100 (Bosch and de Sanjose 2003, Schiffman and Kjaer 2003). Thus, screening for high-risk HPV infection would identify a very large number of women, only a few of whom are at risk of cervical cancer; the sensitivity of the test for risk is high, but the specificity is very low.

3.3 Virology of HPV infection

HPVs are small double-stranded DNA viruses that have icosahedral protein capsids (Van Ranst et al 1992).

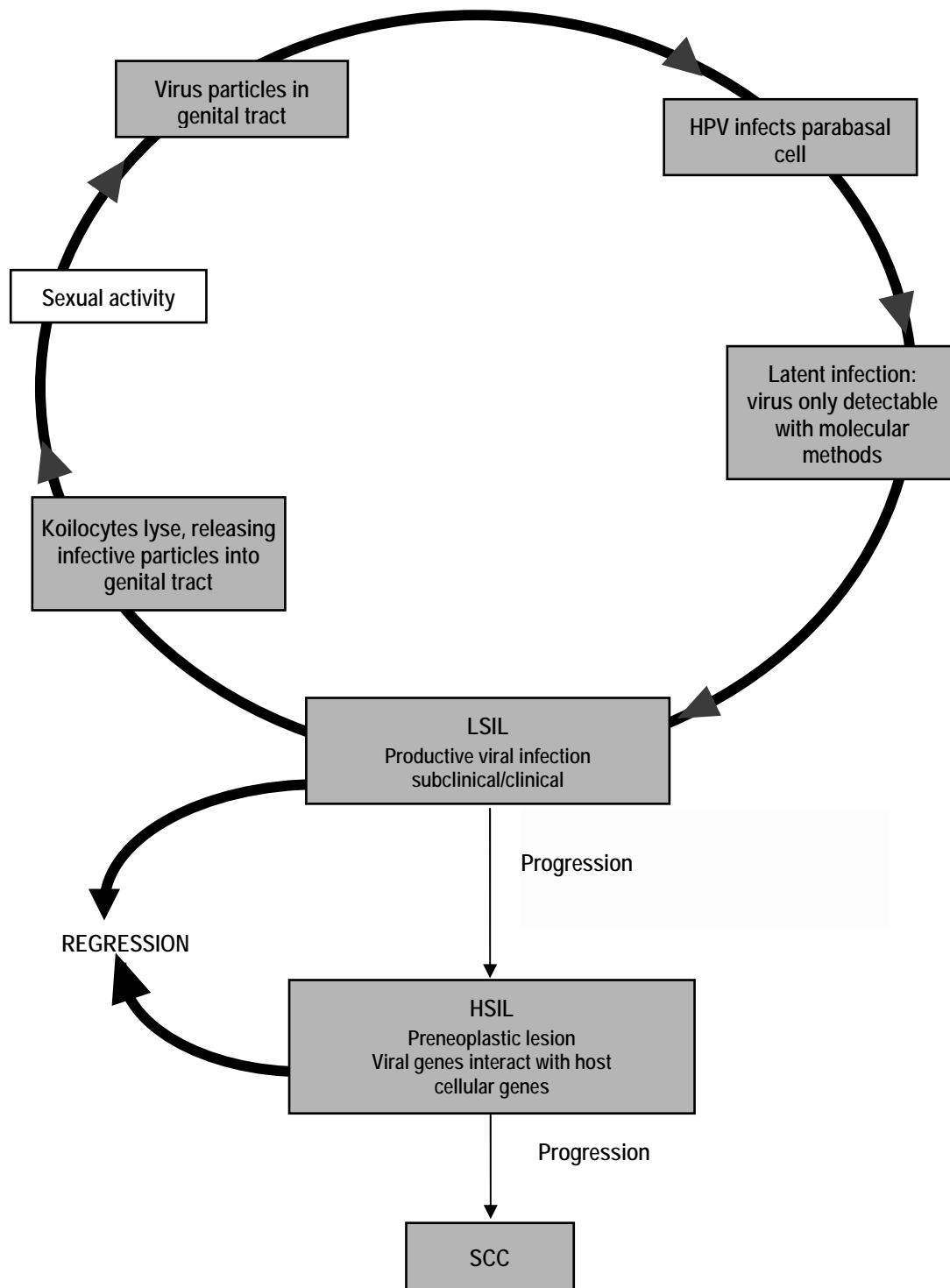
There are more than 100 types of HPV. These are referred to as genotypes, because papillomaviruses are classified by their DNA sequences rather than by serologic reactions. A new HPV type is defined by sequences in selected areas of the genome that differ by more than 10%, compared with any other known HPV type (Stoler 2000). There are two main groups of HPVs: cutaneous and mucosotropic.

The mucosotropic group can be further divided into those that produce genital lesions with a very low risk of progression to cancer and those with a moderate to high risk of progression to cancer (Van Ranst et al 1992). HPV6 and HPV11, which are responsible for genital warts, are classified as low-risk viruses because they are almost never found in invasive anogenital cancers. The high-risk viruses (particularly HPV16, 18, 45 and 31) are found in varying proportions in invasive cancer in different countries, though HPV16 is responsible for more than 50% of cancers in all studies. They have varying potentials for oncogenic transformation, with HPV16 infection conveying significantly higher risk of cancer than infection with the other high-risk types.

Infection with high-risk genital HPV is almost always sexually transmitted (Fairley et al 1993, Rice et al 1999, Dillner et al 1999). Following exposure to a person with a productive anogenital HPV infection, which may be invisible to the naked eye, there is a high probability of transmission, estimated to be greater than 50% following unprotected sexual intercourse. Following introduction of HPV through microabrasions of the anogenital skin, the acute lesion of infection appears after 6–12 weeks. For the high-risk anogenital HPVs, this lesion is usually invisible to the naked eye in both men and women, and can be totally asymptomatic, particularly on the cervix, or may be associated with itch or skin cracking. It is preceded by a period during which HPV can be detected by molecular techniques. It is now thought that a productive infection of the cervix with HPV (low-risk or high-risk) has the cytological and histological appearance of a low-grade squamous intraepithelial lesion (LSIL) (Stoler 2000).

The viral genome replicates only in the nucleus of an infected epithelial cell. It does so as a circular structure in an episomal location, independent of the host DNA. As the cell matures, large numbers of infectious virions are manufactured within the host nucleus. A viral protein product (E4) binds to, and disrupts, the cytoplasmic keratin network, producing the cytological appearance of the koilocyte. Desquamation of mature epithelial cells results in the release of large numbers of infective virions into the genital tract where they are available for further sexual transmission, thus completing the life cycle of the virus.

Figure 3.1 shows the life cycle of HPV in cervical infection and possible progression, first to an LSIL, then to a high-grade squamous intraepithelial lesion (HSIL) and finally to squamous cell carcinoma (SCC) of the cervix.



LSIL = low-grade squamous intraepithelial lesion; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; SCC = squamous cell carcinoma

Figure 3.1 Natural history of HPV infection and cervical cancer precursors

Determinant of persistence of HPV infection

Infections of the cervix with high-risk HPV that persist for more than three years are unlikely to resolve spontaneously, and convey a significant risk of development to HSIL (Moscicki et al 1998). Both HPV infection and the development of cervical cancer precursors are much more common in immunocompromised women (Ho et al 1998), and persistence and progression of high-risk HPV infection appear to be commoner in smokers and women who use oral contraceptives. HSIL resolves spontaneously in a high percentage of subjects, with higher resolution rates in younger women. It can also persist for a lifetime without giving rise to cervical cancer, although it is likely that squamous cervical cancer always arises from a persistent high-grade squamous lesion. It is thought that resolved infection with a high-risk HPV conveys protection against further infection with the specific type of HPV involved in the disease, but not against other high-risk types.

3.4 New evidence about the natural history of LSIL

LSIL cytology is now accepted to represent acute HPV infection. However, cytological abnormalities are not an invariable consequence of HPV infection. Moscicki et al (1998) documented that two-thirds of young women with high viral loads of HPV had no abnormal cytology. Acute infection may sometimes be associated with HSIL cytology. A study of incident HPV infections in teenagers found the risk of HSIL was greatest in the six months after first detection of HPV, with a rapid decline thereafter (Woodman et al 2001). This finding does not appear to have been confirmed by other investigators to date.

The median time to clear an HPV infection varies with how clearance is defined (eg how many tests and over what time period). Estimates range from 8 to 14 months, with longer clearance times for prevalent infection being documented by Nobbenhuis et al (1999).

Nobbenhuis et al (2001a) and Zielinski et al (2001) found that viral clearance occurred approximately three months before cytological regression. However, this finding was not confirmed in a larger case series from the Atypical Squamous Cells of Undetermined Significance and Low-Grade Squamous Intraepithelial Lesions Triage Study (ALTS) (Schiffman and Kjaer 2003). This study found cytological regression occurred five to six months before HPV clearance, a finding that the authors claimed is more plausible given the speed with which cervical epithelium regenerates.

A longitudinal study of the natural history of cervical neoplasia was conducted in Brazil between 1993 and 2002 (Schlecht et al 2003). A total of 2404 women between the ages of 14 and 60 years were seen every four months in the first year of the study and thereafter every six months. Pap smears and HPV tests were performed at every visit.

Cervicography was performed every two years. The Pap smears were reported at McGill University by Dr A Ferenczy, who was blinded to the results of previous Pap smears and all HPV results. Estimates of the progression and regression rates and sojourn times were based on the cytology results and subclassified according to HPV status.

The Brazilian study (Schlecht et al 2003) found that most LSIL regresses over short periods of time and that only a small minority of LSIL progresses and, where this occurs, it happens over comparatively long periods of time (see Table 3.1).

Table 3.1 Regression and progression rates and times for LSIL, Brazilian longitudinal study

Outcome	Mean time	At 6 months	At 12 months
Regression: LSIL to ASCUS ^a or negative	10.5 months ^b (95% CI, 8.1 to 12.9)	51% (95% CI, 42 to 60)	78% (95% CI, 70 to 85)
Progression: LSIL to HSIL	86.4 months (95% CI, 81.9 to 90.9)	1.7% (95% CI, 0.0 to 4.1)	3.6% (95% CI, 0.1 to 7.1)

^a ASCUS = atypical squamous cells of uncertain significance. This is a category of abnormal cytology in the 1991 Bethesda System of terminology. The equivalent categories in Australia are possible LSIL and possible HSIL.

^b Median time = 6.0 months (95% CI, 5.9 to 6.1)

Source: Schlecht et al (2003)

A natural history study (Nobbenhuis et al 2001a) was undertaken in the Netherlands involving 353 women (median age 32 years, range 18–55 years) with abnormal cytology who were monitored every three to four months by cytology, colposcopy and HPV testing. No biopsies were taken during the study. Regression was defined as having at least two consecutive smears reported as normal. Regression rates for women who presented with CIN (cervical intraepithelial neoplasia) 1 cytology were 20.6% (95% CI, 10.4 to 30.8) at 6 months, 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. Regression did not correlate with age.

The Nobbenhuis regression rates are lower than those documented by Schlecht, although the trend over time is similar. The lower regression rate in the Nobbenhuis study is probably due to the stricter definition of regression (ie two consecutive smears reported as normal).

3.5 Natural history of HSIL

Women with persistent infection with an oncogenic HPV are at risk of developing a high-grade abnormality (Nobbenhuis et al 1999). The cells of the transformation zone of the cervix are particularly vulnerable to the adverse effects of persistent infection by high-risk HPVs.

The protein products of two viral genes, E6 and E7, bind to host cell growth regulatory proteins with tumour suppressor functions — p53 and retinoblastoma (rb), respectively. E6 facilitates the degradation of p53 while E7 inactivates rb. Through this process, E6 and E7 expression following HPV infection prevents the arrest of cell division that occurs when epithelial cells differentiate.

While this process is a necessary part of the HPV infectious life cycle, in a proportion of persistent infections the usually circular HPV genome inserts into the host genome in a process known as integration (Arends et al 1998, Flaitz and Hicks 1998). As a consequence of integration, E6 and E7 may be overexpressed, causing host squamous epithelial cells to proliferate in a less orderly fashion, and acquire the cellular appearance of an HSIL. However, the HSIL clones are at risk of acquiring additional genetic errors conveying survival advantage, and increasing the risk of malignant transformation. Possible promoters of this process include smoking, other virus infections and random mutation. A small proportion of HSIL clones of cells, which harbour persistent and commonly integrated HPV, acquire a fully malignant phenotype and, over time, clinically manifest as invasive squamous cell carcinoma (Stoler 2000).

3.5.1 Estimating the risk of progression from HSIL to cancer

Studies examining the natural history of intraepithelial high-grade disease, based on observations made in the 1950s and 1960s, have estimated an annual rate of progression to invasive cervical cancer of less than 1% (Canfell et al 2004). In interpreting these data it is important to bear in mind that these studies were conducted at a time when the age profile of women taking part in screening was older than today, women were less well screened and the quality of cytology was poorer. All of these factors mean that the rate of cancer after HSIL cytology will be greater than we would expect today. Furthermore, these historical studies did not use time-sensitive methods of analysis. Rather, the number of women developing cancer was described; generally, only a broad indication of the time period was provided.

Early diagnosis of cervical cancer after HSIL cytology (eg within one to two years) is more typically due to undercalling of the disease state than to progression from intraepithelial disease to malignancy. The accuracy of the index cytology and the symptom status of the woman thus become crucial determinants of the rate of cancer diagnosis within short periods after HSIL cytology. Consequently, although the long-term progression estimates will be reasonably stable, the estimate of progression in the first one to two years of follow-up will be inflated for the Australian context.

Östör (1993b) summarised all papers written over the preceding 40 years where he considered the natural history of cervical neoplasia could be determined. From these studies, Östör calculated that:

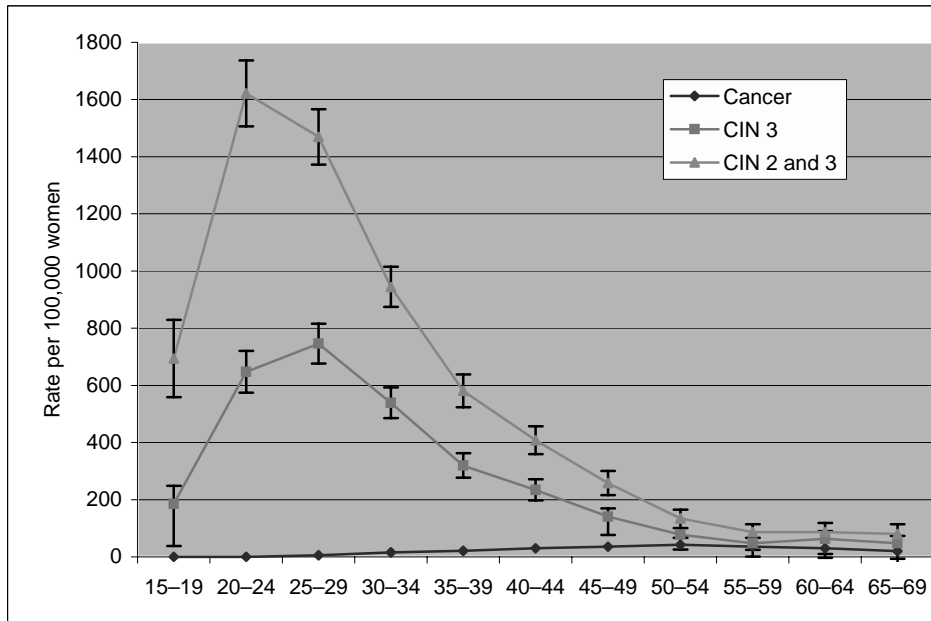
- 43% of CIN 2 regresses, 35% persists as CIN 2, and 22% progresses to CIN 3 over an undefined time period
- 33% of CIN 3 regresses, 56% persists as CIN 3, and 12% progresses from CIN 3 to cancer, again over an undefined time period.

This study (Östör 1993b) described many limitations in the papers reviewed. Fifteen of the 21 studies reviewed by Östör for the natural history of CIN 3 are accessible. In 14 of these publications, Östör identified a small subset of untreated women in whom the natural history could be studied from among a much larger case series (typically women with different entry criteria or women who underwent biopsy and treatment). Few papers provide details about the timing of the cancer diagnosis in relation to the entry status of CIN 3. Where these are provided, they are typically only the range and mean time of follow-up for all women in the study (not just in women in whom the natural history was uninterrupted). Only three studies give details about the time period between the CIN 3 diagnosis and the cancer diagnosis, as well as the time period of observation for women with CIN 3 who did not progress to cancer. These limitations must impact on the ability to accurately estimate progression rates, particularly over short periods of time.

Statistical models have estimated that the average duration between HSIL and cancer is between 10 and 15 years (van Oortmarssen and Habbema 1991, Bos et al 1997). These estimates are broadly in accord with population statistics, histological HSIL now being most commonly diagnosed among women aged 25–29 years compared with cancer in an unscreened population having peak rates in the age range 44–49 years (Gustafsson et al 1997). The duration of occult malignancy has been estimated at around four years (Gustafsson and Adami 1989).

As the age spectrum of women having cervical cytology has progressively broadened to include younger women, the peak age for CIN 3 on cytology has declined and the

frequency of this diagnosis has increased (Mitchell and Medley 1990). The rates of diagnosis of histologically confirmed CIN 2 and CIN 3 among screened women are now vastly in excess of the rate of cervical cancer among unscreened women. The excess is most apparent in premenopausal women (see Figure 3.2).



Source: CIN 2 and CIN 3, VCCR (2003); cancer, Gustafsson et al (1997)

Figure 3.2 Frequency of histologic CIN 2 and CIN 3 per 100,000 screened women versus incidence of cervical cancer per 100,000 unscreened women

The incidence of HSIL is highest among women in their twenties and declines rapidly with age. Even in the absence of screening, cancer is an uncommon outcome of these lesions. The combination of the uncommon cancer outcome and the falling incidence with age implies that there is a very significant rate of regression.

Recent modelling data from the United Kingdom also suggest that at least 80% of high-grade intraepithelial abnormalities will regress without intervention (Raffle et al 2003).

Regression of cytological HSIL in individual women has been observed in more recent natural history studies and can occur over quite short periods of time. The Netherlands study by Nobbenhuis et al (2001a) (see Section 3.4) found one-third of the women with CIN 2 cytology had regressed by 12 months. By 24 months, almost 20% of the women with CIN 3 cytology had regressed to normal (see Table 3.2).

Table 3.2 Cytological regression by time and degree of HSIL, Netherlands natural history study

Cytology	Months	Regression (95% CI)	
CIN 2	6	17.8%	(7.0, 28.6)
	12	33.6%	(19.8, 47.4)
	24	50.5%	(34.6, 66.4)
CIN 3	6	12.4%	(2.9, 21.9)
	12	12.4%	(2.9, 21.9)
	24	18.4%	(6.3, 30.5)

Source: Nobbenhuis et al (2001a)

Recently there has been a move to confine the concept of ‘precancer’ to only CIN 3 lesions, thus excluding CIN 2. This change has been prompted by the recognition that non-oncogenic HPV infections (such as types 6 and 11) are capable of producing CIN 2 lesions (Schiffman and Kjaer 2003). This shift in knowledge is potentially of very great significance for natural history studies, although it is currently difficult to estimate the proportion of CIN 2 that is due to non-oncogenic HPV infection.

3.5.2 Factors influencing progression from HSIL to cancer

Apart from persistent infection with high-risk HPV subtypes, there are two other factors known to influence the progression from HSIL to cancer: the age of the woman and the extent of HSIL.

Age at diagnosis

From the follow-up of women with CIN 3 at the National Women’s Hospital in New Zealand, McIndoe et al (1984) documented that the risk of CIN 3 progressing to cervical or vaginal cancer was age-related. A ten-year increase in the age at diagnosis of CIN 3 had an associated relative risk of cancer of 2.5 (95% CI, 1.9 to 3.3).

Within the Swedish National Cancer Registry, a record linkage study was conducted between women who had had a diagnosis of CIN 3 and women who were diagnosed with cervical cancer (Pettersson and Malaker 1989). The study was large, involving 453,000 women-years at risk. The observed number of cancers was compared with the expected number of cases based on population rates, with cancers diagnosed within one year of the CIN 3 being excluded. Among women aged less than 50 years at the time of CIN 3, the observed number of cancers was 145 compared with an expected number of 77.4, giving an observed:expected ratio of 1.9. Among women aged 50 or more years at the time of CIN 3, the observed number of cancers was 66 compared with an expected number of 10.7, giving an observed:expected ratio of 6.2.

The extent of HSIL

Cervical cancer usually occurs in the presence of extensive HSIL. Biopsy-proven microinvasive cancer is typically associated with extensive CIN 3 (Östör 1993b, Al-Nafussi and Hughes 1994), both on the surface epithelium and also affecting the deep endocervical crypts.

During the HSIL phase, there are several markers of the extent (quantum) of HSIL that is present. This is important, given that invasion usually occurs after years of persistence and intraepithelial expansion of CIN 3 (Sherman et al 2003b).

The size of the HSIL and its relationship to the degree of cytological abnormality has been clarified in two studies. Tidbury et al (1992) reviewed consecutive cone biopsies to identify those containing a microcarcinoma; the extent of associated CIN 3 was determined for these cases. This was compared with the size of CIN 3 found on cone biopsies when the cytology was reported as CIN 1, CIN 2 and CIN 3. Microcarcinoma was associated with a mean size of associated CIN 3 that was 100 times the size of CIN 3 found when the cytology had been reported as CIN 1 (see Table 3.3).

Table 3.3 Size of CIN 3 in the presence of microcarcinoma and for varying grades of CIN on cytology, cone biopsy study

Cytology	Histology	Mean length of CIN 3 (SD)
CIN 1	CIN 3	0.6 mm (1.7)
CIN 2	CIN 3	5.3 mm (15.7)
CIN 3	CIN 3	9.5 mm (15.5)
Not stated	Microcarcinoma	63.5 mm (37.2)

SD = standard deviation
Source: Tidbury et al (1992)

More recently, a relationship between the severity of the cytology report and the size of the CIN 3 was found in the ALTS trial (Sherman et al 2003b). One pathologist, blinded to the cytology report, the study arm and the phase of the trial, reviewed all available CIN 3 biopsies. A summary statistic known as total dimension score (TDS) was calculated to indicate the degree of circumferential involvement of the cervix by the CIN 3. The TDS reflected the distal–proximal length of each CIN 3 focus and the number of tissue pieces involved (see Table 3.4).

Table 3.4 Total dimension score (TDS) for CIN 3 at exit visit, ALTS trial

Cytology	Mean TDS for histologic CIN 3 (SE)
Negative	2.0 (0.3)
ASCUS	2.8 (0.6)
LSIL	3.2 (0.7)
HSIL	6.2 (1.9)

SD = standard error
Source: Sherman et al (2003b)

These relationships are further elucidated by a detailed study of 319 cone biopsies (Abdul-Karim et al 1982). This research found that age was correlated with both the severity of the lesion and its size. The lesions in older women were more extensive for the same grade of CIN than those in younger women.

The risk of progression to cancer is also influenced by the degree of HSIL that is present. After excluding cancers diagnosed within one year of biopsy-proven HSIL, the rate of cervical cancer after treatment for CIN 3 is more than four times higher than after treatment for CIN 2 or CIN 2/3 (Mitchell and Hocking 2002). After CIN 3, the rate was 1.45 cancers per 1000 years of follow-up (95% CI, 1.2 to 1.8) compared with a rate of 0.33 cancers per 1000 years of follow-up (95% CI, 0.2 to 0.5) after CIN 2 and CIN 2/3.

In summary, the malignant potential of histologically confirmed HSIL is not uniform. The age of the woman, the size of the lesion and the degree of abnormality (CIN 2 versus

CIN 3) all have a demonstrable impact on the likelihood of progression. Sherman et al (2003b) stated:

Women with ASCUS and LSIL cytology represent a large reservoir of mostly young women with CIN 3, which has remained occult previously but is now increasingly discovered with more sensitive methods such as liquid-based cytology and HPV testing. Aggressive follow-up of ASCUS in the United States has resulted in **lead-time bias** with regard to many cases of CIN 3, which **would not have resulted in interval cancers among routinely screened patients if they had been detected later.** (Emphasis added)

4 Terminology

4.1 Background

In 1991, the United States National Cancer Institute (NCI) sponsored a multidisciplinary meeting in Bethesda, Maryland to consider Pap smear terminology. Pathologists, cytotechnologists, gynaecologists and family practitioners, predominantly from the United States but also from other countries, participated in the workshop. The participants agreed on a consistent system for reporting Pap smears, *The Bethesda System 1991* (TBS 1991).

Problems with TBS 1991

TBS 1991 had three major problems. First, the three-tier system for assessing whether or not a smear was satisfactory meant that Pap smears could be designated as ‘satisfactory’, ‘satisfactory but limited by ...’, or ‘unsatisfactory’. The category of ‘satisfactory but limited by ...’ created substantial difficulties in the United States by forcing clinicians to treat these smears as unsatisfactory, resulting in a large number of early repeat smears.

Second, TBS 1991 did not formally recognise adenocarcinoma in situ (AIS). These cases were placed in a category of ‘atypical glandular cells of undetermined significance’ (AGUS), together with cases in which much less atypia was observed in glandular cells. It is now regarded as unsafe to include smears that show evidence of AIS under this heading, since most smears in this category require less aggressive follow-up than AIS smears.

Third, the heading ‘atypical squamous cells of undetermined significance’ (ASCUS) included possible high-grade abnormalities together with a much larger number of cases of possible low-grade abnormalities. The follow-up of women in whom a high-grade lesion is suspected but cannot be confidently predicted on the basis of a Pap test needs to be more aggressive than the follow-up of women whose smears show changes suggesting the possibility of a low-grade abnormality.

NHMRC-endorsed Australian terminology, 1994

As part of preparing the first National Health and Medical Research Council guidelines for the management of women with screen-detected abnormalities (NHMRC 1994), the Australian working party considered the Bethesda terminology and recommended a range of modifications to overcome the three major problems outlined above. This resulted in a unique Australian terminology system.

Revised Bethesda System (TBS 2001)

In 2001, the NCI reviewed TBS terminology and a number of changes were made to overcome the previous problems, bringing the system closer to the NHMRC-endorsed reporting system developed in Australia (Solomon and Nayer 2004).¹

TBS 2001 includes a two-tiered classification in relation to whether or not Pap smears are satisfactory, and a category that accommodates a definite prediction of AIS. Unlike TBS 1991, it also includes two separate categories for undetermined cases:

- when a possible low-grade abnormality is suspected, it is called ‘atypical squamous cells of undetermined significance’ (ASC-US)
- when a possible high-grade lesion is suspected, it is called ‘atypical squamous cells, possible high-grade lesion’ (ASC-H).

4.2 Australian Modified Bethesda System 2004 (AMBS 2004)

The previous NHMRC-approved Australian terminology (NHMRC 1994) had structural differences from TBS 2001. The major difference related to the structure of the low-grade abnormalities. This difference is particularly important because TBS 2001 has been adopted internationally by the United States and a large number of other countries, and women with low-grade abnormalities are currently the subjects of a number of clinical trials investigating the optimal management of these cases. Applicability of international research to the Australian context is exceedingly difficult while structural differences in terminology systems persist. Finally, the NHMRC Australian terminology system, which was based on human papillomavirus (HPV)/cervical intraepithelial neoplasia (CIN) terminology, contained subdivisions between HPV and CIN 1 that are not supported by evidence that the distinctions are reasonably reproducible (see Section 4.5) or by different clinical outcomes.

After extensive consultation undertaken by the Australian Society of Cytology, with the introduction of these guidelines, Australia will adopt a revised terminology system, to be known as the *Australian Modified Bethesda System 2004* (AMBS 2004).

In adopting the new Australian terminology, consensus has been reached to accept the underlying structure of TBS 2001 but to relabel a number of categories. In particular, there was strong opposition from some to the ‘atypical squamous cells of undetermined significance’ category.

One remaining substantial difference between TBS 2001 and the previous NHMRC-endorsed terminology related to the structure of the low-grade abnormalities. AMBS 2004 incorporates the separation of suspected from confidently predicted low-grade abnormalities. AMBS 2004 reflects a modern understanding of HPV infection, and cervical cancer and its precursors. It is compatible with terminology systems used internationally and it does not mandate distinctions for which there is poor evidence for reproducibility or clinical significance.

Note: The AMBS 2004 terminology described here relates only to cervical cytology. Terminology for reporting cervical tissue samples (histopathology) remains unchanged.

¹ <http://bethesda2001.cancer.gov/terminology.html> (Accessed 19 July 2004)

Therefore, in these guidelines, intraepithelial lesions confirmed histologically will still be reported according to the CIN terminology and other SNOMED terms.²

4.3 Explanation and definition of AMBS 2004 terminology

This section outlines AMBS 2004 terminology. Table 4.1 shows a comparison of AMBS 2004 with the previous NHMRC-endorsed Australian terminology (NHMRC 1994) and TBS 2001.

Squamous abnormalities

Possible low-grade squamous intraepithelial lesion

The category of possible low-grade squamous intraepithelial lesion is to be used when the reporting scientist/pathologist observes changes in squamous cells that may represent a low-grade squamous intraepithelial lesion, but the changes are not so clear-cut as to justify a 'definite' diagnosis. This category specifically excludes changes that are within the scope of reactive processes. It corresponds to 'nonspecific minor squamous cell changes' in the previous Australian NHMRC-endorsed terminology (NHMRC 1994).

Low-grade squamous intraepithelial lesion

The low-grade squamous intraepithelial lesion (LSIL) category is the morphological correlate of productive viral infection. It is to be used when the scientist/pathologist observes changes that would have been described as 'HPV effect' or 'CIN 1' in the previous Australian terminology and represents part of the previous 'low-grade squamous epithelial abnormality' category.

Possible high-grade squamous lesion

The category of possible high-grade squamous lesion is to be used when the reporting scientist/pathologist suspects the presence of a high-grade squamous abnormality, such as possible CIN 2, CIN 3 or squamous cell carcinoma (SCC), but the changes are insufficient to justify a confident cytological prediction of a high-grade lesion. It corresponds to the 'inconclusive possible high-grade squamous abnormality' category in the previous Australian terminology.

High-grade squamous intraepithelial lesion

The high-grade squamous intraepithelial lesion (HSIL) category is the morphological correlate of a true preneoplastic change occurring in squamous cells as a result of HPV infection. It is to be used when the scientist/pathologist observes changes that would have previously been described as CIN 2 or CIN 3. Cases in this category would have accounted for almost all cases in the 'high-grade squamous epithelial abnormality' category in the previous Australian terminology.

If, in addition to the presence of a definite intraepithelial high-grade abnormality, there are features that suggest the presence of an invasive component, this should be noted in the 'specific diagnosis' section of the report.

² Systematized Nomenclature of Medicine; <http://www.snomed.org> (Accessed 19 July 2004)

Squamous cell carcinoma

The SCC category is self-explanatory. In the previous Australian terminology, these cases would have fallen under the heading of ‘high-grade epithelial abnormality’.

Glandular abnormalities

Atypical endocervical cells of undetermined significance

Atypical glandular cells of undetermined significance

These categories encompass those changes in glandular cells that the reporting scientist/pathologist believes are outside the scope of a definite reactive process. It has been well documented that productive HPV infection does not exist in glandular cells, and therefore there is no glandular correlate to the low-grade squamous abnormality.

Nevertheless, the morphological changes observed in glandular cells encompass a spectrum of changes. These categories should be used when such changes are insufficient to raise the possibility of a neoplasm, such as AIS, but are beyond those accepted as definitely representing a reactive process. Cells in this category are to be designated as follows:

- *atypical glandular cells* when the reporting scientist/pathologist is not sure whether the cells are endocervical
- *atypical endocervical cells* when the reporting scientist/pathologist is confident that the cells are endocervical.

Possible high-grade glandular lesion

This category is to be used when the reporting scientist/pathologist suspects the presence of a high-grade glandular abnormality such as possible AIS, possible endocervical adenocarcinoma or possible endometrial adenocarcinoma, but is unable to make a confident prediction. It corresponds to the ‘inconclusive possible high-grade glandular abnormality’ category in the previous Australian terminology.

Endocervical adenocarcinoma in situ

The endocervical AIS category is self-explanatory. The diagnosis is to be used when the reporting scientist/pathologist is confident of the presence of AIS.

Adenocarcinoma

The adenocarcinoma category is self-explanatory. The reporting scientist/pathologist has the option of designating whether they believe the adenocarcinoma is endocervical, endometrial or extrauterine in origin.

Table 4.1 Comparison of the Australian Modified Bethesda System (AMBS 2004) with previous Australian terminology and The Bethesda System (TBS 2001)

AMBS 2004	Australian NHMRC- endorsed terminology 1994	TBS 2001	Incorporates
Squamous abnormalities			
Possible low-grade squamous intraepithelial lesion	Low-grade epithelial abnormality	Atypical squamous cells, undetermined significance (ASC-US)	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 (ASC-H)	Changes that suggest, but fall short of, CIN 2, CIN 3 or SCC
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, AIS or adenocarcinoma
Endocervical adenocarcinoma in situ	High-grade epithelial abnormality	Endocervical adenocarcinoma in situ	Adenocarcinoma in situ
Adenocarcinoma	High-grade epithelial abnormality	Adenocarcinoma	Adenocarcinoma

4.4 Preparation of cervical cytology reports using AMBS 2004

Cervical cytology reports should contain the following components.

Specimen type and site

- Indicate conventional Pap smear versus liquid-based versus other.³
- Indicate that the specimen is cervical in origin.

³ In the case of split samples, a single combined report should be issued and this field should indicate that the report is based on, for example, a conventional Pap smear and a ThinPrep or an Autocyte Prep sample.

Interpretation/result

- This should consist of the appropriate category heading, selected from the section below.
- A statement regarding the presence or absence of an endocervical component should be included.⁴
- The laboratory may, at its discretion, also include a more specific diagnosis. Some practitioners have expressed a strong preference that laboratories continue to distinguish between CIN 2 and CIN 3 within the HSIL category (see Section 4.5).

Recommendation

- Concise management recommendations, as set out in the following sections of these guidelines, should be included in the report. Explicit reference to these guidelines can be included in the report.

Categories of results

Unsatisfactory for evaluation (*specify reason*)⁵

Negative for intraepithelial lesion or malignancy

Organisms

- *Trichomonas vaginalis*
- fungal organisms morphologically consistent with *Candida* spp
- shift in flora suggestive of bacterial vaginosis
- bacteria morphologically consistent with *Actinomyces* spp
- cellular changes consistent with herpes simplex virus.

Other non-neoplastic findings (*optional to report; list not exclusive*)⁶

- reactive cellular changes associated with:
 - inflammation and repair
 - radiation
 - intrauterine contraceptive device
- glandular cells after hysterectomy
- atrophy

⁴ An endocervical component should include at least two groups of well-preserved endocervical and/or squamous metaplastic cells, with each group containing at least five cells.

⁵ See Chapter 5 (Management of women with unsatisfactory Pap smears)

⁶ Because of the evidence that asymptomatic postmenopausal women with cytologically normal endometrial cells in their Pap smears do not have an increased risk of endometrial adenocarcinoma, the presence of normal endometrial cells should not be reported in any age group. The presence of cytologically abnormal endometrial cells must be reported.

Epithelial cell abnormalities

Squamous abnormalities:

- possible low-grade squamous intraepithelial lesion
- low-grade squamous intraepithelial lesion
- possible high-grade squamous lesion
- high-grade squamous intraepithelial lesion
- squamous cell carcinoma.

Glandular abnormalities:

- atypical endocervical cells of undetermined significance
- atypical glandular cells of undetermined significance
- possible high-grade glandular lesion
- endocervical adenocarcinoma in situ
- adenocarcinoma.

Note: ‘Atypical’ cells are those that deviate from a normal or typical state. In cytology, this includes any deviation from normal cellular appearances, but conveys no information about aetiology. Atypical cells may be due to physiological processes such as repair or response to radiation, or to disease processes such as dysplasia or cancer. The term should therefore not be used alone, but should be further qualified and accompanied by a clear recommendation for management.

Examples of reports conforming to the new terminology requirements are presented in Appendix 5.

4.5 Review of cervical smear data using previous and new Australian terminology

The Royal College of Pathologists of Australasia Quality Assurance Program in cytopathology involves laboratories reviewing cervical smears for which target diagnoses have been established through histological follow-up, where abnormal, and through a history of subsequent negative smears, where normal (Royal College of Pathologists Australasia 2003). Data for the years 2000 to 2002 were examined. There were 5575 responses submitted to the quality assurance program against 1139 gynaecological cytology cases (most slides were sent to several laboratories for assessment and hence there were more responses than target diagnoses). A cross-tabulation of target diagnosis versus submitted diagnosis is presented in Table 4.2.

For the 273 cases in which HPV was the target diagnosis, 196 responses were of HPV, giving a target response rate of 72%. For the 283 in which the target diagnosis was CIN 1, the 175 submitted diagnoses of CIN 1 gave a target response rate of 62%.

Table 4.2 Royal College of Pathologists of Australasia Quality Assurance Program correlations

TARGET CODE		SUBMITTED DIAGNOSIS CODE														Total			
Previous NHMRC terminology	Revised NHMRC terminology	Unsatisfactory	Negative	Minor atypia SQ	HPV	CIN 1	Inconclusive SQ	CIN 2	CIN 3	SCC	Minor atypia GL	Inconclusive-GL	AIS	Endocervical AC	Endometrial AC	Adeno-carcinoma	Carcinoma NOS	No response	
		Unsatisfactory	Negative	Possible LSIL	LSIL	LSIL	Possible HSIL	HSIL	HSIL	SCC	Atypical glandular / endocervical cells	Atypical glandular cells, possibly neoplastic	AIS	Endocervical AC	Endometrial AC	Adeno-carcinoma	Carcinoma NOS	No response	
Unsatisfactory	Unsatisfactory	228	53	0	0	0	0	0	0	0	2	0	0	0	0	0	0	0	283
Negative	Negative	62	2957	36	10	3	14	2	6	1	26	12	15	3	3	1	2	0	3153
Minor atypia SQ	Possible LSIL	0	5	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0	6
HPV	LSIL	2	12	3	196	58	0	2	0	0	0	0	0	0	0	0	0	0	273
CIN 1		0	8	6	36	175	1	52	4	1	0	0	0	0	0	0	0	0	283
Inconclusive SQ	Possible HSIL	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
CIN 2	HSIL	1	4	1	3	39	6	113	108	2	0	0	0	0	0	0	0	0	277
CIN 3		1	8	1	1	6	16	42	431	34	2	6	4	5	1	0	2	0	560
SCC		1	0	0	0	0	5	2	37	289	0	2	0	7	10	3	8	0	364
Minor atypia GL	Atypical glandular / endocervical cells	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Inconclusive GL	Possible high-grade glandular lesion	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
AIS		1	4	0	0	0	1	0	1	0	2	8	81	19	0	2	0	0	119
Endocervical AC	Endocervical AC	0	1	0	0	0	0	0	7	10	0	2	34	83	6	13	3	1	160
Endometrial AC	Endometrial AC	0	3	0	0	0	1	0	0	1	2	6	0	6	70	8	0	0	97
Adenocarcinoma	Adenocarcinoma	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Carcinoma NOS	Carcinoma NOS	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
No response		0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total		296	3055	48	246	281	44	213	594	338	34	36	134	123	90	27	15	1	5575

Exact agreement (previous terminology) OR Exact agreement (revised terminology) +

AC = adenocarcinoma of the cervix; AIS = adenocarcinoma in situ; CIN = cervical intraepithelial neoplasia; GL = glandular lesion; HPV = human papillomavirus; HSIL = high-grade squamous intraepithelial lesion; SQ = squamous lesion; LSIL = low-grade squamous intraepithelial lesion; NOS = not otherwise specified; SCC = squamous cell carcinoma. Source: Royal College of Pathologists of Australasia (2003)

However, combining these cases gives 556 occasions in which either HPV or CIN 1 was considered the target diagnosis, with 465 target responses. Accordingly, the target response rate for the new category of LSIL, incorporating both HPV and CIN 1, would have been 84%.

For the 277 cases in which CIN 2 was the target diagnosis, 113 responses were of CIN 2 (target response 41%). For the 560 cases in which the target diagnosis was CIN 3, there were 431 submitted diagnoses of CIN 3 (target response 77%). However, combining these cases gives 694 target responses for the 837 cases in which either CIN 2 or CIN 3 was considered the target diagnosis, so the target response rate for the new category of HSIL, incorporating both CIN 2 and CIN 3, would have been 83%.

As part of the Atypical Squamous Cells of Undetermined Significance (ASCUS) and LSIL Triage Study (ALTS), 3901 slides were independently reassessed by investigating pathologists. Table 4.3 shows the kappa scores obtained.

Table 4.3 Kappa scores for reassessment of slides

Categorisation	No. slides	Kappa
Benign vs ASCUS	1463	Fair (0.24)
ASCUS vs HPV	856	Good (0.55)
HPV vs CIN 1	794	Poor (0.16)
CIN 1 vs CIN 2	609	Good (0.43)
CIN 2 vs CIN 3	179	Fair (0.28)

Source: ASCUS and Low Grade Squamous Intraepithelial Lesions Triage Study (D Solomon, National Cancer Institute, Bethesda, MD, USA, personal communication)

These results support reasonable reproducibility in the distinction between ASCUS and LSIL and between LSIL and HSIL. However, the results suggest that agreement, beyond that expected by chance alone, is poor for distinction between HPV and CIN 1 and between CIN 2 and CIN 3.

Nevertheless, there may be some clinical relevance in retaining a subdivision between CIN 2 and CIN 3 for routine reporting. Data from Australian registries, shown in Table 4.4, suggest that there are clear differences in outcomes for a cytological diagnosis of CIN 2 compared to CIN 3. Accordingly, laboratories may wish to continue to provide specific diagnoses of CIN 2 or CIN 3, when the result is HSIL.

Table 4.4 Positive predictive value and outcomes of CIN 2 or 3 prediction

Source of data	PPV (%) ^a		Inv Ca (%) ^b	
	CIN 2	CIN 3	CIN 2	CIN 3
MSAC review; pooled data from Australian CCRs 1999	61.3	83.1	0.2	1.6
Victorian CCR, Annual Report 2001	65.5	86.1	0	3.4
Victorian CCR, Annual Report 2000	62.5	83.8	0	2.4
Western Australian CCR, Annual Report 2001	64.0	87.8	0.2	5.2

MSAC = Medical Services Advisory Committee; CCR = cervical cytology register

^a PPV = positive predictive value = % of cases in this category in which biopsy shows a high-grade abnormality (CIN 2/3, AIS or invasive carcinoma)

^b Inv Ca = % of cases in this category where biopsy shows invasive carcinoma

5 Management of women with unsatisfactory Pap smears

5.1 Background

Previous guidelines for Australian reporting did not define specimen adequacy. The original Bethesda System (TBS 1991) included a 'satisfactory but limited by' category and recommended 10% slide coverage as a minimum threshold for specimen adequacy. This approach was not endorsed in the Australian NHMRC 1994 terminology and has been modified in the recent Bethesda review (TBS 2001).

5.2 Australian definition of unsatisfactory Pap smear

There is no agreement in the literature regarding the number of cells visible on a Pap smear (cellularity) below which there is a significant fall in sensitivity. The TBS 2001 recommendation for conventional smear squamous cellularity is that specimens should have a minimum of 8000 to 12,000 well-preserved and well-visualised squamous epithelial cells. This minimum range applies only to squamous cells.

An unsatisfactory Pap smear is defined in these guidelines as one that contains fewer than 10,000 well-visualised squamous epithelial cells for conventional Pap smears (or 5000 for liquid-based preparations), either because there are fewer cells present or because of problems with preservation or obscuring agents. The threshold for liquid-based cytology samples is lower than that recommended for conventional smears because of the reported sample homogeneity achieved with liquid methods.

Specimens should not be classified unsatisfactory on the basis of an absence of an endocervical component alone.

This approach is based on the TBS 2001 definition, promotes international consistency and will facilitate the application of overseas research in Australia, particularly research focused on unsatisfactory smears. However, the minimum number of well-visualised cells required for a satisfactory negative result may require revision if further evidence becomes available.

5.3 Application

The laboratory report should state why the smear is unsatisfactory.

The cellularity of specimens should be estimated rather than counted. Estimation of smear cellularity based on reference images is suggested as a more reliable and reproducible method than estimating slide coverage (Solomon and Nayer 2004). Reference images and information on the method may be downloaded from the United States National Cancer Institute's Bethesda System website.⁷ Hierarchical review may help in borderline cases.

⁷ http://bethesda2001.cancer.gov/postwrkshp_recgs.html (Accessed 19 July 2004)

In some samples prepared from liquid-based cytology, the epithelial cells are concentrated at the edge of the cell button. This should be taken into account when estimating cellularity. The cell count should be estimated by evaluating a minimum of 10 fields along the diameter of the preparation (details are provided at the Bethesda website).

It is further emphasised that the threshold is not rigid and that some presentations and clinical settings, such as cell clustering, atrophy or cytolysis may influence the estimation and application of the minimum threshold. Adequate repeat preparations may be achieved in some cases by recognising and dealing with technical problems. However, where more than one slide is prepared, specimen adequacy should be determined separately rather than cumulatively.

Any specimen with abnormal cells should be reported as satisfactory for evaluation, and the abnormality should be reported.

5.4 Management of unsatisfactory Pap test results

A woman with an unsatisfactory Pap test report should have a repeat smear. If the reason for the unsatisfactory smear has been identified, this problem should be corrected, if possible, before the repeat smear is collected.

To avoid any possible increased false negative rate caused by tissue repair and recovery after the initial test, the Pap test should be repeated no sooner than 6 weeks after the initial smear, but within 12 weeks.

Guideline —Unsatisfactory Pap test reports	
A woman with an unsatisfactory Pap test report should have a repeat smear in 6–12 weeks, with correction, when possible, of the problem that caused the unsatisfactory smear.	Consensus

6 Management of low-grade squamous abnormalities

6.1 Introduction

The Australian Modified Bethesda System (AMBS) 2004 for the reporting of low-grade squamous abnormalities recognises two categories, based upon the confidence of the cytological prediction:

- possible low-grade squamous intraepithelial lesion (LSIL)
- definite LSIL.

This is a major change from the previous NHMRC-endorsed Australian terminology (NHMRC 1994), which allowed for three subcategories of low-grade epithelial abnormality (LGEA):

- nonspecific minor change (NSMC)
- human papilloma virus (HPV) effect
- cervical intraepithelial neoplasia (CIN 1).

These categories did not correspond with the 1991 Bethesda system (TBS 1991; see Chapter 4), the United Kingdom terminology (NHSCSP 2004), the KOPAC classification (a Pap classification system used in the Netherlands; Bos et al 2002) or the original Papanicolaou classes, making comparisons with the published international literature very difficult.

6.2 Australian evidence

Low-grade cytology reports are very common in Australia. In part, this is because screening is started at a young age (18–20 years), but it also reflects the short two-yearly rescreening interval that results in greater detection of transient abnormalities.

Table 6.1 shows the prevalence of low-grade cytology reports among women screened in New South Wales in 2002.

Table 6.1 Prevalence of squamous intraepithelial lesions in NSW women, by age

Age group	Prevalence of cytologically predicted LGEA (per 100,000 women per year)
20–24	9399 (9.4%)
25–29	6239 (6.2%)
30–34	4283 (4.3%)
35–39	3807 (3.8%)
40–44	3735 (3.7%)
45–49	3436 (3.4%)
50–54	2932 (2.9%)
55–59	2210 (2.2%)
60–64	2088 (2.1%)
65–69	1947 (1.9%)
All (20–69)	4283 (4.3%)

LGEA = low-grade epithelial abnormality

Source: NSW Pap Test Register data 2002

As part of this guidelines review, outcomes for Australian women whose first cytology report during 1999 was of an LGEA were studied over 24 months. This study — the 1999 Australian low-grade cohort study — used data held in the Australian Pap test registers in late 2002. Both symptomatic and asymptomatic women were included in the study, as the Pap test registers do not record information about symptom status. However as these guidelines apply only to asymptomatic women, the outcomes from this cohort study represent a worst-case scenario. A detailed report of the findings of the cohort study is presented in Appendix 7.

A total of 90,566 women had an LGEA as their first cytology report in the 1999 calendar year, representing 4.5% of screened women. Follow-up information covering the following 24 months was available for 76,709 of these women. There was wide variation in the use of the three subcategories of LGEA across Australia, consistent with poor repeatability between laboratories (see Table A7.2 in Appendix 7).

As shown in Appendix 7, a total of 41 women had cancer of the cervix diagnosed during the following two years. Twenty of these were diagnosed within six months of the index low-grade smear and 21 between six and 24 months after the index smear. This represents a risk of between 0.53 in 1000 (including only women with documented follow-up) and 0.43 in 1000 (including all women with an LGEA report) of developing cancer within two years.

The most common outcome state for women of both age groups (under 30 years and 30 years or over), and for all three subcategories of LGEA, was of no abnormality or only low-grade disease during the 24 months of follow-up. Nevertheless, 7148 women had an outcome of high-grade intraepithelial disease, with the diagnosis being made mainly on biopsy. High-grade intraepithelial disease was diagnosed more commonly in women under 30 years (13%) than in women aged 30 years and over (6%), even though the risk of malignancy increases with increasing age.

Women under 30 years were more likely to have a biopsy during the 24 months than older women (44% versus 32%), and women with CIN 1 cytology were more likely to have a biopsy than women with HPV or NSMC cytology.

Review of the outcomes over two years following the initial LGEA cytology report found no difference in the risk of detection or progression to cancer between the three subcategories of LGEA, although a differential treatment effect due to the management of detected high-grade abnormalities cannot be excluded in this observational study (see Table A7.9 in Appendix 7).

6.3 Why are cancers diagnosed after low-grade cytology reports?

Cancers are diagnosed within one to two years of low-grade cytology for three reasons:

- undercalling a true state of cancer
- undercalling a true disease state of HSIL, which then progresses to cancer
- progression from a true disease state of LSIL to cancer.

Undercalling a true disease state of cancer

In this case, the woman already has cancer but the cytology is reported only as a low-grade abnormality. This may be because the sample of cells taken from the cervix does not include the malignant cells.

Alternatively, malignant cells can be present on the slide but be missed or misinterpreted at the time the smear is reported. Reporting errors can be determined by a review of the cytology. However, if the slide review still confirms that only low-grade changes are present, sampling difficulties can be inferred only if other tests (either cytology or histology) taken close to the same time demonstrate the malignancy.

Sixteen of the 41 cancers in the 1999 Australian low-grade cohort study were diagnosed at Stage 1B or worse within six months of the index low-grade cytology. An additional 15 Stage 1B or worse cancers were diagnosed between six and 24 months. In studies that evaluate the progressive potential of intraepithelial lesions (eg Östör 1993a), these cancers would have been classified as ‘progressions’, although true progression from a low-grade intraepithelial lesion to Stage 1B cancer or worse in such a short period is unlikely.

Undercalling a true disease state of HSIL, which then progresses to cancer

In this case, women with HSIL are misdiagnosed as having a low-grade abnormality on cytology. This is an area of concern, given that HSIL can be present in up to 20% of biopsies taken from women with LSIL cytology (see Appendix 7). It is a complex issue to research, involving both undercalling and progression. It is further complicated because CIN 2, which is the dominant high-grade lesion diagnosed histologically when the cytology has been reported as low-grade (VCCR 2003), includes both oncogenic and non-oncogenic HPV infection (see Section 3.3).

In the 1999 Australian low-grade cohort study, 7148 women had HSIL as their outcome over the two years of follow-up. More than 60% of these HSILs were found in women under 30 years of age, an age group at very low risk of cancer (5–15 cancers per 100,000 women per year in an unscreened population; IARC 1986).

Progression from a true disease state of LSIL to cancer

This describes the case in which a correctly diagnosed low-grade abnormality progresses to cancer during the 1–2-year period. However, progression is biologically unlikely to account for many cancers over such a short period in women with normal immune systems.

In reviewing the published literature, true progression has not been distinguished from undercalling in any published study. Furthermore, because concerns about privacy and litigation result in understandable reluctance on the part of laboratories to submit slides for external review, such a study is now unlikely.

The 1999 Australian low-grade cohort study documented the screening history of the 10 women who were diagnosed with microinvasive cancer within two years of a low-grade cytology report (see Appendix 7, Table A7.10). It is probable that five of the ten women (cases 3, 4, 7, 8, and 9) were undercalled by their low-grade cytology. It is of interest that four women appeared to have undercalling on their first biopsy (cases 1, 2, 4 and 10), consistent with the findings of Paraskevaidis et al (1992) that referral for colposcopy does not always prevent or reveal an outcome of microinvasive cancer.

Thus, cancer that is diagnosed after low-grade cytology represents a combination of two main influences — undercalling on the index cytology and true progression over time from an intraepithelial abnormality. The relative weights of these two influences vary with time. In the short term (eg 1–2 years after the index cytology), undercalling will have much greater importance. In the medium and long term, true progression will have greater importance.

The extent of undercalling reflects the quality of the cytology sampling and the quality of the reporting. The reporting of cytology specimens is a human interpretation. As such, the accuracy of the report reflects the training, ability, working conditions and quality measures of the staff involved. Undercalling rates are not generalisable from one country to another, or from one time period to another. By contrast, true progression represents the natural history of the disease and should be generalisable, provided other influences (eg age and intensity of previous screening) are taken into account.

The lack of generalisability in relation to undercalling is illustrated by comparing cancer rates in the 1999 Australian low-grade cohort study with those of the recent ALTS trial in the United States. Eligibility for enrolment in the ALTS trial required a cytological report of ASCUS or LSIL from a community laboratory. Five cancers were diagnosed at inception among the 1572 women with LSIL cytology in the ALTS trial, representing one woman in 314 (Sherman et al 2003a). In the 1999 Australian low-grade cohort study, 20 cancers were diagnosed within six months of low-grade cytology among 76,709 women with follow-up information, representing one woman in 3835.

6.4 Management options

Three management tools are available for women with LSIL/possible LSIL cytology:

- cytological surveillance at various intervals
- referral for colposcopy
- HPV testing.

Option 1 — cytological surveillance

Cytological surveillance involves repeating the cytology after a shorter interval than recommended after negative cytology. Further diagnostic procedures are delayed until the cytologic abnormality worsens or is found to be persistent. This is the initial recommended management in these guidelines for asymptomatic Australian women. The rationale for this recommendation is described in later sections of this chapter.

Option 2 — referral for colposcopy

Immediate colposcopy for women with LSIL and possible LSIL cytology is advocated by some to identify and treat those women with occult HSIL. The rationale for this approach is twofold: first, concern that some occult HSILs will remain undetected and progress to cancer during a period of cytological surveillance, and second, concern that some women will not comply with cytological surveillance.

This option was considered as part of the review and rejected. There is no evidence from randomised controlled trials that this early intervention confers a health gain additional to that achieved by performing the colposcopy after a period of cytological surveillance.

Furthermore, the Guidelines Review Group had concerns that such an approach would entail up to 5% of screened women having a colposcopy each year, for a disease with a lifetime risk of 1.6% (IARC 1986). This would be a substantial imbalance. Already Australian women have been documented as having a 76.8% chance of having a colposcopy during their lifetimes (Kavanagh et al 1996) and the Guidelines Review Group did not wish to increase these chances.

The negative sequelae of labelling such a high proportion of women as requiring investigation for a rare cancer are considerable (see Section 6.11). Furthermore, early colposcopy ignores current knowledge that low-grade cytology is a manifestation of a viral infection that will resolve spontaneously in almost all women (see Ho et al 1998, Moscicki et al 1998, Woodman et al 2001 and Chapter 3).

The cost implications of recommending colposcopy for all women with LSIL/possible LSIL cytology would necessitate a large additional financial investment in the National Cervical Screening Program without evidence of sufficient health gain. This issue is explored further in Section 11.3.

Option 3 — HPV testing

In 2002, the Medical Services Advisory Committee (MSAC) completed a literature review and cost-effectiveness assessment of the Hybrid Capture-II (HC-II) test in women with a cytological prediction of low-grade abnormality. The review concluded that there was insufficient evidence about the use of this test to support public funding at the time of the review (MSAC 2002).

MSAC suggested that further research into the cost-effectiveness of HPV testing in the Australian setting would be useful, particularly for women over the age of 30 years, but this research has not been forthcoming. Accordingly, this review of guidelines did not give further consideration to HPV testing.

Guideline — Human papilloma virus (HPV) testing	
There is insufficient evidence to support the use of HPV testing in the triage of low-grade squamous intraepithelial lesions.	MSAC 2002

6.5 Management of a cytological prediction of possible or definite LSIL

These guidelines explicitly exclude symptomatic women. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists has issued management guidelines for women with intermenstrual and postcoital bleeding which take precedence over these guidelines (see Appendix 9) (RANZCOG 2002).

The data from the 1999 Australia low-grade cohort study and the natural history of cervical neoplasia suggest there is a very low risk of cervical cancer being diagnosed within a two-year period after a single report of possible or definite LSIL on cytology in an Australian laboratory. Information derived from natural history studies (see Chapter 3) support a delay in the timing of further intervention to allow spontaneous resolution of the viral infection (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001). Accordingly, it is recommended that further assessment of a woman with a LSIL cytology prediction should include repeat cytology at 12 months from the index smear (see Figure 6.1).

Women with possible LSIL cytology should be managed in the same way as women with definite LSIL cytology. Terminology differences preclude the use of international literature in this area, so the basis for this recommendation derives from the 1999 Australian low-grade cohort study. Two points appear salient. First, a comparatively high number of cancers ($n = 25$) were diagnosed among women with NSMC (now referred to as possible LSIL). Second, the rate of HSIL found on biopsies performed within six months of NSMC and HPV effect cytology was similar. Consequently, it is recommended that a woman with a Pap test report of LSIL should be managed in the same way, irrespective of whether the abnormality is regarded as possible or definite and should be recommended for a repeat Pap test in 12 months.

Guideline — Index Pap test report of low-grade squamous intraepithelial lesions (LSIL)	
A woman with a Pap test report of LSIL should be managed in the same way irrespective of whether the abnormality is regarded as possible or definite and should be recommended for a repeat Pap test in 12 months.	Australian registry data; Level III-2: three cohort studies of clearance interval (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001)

An exception to this recommendation can be made for women over the age of 30 years without a history of negative cytology in the preceding two to three years. Either early colposcopy or repeat cytology within six months is recommended for these women to facilitate diagnosis of any occult HSIL that may have advanced further in the sequence from HSIL towards cancer. Statistical models have estimated that the average duration

from development of HSIL and progression to cancer is between 10 years and 15 years (van Oortmarssen and Habbema 1991, Bos et al 1997). While women with negative cytology in the preceding two to three years would typically be located in the early part of the HSIL progression, women without such a history of negative cytology may be more advanced towards HSIL. This added safeguard ensures that women who lack the protection of previous negative screening will be recommended for diagnostic intervention sooner than otherwise proposed for regularly screened women.

Guideline — Index Pap test reports of LSIL in women aged 30+ years	
A woman aged 30 years or more with a Pap test report of LSIL, without a history of negative smears in the preceding two to three years, should be offered either immediate colposcopy or a repeat Pap smear within six months.	Australian registry data

The basis for the cutoff point at age 30 years is twofold. First, HPV prevalence falls very quickly with age while women are in the teenage or 20–29 year age group; over 30 years of age the prevalence is comparatively low and subsequently declines more slowly (Schiffman and Kjaer 2003). Bosch and de Sanjose (2003) state that the point prevalence among women aged 30+ years approximates the status of being a persistent carrier. Persistent HPV infection is a strong risk factor for cervical cancer. Second, more intensive care of women with low-grade cytology aged 30+ years provides a 5–15-year time period until the underlying incidence of squamous cervical cancer increases to high levels (IARC 1986, Gustafsson et al 1997).

The rationale underpinning the Australian recommendation that the repeat cytology be performed at 12 months (rather than 6 months) is the recently published evidence of the median time for HPV clearance being between 8 and 14 months (Moscicki et al 2004). Repeating the cytology earlier than 12 months means a higher proportion of women will still have the infection and the consequent cytologic abnormality. Under these circumstances, a further abnormal Pap smear can unnecessarily reinforce the impression of ‘disease’ even though the infection is still very likely to clear spontaneously. It appears that delaying the repeat cytology test until 12 months, rather than repeating it at 6 months, may allow a further 20–25% of LSIL to regress. Given that 90,000 Australian women per year receive these reports, a substantial number of women could potentially avoid unnecessary intervention.

An important change compared with the 1994 guidelines is that all women with LSIL/possible LSIL cytology will now have an endpoint of colposcopy. The 1994 guidelines recommended indefinite annual cytology for women with NSMC. This may have contributed to the relatively high number ($n = 25$) of women with cancer after an NSMC report in the 1999 Australian low-grade cohort study.

6.6 Subsequent management

The results of the 12-month repeat cytology will determine the subsequent management. If the 12-month repeat cytology shows high-grade changes (definite or possible), management should be conducted according to the guidelines in Chapter 7 (Schoolland et al 1998, Sparkes et al 2000, Performance Standards 2003). Persistent LSIL in a woman over the age of 30 years suggests persistent HPV infection with a corresponding increased

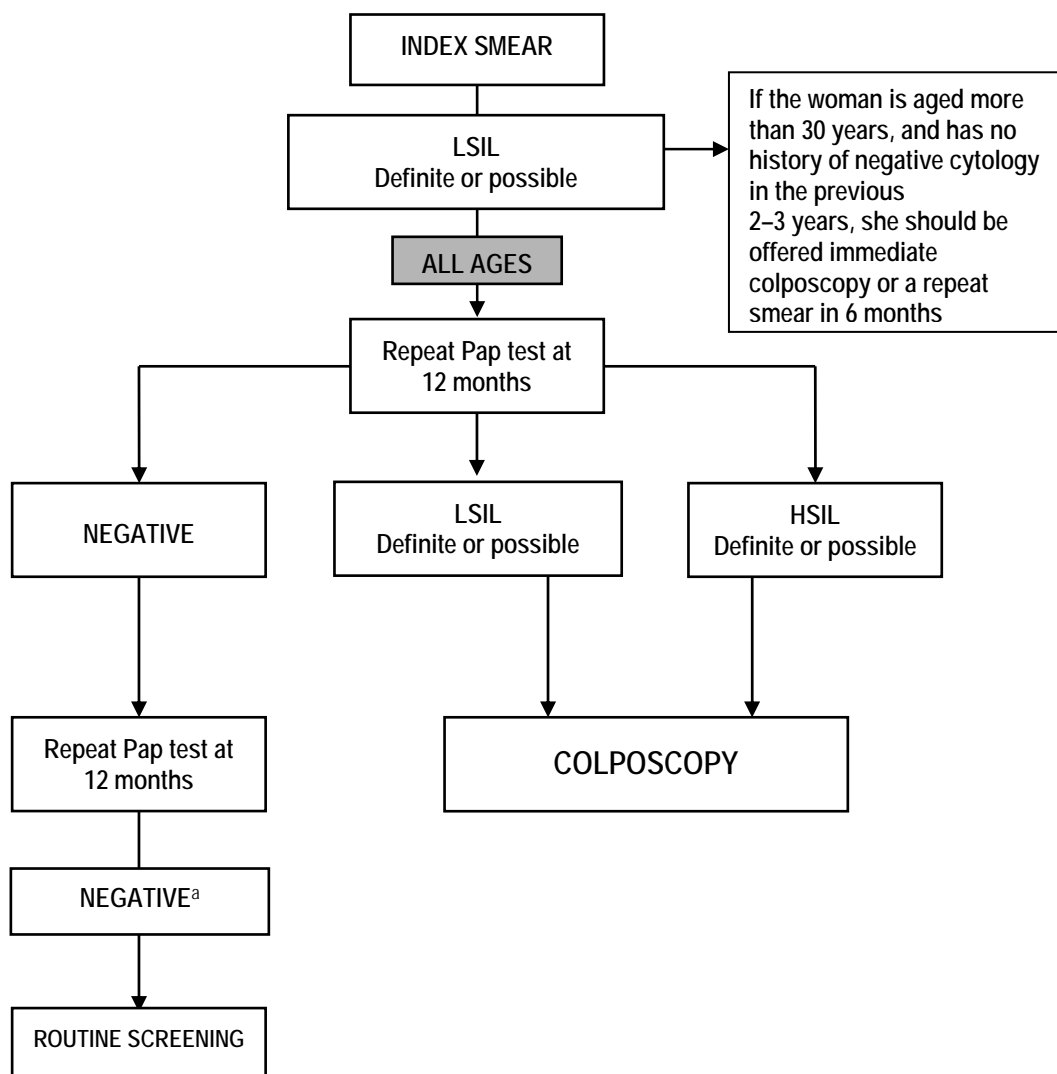
risk of harbouring significant cervical disease. In this age group, colposcopy is therefore recommended. In younger women, however, significant cervical pathology is still unlikely and, based on the evidence, a further delay in colposcopic intervention could be recommended (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001).

In initial drafts of these guidelines released for public consultation, the Guidelines Review Group recommended this management but it became clear during the public and professional consultation that that this approach would not be politically or practically acceptable to some sections of the medical community. We therefore recommend that all women (irrespective of age) whose repeat smear at 12 months shows persistent low-grade change should be referred for colposcopic evaluation as detailed in the guidelines below.

The Guidelines Review Group recommends, in addition to the monitoring outlined in Appendix 12, that this would be a productive area for future research, particularly into the costs and benefits of immediate versus delayed intervention for low-grade abnormalities.

The recommended management is shown diagrammatically in Figure 6.1.

Guidelines —Twelve-month repeat Pap test after index test results of LSIL	
If the 12-month repeat Pap test is reported as showing high-grade changes (definite or possible), the woman should be referred for colposcopic assessment.	Level IV (Schoolland et al 1998, Sparkes et al 2000, Performance Standards 2003)
Any woman whose repeat Pap test at 12 months is again reported as showing changes suggestive of LSIL (whether possible or definite), should be referred for colposcopic assessment.	Level III-2: three cohort studies of clearance interval (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001)
If the 12-month repeat Pap test is reported as normal, the woman should have a further repeat Pap test in 12 months (ie 24 months after the index smear).	Level III-2: three cohort studies of clearance interval (Ho et al 1998, Moscicki et al 1998, Woodman et al 2001)



LSIL = low-grade squamous intraepithelial lesion; HSIL = high-grade squamous intraepithelial lesion

^a See Section 6.7 for discussion and a guideline on fluctuating abnormalities

Figure 6.1 Management of a cytological prediction of possible or definite LSIL

6.7 Fluctuating abnormalities

A fluctuating status between low-grade change and negative cytology is not uncommon. When, following a normal repeat smear, either the 24-month smear or any subsequent smear again shows possible or definite LSIL, the significance of such alternating or fluctuating low-grade changes is unclear.

The Guidelines Review Group considered two possible explanations for such a clinical scenario and also considered the lack of reliable data or evidence to support one explanation over the other, or of one recommendation of management over another.

The first explanation is that there is a transition from active HPV infection to resolution of the infection, followed by reinfection. It is assumed that if this explanation is correct, the woman would be at very low risk and could safely be screened at conventional intervals.

The second explanation is that there could be some definite, underlying and persistent lesion present that is either not being consistently sampled or is not being detected on cytology. This explanation would warrant a more aggressive risk assessment, with a recommendation for colposcopy.

It is possible that other modalities, such as HPV testing, could be useful in this setting, but there is currently no evidence to support such an approach or suggest that it would be reliable, useful or cost-effective. The Guidelines Review Group felt that this would be a useful area for further research.

Pending the results of such research, it is recommended that referral for colposcopy be considered for a woman with two LSIL reports (at least 12 months apart).

Guideline — Fluctuating repeat Pap test results	
Referral for colposcopy should be considered for a woman if she has two LSIL/possible LSIL reports (at least 12 months apart) within a 3-year timeframe, regardless of intervening normal cytology reports.	Consensus

6.8 Early referral for colposcopy in exceptional circumstances

In exceptional circumstances, there may be a case for early referral for colposcopy. It is acknowledged that up to one-fifth of women with low-grade cytology will have an occult HSIL on biopsy, and that a small number of women with low-grade cytology will be diagnosed with microinvasive or invasive cancer within two years of the index smear. However, asymptomatic women, who are the focus of these guidelines, are almost certainly at much lower risk.

Appropriate educational materials about these guidelines and the evidence underpinning them and their safety will be developed. It is assumed that all women will be given a careful explanation of the significance of their low-grade cytology result and of their very low risk of harbouring or developing a cancer. It is expected that most asymptomatic women will be reassured by such an explanation and will follow the recommended guidelines.

If a general practitioner considers a woman who has been regularly screened to be unduly anxious about her LSIL result, or if she specifically requests specialist reassurance, referral for colposcopic assessment may help alleviate her anxiety, even though colposcopic assessment is not a complete safeguard against the eventual diagnosis of occult HSIL or cervical cancer (see discussion of ALTS below). In the event that LSIL is confirmed, it is recommended that she be followed by cytology alone according to the above guidelines.

If a woman is symptomatic or if her general practitioner is concerned about the clinical appearance of the cervix, her circumstances fall outside these recommendations and she must be investigated appropriately with colposcopic assessment (see Appendix 9) (RANZCOG 2002).

6.9 What evidence is available about the safety of cytological surveillance for women with low-grade cytology?

Randomised controlled trials

Three randomised controlled trials comparing immediate colposcopy with cytological surveillance have been published (Flannelly et al 1994, Shafi et al 1997, ALTS 2003ab). Because of terminology differences, none of these studies fully encompasses the LSIL/possible LSIL spectrum in Australia.

None of the studies showed a significant difference when HSIL was the outcome measure, but the studies were too small (Flannelly 793 women, Shafi 353 women, ALTS 3488 women with ASCUS and 1572 women with LSIL) to detect a difference when cancer was the outcome. In Flannelly's study, women who underwent immediate colposcopy had the highest rate of diagnosis of HSIL; women who underwent cytological surveillance (for up to 24 months) had lower rates of HSIL.

The ALTS trial was a multicentre, randomised trial sponsored and funded by the National Cancer Institute in the United States at an estimated cost of US\$30 million. The trial compared the sensitivity and specificity of three management strategies to detect CIN 3 in women with a community-based cytology report of ASCUS and LSIL:

- immediate colposcopy (reference standard)
- triage to colposcopy based on HPV results from Digene Hybrid Capture II (HC-II) test and liquid-based cytology results
- triage based on cytology results alone.

Randomisation of the ASCUS patients yielded 1163 in the immediate colposcopy arm, 1161 in the HPV triage arm, and 1164 in the conservative management arm (cytology alone); randomisation of the LSIL patients yielded 673 in the immediate colposcopy arm, 224 in the HPV triage arm, and 675 in the conservative management arm (cytology alone). Fewer women with LSIL were randomised to the HPV arm, as this arm closed early.

Tables 6.2 and 6.3 demonstrate the rates of detection of CIN 3 after a community-based cytology report of ASCUS or LSIL, respectively, in the three different arms of the ALTS trial. In each arm, a substantial proportion of CIN 3 diagnoses were not made before the mandated excisional procedure at the end of the study period, highlighting the potential diagnostic difficulties inherent in any approach.

Table 6.2 Detection of CIN 3 after ASCUS in ALTS

	Immediate colposcopy (IC) 1163 patients	HPV triage 1161 patients	Cytologic follow-up (CF) 1164 patients	Total CIN 3 3488 patients
Enrolment	58 (59.8%)	76 (75.2%)	44 (40.7%)	178 (58.2%)
Follow-up	14 (14.4%)	6 (5.9%)	22 (20.4%)	42 (13.7%)
Exit	25 (25.8%)	19 (18.8%)	42 (38.9%)	86 (28.1%)
Total	97 (100%)	101 (100%)	108 (100%)	306 (100%)

HPV = human papillomavirus

Note: Includes two invasive cancers (one each in IC arm and CF arm)

Source: ALTS Study Group (2003a)

Table 6.3 Detection of CIN 3 after LSIL in ALTS

	Immediate colposcopy (IC) 673 patients	HPV triage ^a 224 patients	Cytologic follow-up (CF) 675 patients	Total CIN 3 1572 patients
Enrolment	64 (62.7%)	28 (68.3%)	34 (36.6%)	126 (53.4%)
Follow-up	20 (19.6%)	4 (9.6%)	25 (26.9%)	49 (20.8%)
Exit	18 (17.6%)	9 (22.0%)	34 (36.6%)	61 (25.8%)
Total	102 (100%)	41 (100%)	93 (100%)	236 (100%)

HPV = human papillomavirus

^a Fewer women randomised to this arm because the HPV triage arm closed early
 Note: Includes five invasive cancers (two each in IC and CF arms and one in HPV arm)
 Source: ALTS Study Group (2003b)

Given the lead-time bias from identifying tiny CIN 3 lesions when women with low-grade cytology are intensively investigated (Sherman et al 2003b), the fact that CIN 2 can be caused by non-oncogenic viruses, and the regression of some HSIL lesions over time, use of HSIL as an outcome measure in randomised controlled trials may be problematic.

A randomised trial comparing immediate colposcopy and cytological surveillance with treatment of HSIL, but using an outcome of cancer to determine the necessary sample size, would require an extremely large number of participants. Table 6.4 shows the required sample size in each arm of a randomised controlled trial to detect a difference when cancer is the outcome. Two sets of figures are provided, one using an underlying cancer rate of 20 per 100,000 women and the other of 40 per 100,000 women. The rate of cancer diagnosis among asymptomatic women with LSIL/possible LSIL cytology is unknown, as the Australian Pap test registers do not currently record symptom status.

These sample sizes are so large that to detect even a 50% increase in an underlying cancer rate of 40 per 100,000 women would require a study in Australia to run for longer than five years. Furthermore, if cluster randomisation or interim analyses were part of the study protocol, an even larger sample size would be required.

Table 6.4 Sample size estimations ($P < 0.05$, 2-sided, power 90%)

Relative risk	No. of women per study arm if underlying cancer rate is 20 per 100,000 women	No. of women per study arm if underlying cancer rate is 40 per 100,000 women
1.1	11,130,450	5,564,066
1.2	2,938,897	1,439,130
1.3	1,375,635	687,662
1.4	812,864	406,336
1.5	545,237	272,552

Note: Using formula from Armitage and Berry (1994), with continuity correction proposed by Fleiss (1981)

Historical outcome studies

In theory, the impact of cytological surveillance can be determined by applying cancer rates documented after low-grade cytology from time periods when these abnormalities were not subject to investigations (such as biopsies) that can change the natural history. However, to be relevant to the context of these Australian guidelines, we consider that such studies need to satisfy all of the following criteria:

- the spectrum of cytological abnormality must be the same
- the underlying risk of cancer must be the same
- the effect of age on risk of malignancy must be able to be taken into account
- the quality of cytology sampling and reporting must be comparable
- undercalling must be able to be separated out from true progression
- symptomatic women must be excluded.

All published historical studies (eg Pettersson et al 1986, Melnikow et al 1998, Holowaty et al 1999) have difficulty in meeting the above criteria. Because of these problems, estimates derived from these studies are not relevant to these Australian guidelines.

The accuracy of the cytology report that assigns a woman to the ‘starting point’ in natural history studies is particularly important in calculating short-term progression rates. Because of this, generalisations about the risk of cervical cancer over short periods of time (compared to the medium and long term) are necessarily imprecise.

Evidence from other countries

Each country that undertakes cervical screening sets its own policy about the management of screen-detected abnormalities. Detailed evidence underpinning the policy is frequently not provided. It is likely that a range of influences within each country influences the policy, including the age range for screening, the recommended interval between screens for women with normal results, the availability of reminder systems, the resource constraints under which the screening program operates, and the medicolegal climate in the country.

Table 6.5 summarises the policy for some countries where cervical screening is well established. Again, exact mapping to the Australian LSIL/possible LSIL range is not possible for any of these countries because of differences in the terminology used to report cervical cytology.

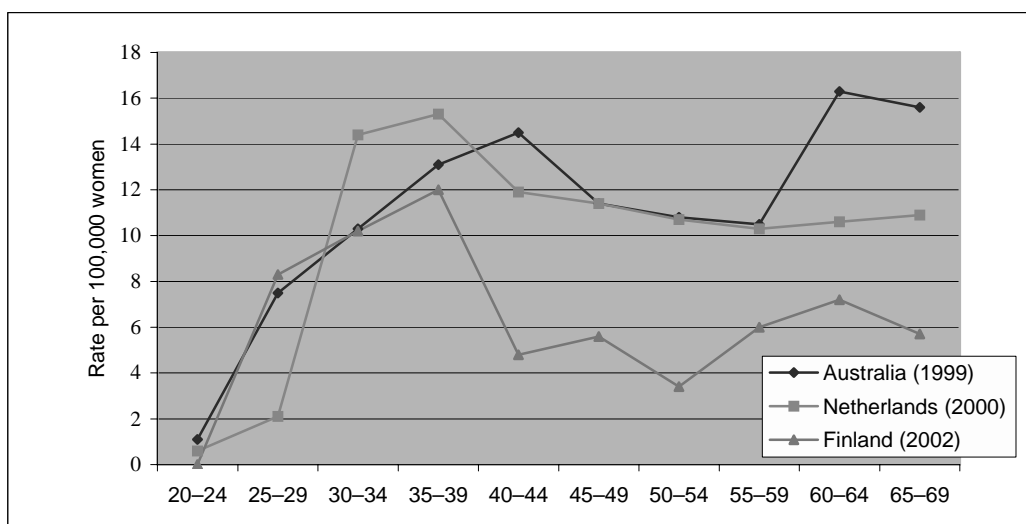
Table 6.5 Recommended management for women with abnormal cytology, by country

Country	Screening interval (years)	Recommended management of minor cytological abnormalities	Reference
Canada	3	ASCUS/LSIL: repeat cytology in 6 months	Health Canada (1998)
Finland	5	Pap Group 1 & 2: not referred for further examination unless repeated cytology or other results are suggestive of cancer	Anttila et al (2004); Cancer Registry Finland (2004)
France	3	ASCUS: repeat cytology / colposcopy / HPV testing LSIL: repeat cytology at 4–6 months / colposcopy	Anttila et al (2004); ANAES (2002)
Netherlands	5	Pap 2 & 3a1 & 3a2: repeat cytology in 6 months	Anttila et al (2004); Bos et al (2002)
New Zealand	3	ASCUS/LSIL: repeat cytology in 6 months	New Zealand National Cervical Screening Programme (1998)
Sweden	3 and 5	No national policy	Anttila et al (2004); Dillner (2000)
UK	3 and 5	Borderline change: colposcopy after 3 tests Mild dyskaryosis: ideally colposcopy but repeat cytology acceptable	NHSCSP (2004)
US	2–3 ^a	ASC-US: repeat cytology / colposcopy / HPV testing LSIL: colposcopy	Saslow et al (2002); Wright et al (2002)

^a Over 30 years of age and after three negative smears

Table 6.5 shows the diversity of policies in different countries. The interval for repeat cytology testing, if specified, is typically six months. However, all countries shown in the table recommend screening on a 3–5-yearly basis versus the 2-yearly policy in Australia. Thus a 12-month period of cytological surveillance in Australia will allow detection of occult HSIL either at the same time as or earlier than would be the case in most countries overseas.

Screening policy in Finland and the Netherlands is of particular interest because these countries have incidence and mortality rates that are the same or better than Australia, yet both screen much less frequently (5-yearly tests between the ages of 30 and 60) and neither aggressively investigates minor abnormalities on Pap smears (Cancer Registry Finland 2004; see Figure 6.2).



Sources: Australia, AIHW (2003); Netherlands, Bos et al (2002); Finland, Cancer Registry Finland (2004)

Figure 6.2 Age-specific incidence rate for cervical cancer for Australia, the Netherlands and Finland

It is interesting to compare Finland (Cancer Registry Finland 2004) and Victoria (CCV 2004) because both publish incidence rates for histologically confirmed CIN 3; no other cancer register in Australia publishes CIN 3 rates. While the incidence and mortality from cervical cancer are very similar, Victoria has a very much higher rate of CIN 3 recorded by the cancer registry (see Table 6.6). These findings suggest Australia could treat a much lower number of cases of CIN 3 without adversely impacting on the incidence and mortality.

Table 6.6 Vital statistics for cervical neoplasia for Finland and Victoria

	Finland (2002)	Victoria (2002)
Mortality	1.2	1.0
Incidence of cervical cancer	3.8	4.7
Incidence of histologic CIN 3	6.4	82.8
Ratio CIN 3:cancer	<2:1	18:1

Note: All rates are per 100,000 and are age standardised to the World Standard Population.

Sources: Cancer Registry Finland 2004, CCV 2004

The Netherlands substantially revised its screening program in 1996 and, since that time, has made a conscious effort to issue fewer abnormal cytology reports (Bos et al 2002). Even women whose cytology is reported as CIN 2 are not immediately referred for colposcopy. Rather, these women are requested to have repeat cytology in six months and are only referred for colposcopy if the abnormality persists or progresses.

6.10 Estimate of net effect of these guidelines on incidence of cancer

Modelling of the likely net effect of these guidelines on the number of cancers diagnosed after low-grade cytology has been undertaken and is presented in Appendix 10.

It is concluded that the likely net effect is no change in the number of cancers. Any negative outcome due to the period of cytological surveillance appears to be balanced by earlier diagnosis from earlier intervention, particularly among women with possible LSIL cytology and women with fluctuating abnormalities. This estimate of no net change in the number of cancers is necessarily predicated on a number of assumptions, including the quality of cytology and the participation of women in the National Cervical Screening Program remaining at least at current levels.

6.11 Balancing the risks of investigation and treatment with the risk of cervical cancer

Invasive cervical cancer is a rare disease. The annual incidence was below 15 per 100,000 in Australia even before the National Cervical Screening Program began (see Figure 2.2), but current screening is detecting some kind of abnormality in about 5000 women of every 100,000 screened (AIHW 2003).

The benefits for women of participating in a cervical screening program need to be balanced against the potential harms. Potentially negative effects for women may arise anywhere along the screening pathway from the point of invitation onwards (Nathoo 1988). These negative effects may be seen as relatively insignificant for the very small number of women who are prevented from developing invasive cervical cancer, but over-detection and overtreatment may become important problems with potentially significant adverse outcomes when large numbers of women are involved. Optimal detection of significant cervical pathology must be balanced against the risks associated with unnecessary and potentially harmful interventions and, because of the large numbers of women involved, this balance is crucial in the assessment of women with low-grade changes.

The receipt of an abnormal Pap smear result and the recommendation of a colposcopic examination are associated with a significant degree of anxiety, stress and fear (Marteau et al 1990, Wilkinson et al 1990, Rogstad 2002). The level of anxiety in some women undergoing colposcopy is high, and similar to the anxiety of women before surgery (Rogstad 2002). A number of studies have investigated interventions designed to reduce anxiety and have found that the interventions do little to reduce anxiety, although personal knowledge of the procedure is increased (Tomaino-Brunner et al 1998, Howells et al 1999, Freeman-Wang et al 2001, Byrom et al 2002).

In addition, some studies have suggested adverse psychosexual sequelae both after referral to colposcopy and after treatment (Boneuski et al 1998, Howells et al 1999), but others have shown little or no effect on sexual function (Campion et al 1988).

The extent of physical side effects from treatment of cervical pathology was documented in the Royal Australian College of Obstetrics and Gynaecologists National Quality Assurance in Colposcopy Project (RACOG 1997). In this study, of 5710 women who received treatment, 342 (6%) experienced acute complications, including primary or secondary haemorrhage, infection and other problems. Seventy-seven or 1.3% of them required hospital readmission. Of 3853 patients with documented follow-up, 243 (6.3%) had residual disease, with 131 of them (3.4%) listed for further treatment.

In addition to the immediate complications of fertility-sparing treatment for cervical pathology, there is growing concern that preterm delivery rates may be increased in subsequent pregnancies. Early studies investigating pregnancy outcome following

different local ablative and excisional treatments were small, lacked statistical power and did not control for potential confounders such as smoking (Crane 2003). The majority of these early studies did not show adverse outcomes.

In contrast, two large registry-based studies investigating outcomes after a variety of treatment modalities including conisation suggested some evidence of an increased risk of preterm labour (Kristensen et al 1993, El-Bastawissi et al 1999). Furthermore, one recent large retrospective cohort study has suggested that treatment by either laser conisation or loop electro-excisional procedure (LEEP) is associated with premature rupture of membranes resulting in preterm delivery (Sadler et al 2004). In support of this, a systematic review also concluded that women who had undergone LEEP were more likely to have a preterm delivery (Crane 2003).

Finally, concern has been raised that treatment may adversely affect fertility (Hammond and Edmonds 1990, Fox and Cahill 1991, Kennedy et al 1993) but this concern has not been confirmed.

The Guidelines Review Group recognises the limitations of the available data on the impact of investigation, treatment or delay in diagnosis of cytological abnormalities, and recommends that this would be a worthwhile area for further research.

6.12 Safety monitoring

A protocol for intensively monitoring the safety of the recommendations has been developed (see Appendix 12). The protocol specifies:

- when the safety monitoring should commence
- how the relevant information can be collected
- who has responsibility for making sure the monitoring is occurring
- the reporting line for the results of the monitoring.

This means that, if an increase in cervical cancer occurs as a result of the new approach to managing low-grade abnormalities, an early alert mechanism will be in place. The monitoring approach is similar to that used for adverse drug reactions when a new pharmaceutical preparation is released on to the market.

6.13 Why is repeat cytology at 12 months safe for Australian women with LSIL cytology?

The safety of the proposed management of women with LSIL cytology derives from the following factors:

- The two-year screening policy of Australia since 1990 means most women with LSIL/possible LSIL cytology but occult HSIL will be in the early period of this phase of cervical neoplasia. The requirement that women aged 30 years or over have negative cytology in the preceding two to three years reflects the age relationship between HSIL and cancer, and the typical sojourn time of any occult HSIL that is destined to become malignant.

- The quality of cervical cytology in Australia is high and is routinely measured. Since 1999, laboratories must present annual data relating to quantitative national performance measures as part of their triennial accreditation. It is vital that there be a continuation of high-quality training and education of cytologists in Australia, and of laboratory accreditation processes.
- Symptomatic and immunosuppressed women are explicitly excluded from the recommendation for cytological surveillance. General practitioners already understand well not to rely on a cytology report in symptomatic women, this having been a major educational thrust during the past decade.
- Pap test registers, which operate in all states and territories, can send recall or reminder letters to women who fail to have a repeat cytology test at 12 months.
- A safety monitoring program has been developed (see Appendix 12) and this will allow early scrutiny of the number of cancers occurring among women with LSIL/possible LSIL cytology. The safety monitoring will be overseen by a multidisciplinary group (including consumers) and will be transparent. Early policy review can be instituted if needed.

6.14 Colposcopic assessment and management of a woman with a cytological prediction of LSIL

Colposcopic assessment should comply with the guidelines published by the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), and the Australian Society of Colposcopy and Cervical Pathology (RANZCOG 2001). The aim of any colposcopy following an abnormal Pap smear is to assess the nature, severity and extent of the abnormality. If there is colposcopic evidence of a high-grade lesion, targeted biopsy should be performed for histological confirmation before definitive therapy is undertaken (see Chapter 7).

Histologically confirmed low-grade squamous abnormalities can be safely managed by repeat cytology at 12 and 24 months. If both smears are negative, it is recommended that the woman return to screenings at the intervals recommended for the average woman. If either repeat smear shows possible or definite LSIL, the woman should be advised to continue having annual smears until at least two are negative, at which time she can return to routine screening (see Section 6.6). Treatment of histologically confirmed low-grade squamous lesions is not recommended, as such lesions are considered to be an expression of a productive HPV infection (see Chapter 3).

Colposcopic recognition of early asymptomatic cancer is critical, as a failure to recognise it may lead to inappropriate treatment and subsequent recurrence.

Guidelines — Colposcopic assessment of women with Pap test reports of LSIL	
If, at colposcopy, a high-grade lesion is seen or suspected, targeted biopsy should be performed for histological confirmation before definitive therapy.	Consensus (RANZCOG 2001)
If the colposcopic assessment is normal, the woman should be referred back for annual cytological surveillance until two normal smears are obtained, and then resume routine screening according to the recommendation for the average population.	Consensus (RANZCOG 2001)
If the colposcopic assessment is satisfactory and a low-grade lesion is suspected, target biopsy can be performed to confirm this diagnosis. Treatment of histologically confirmed low-grade squamous lesions is not recommended, as such lesions are considered to be an expression of a productive HPV infection.	Consensus (RANZCOG 2001)
Histologically confirmed low-grade squamous abnormalities can be safely managed by repeat cytology at 12 and 24 months. If both smears are negative, it is recommended that the woman return to screenings at the intervals recommended for the average woman. If either repeat smear shows possible or definite LSIL, the woman should be advised to continue having annual smears until at least two are negative, at which time she can return to routine screening.	Consensus (RANZCOG 2001)
If the colposcopic assessment is unsatisfactory, consideration should be given to repeating the Pap test in 6–12 months. In asymptomatic women and in the absence of any cytologic, colposcopic or histologic suggestion of high-grade disease, further diagnostic procedures, such as cone biopsy or loop excision, are not indicated.	Consensus (RANZCOG 2001)

These guidelines support the approach taken in the RANZCOG guidelines (RANZCOG 2001), which is to recommend that a ‘see-and-treat’ approach should not be used. In the presence of a low-grade Pap test prediction, ‘see-and-treat’ should only be carried out when there is a colposcopic suggestion of a significant high-grade lesion and major concern about patient compliance, or logistical problems, such as when the patient lives a long way from the treatment centre.

7 Management of high-grade squamous abnormalities

7.1 Introduction

The Australian Modified Bethesda System (AMBS 2004) for reporting high-grade squamous abnormalities recognises three categories, based on the confidence of the cytological prediction:

- possible high-grade squamous lesion
- high-grade squamous intraepithelial lesion (HSIL)
- squamous cell carcinoma (SCC).

This is a major change from the previous NHMRC-endorsed Australian terminology (NHMRC 1994), which combined squamous and glandular abnormalities under the following categories:

- inconclusive, possible high-grade squamous or glandular abnormalities
- high-grade epithelial abnormalities, which included CIN 2 (cervical intraepithelial neoplasia), CIN 3, SCC, adenocarcinoma in situ (AIS) and adenocarcinoma.

The new category ‘possible high-grade squamous lesion’ also corresponds to ‘atypical squamous cells, possible high-grade lesion (ASC-H)’ in The Bethesda System 2001 (TBS 2001; see Chapter 4).

7.2 Evaluation of women with high-grade squamous abnormalities on cytology report

Possible high-grade squamous lesion

The ‘inconclusive, possible high-grade squamous lesion’ category of cytological abnormality was unique to the previous NHMRC-approved Australian terminology until revision of TBS in 2001, when it was included as ASC-H. Several Australian outcome studies suggest that women with possible high-grade squamous lesion cytology reports have a 45–65% chance of harbouring HSIL and 1.3–3% chance of SCC (Schoolland et al 1998, Sparkes et al 2000, VCCR 2002).

Women with possible high-grade squamous cytology reports should therefore be referred to a gynaecologist for colposcopic assessment and targeted biopsy where indicated.

Guideline — Referral of women with Pap test reports of possible high-grade squamous lesions	
A woman with a Pap test report of possible high-grade squamous lesion should be referred to a gynaecologist for colposcopic assessment and targeted biopsy where indicated.	Level IV (Schoolland et al 1998, Sparkes et al 2000, VCCR 2002)

High-grade squamous intraepithelial lesion

Case-series data from Australian laboratories suggest that women with HSIL cytology reports have a 62–89% chance of harbouring high-grade cervical intraepithelial disease and a 0–3% chance of having an invasive cervical cancer, depending on the severity of the cytology (Sparkes et al 2000, VCCR 2002).

Although there are no data on which to directly base referral timeframes, it is ideal if asymptomatic women with HSIL cytology reports are assessed within two months. Women with abnormal bleeding and a high-grade cytology report should be assessed as a matter of urgency, ideally within two weeks.

Guideline — Referral of women with Pap test reports of high-grade squamous intraepithelial lesions (HSIL)	
A woman with a Pap test report of HSIL should be referred to a gynaecologist for colposcopic assessment and targeted biopsy where indicated.	Level IV (VCCR 2002, Sparkes et al 2000)

High-grade squamous intraepithelial lesion with additional features suggestive of an invasive component

There are occasions when cytologists observe subtle cytological features that suggest cervical stromal invasion. Women with such a report are at significant risk of being diagnosed with early invasive or invasive cervical cancer. Therefore, early colposcopic assessment by a gynaecologist with expertise in colposcopic evaluation of suspected gynaecological malignancies or by a gynaecological oncologist is advised.

Guideline — Referral of women with Pap test reports of HSIL with additional features suggestive of an invasive component	
A woman with a Pap test report of HSIL, with additional features suggestive of an invasive component, should be referred to a gynaecologist with expertise in colposcopic evaluation of suspected gynaecological malignancies or to a gynaecological oncologist, ideally within two weeks.	Consensus

Squamous cell carcinoma (SCC) of the cervix

The management of invasive carcinoma of the cervix is outside the scope of these guidelines, but a woman with such a report should be referred to a gynaecological oncologist or to a gynaecological oncology unit for urgent evaluation.

Guideline — Referral of women with Pap test reports of SCC	
A woman with a Pap test report of SCC should be referred to a gynaecological oncologist or to a gynaecological oncology unit for urgent evaluation, ideally within two weeks.	Consensus

7.3 Histological confirmation

Best practice in Australia has considered histological confirmation of high-grade disease to be necessary before proceeding to treatment, except in exceptional circumstances.

Treatment undertaken at the time of initial colposcopic assessment is known as ‘see-and-treat’. See-and-treat should be considered only when concerns exist about the ability of the woman to return for treatment or about the likelihood of default, or when there are significant financial and/or resource allocation considerations.

If a see-and-treat approach is used, it should be undertaken only when both colposcopic assessment and referral cytology confirm a high-grade lesion, when the lesion can be fully visualised, and when the woman has been adequately counselled and prepared.

Guideline — Histological confirmation	
Histological confirmation of a high-grade lesion is required before definitive treatment is undertaken.	Consensus
‘See and treat’ is not recommended.	Consensus

7.4 Management and treatment of women with histological diagnoses of high-grade squamous intraepithelial lesions

A review of the literature on the natural history of cervical intraepithelial neoplasia since 1950 (Östör 1993b) showed that women with histological evidence of CIN 2 have a 5% chance of progression to cervical cancer, and women with CIN 3 have a 12% chance of progression. Women with a histological diagnosis of CIN 2 or CIN 3 should therefore be treated in order to reduce their risk of developing SCC.

Guideline — Treatment of a high-grade squamous intraepithelial abnormality	
Women with a histological diagnosis of CIN 2 or CIN 3 should be treated in order to reduce the risk of developing invasive cervical carcinoma.	Level III-2 (Östör 1993b)

There are two broad categories of fertility-sparing treatments available for the management of CIN: ablative and excisional. Fertility-sparing local ablative treatments were developed in the late 1970s. Topographic data suggest that, as well as tailoring treatment to the extent of the colposcopic lesion, glandular involvement should be taken into consideration. As many as 89% of women with a histological diagnosis of CIN 3 demonstrate glandular involvement to a mean depth of 1.24–1.6 mm (Anderson and Hartley 1979, Boonstra et al 1990); 99.7% of women have glandular involvement not exceeding 3.8 mm, although a maximum of 5.22 mm is observed (Anderson and Hartley 1979). Because of the documented depth of glandular involvement by CIN 3, and also the results of initial case series for women managed with ablative treatments, it was concluded that local ablative treatments should destroy or remove tissue to a depth of at least 7 mm (Burke 1982, Jordan et al 1985).

A systematic review of alternative surgical treatments for cervical intraepithelial neoplasia showed no clearly superior method of fertility-sparing treatment for CIN 2 and 3 (Martin-Hirsch et al 2000).

Guidelines — Fertility-sparing treatments	
Local ablative or excisional treatments should destroy or remove tissue to a depth of at least 7 mm.	Level IV (Burke 1982, Jordan et al 1985)
There is no clearly superior method of fertility-sparing treatment for CIN 2 and 3.	Level I (Martin-Hirsch et al 2000)

Treatment may be undertaken under local anaesthetic as an office procedure, or a general anaesthetic may be required. The wishes of individual women, the preference of the practitioner and the size and location of the lesion may all influence the choice of treatment and anaesthesia.

Ablative therapy

Ablative therapies include carbon dioxide (CO₂) laser, cold coagulation, radical diathermy and cryotherapy, and are indicated for the treatment of histologically confirmed HSIL provided that the following conditions are met:

- the cervix has been assessed by an experienced colposcopist
- a targeted biopsy has confirmed the diagnosis
- there is no evidence of an invasive cancer on cytology, colposcopic assessment or biopsy
- the entire cervical transformation zone (TZ) has been visualised
- there is no evidence of a glandular lesion on cytology or biopsy.

If these conditions do not apply, an excisional procedure is indicated.

Guideline — Ablative therapy	
<p>Ablative therapy may be considered, provided:</p> <ol style="list-style-type: none"> 1. The cervix has been assessed by an experienced colposcopist. 2. A targeted biopsy has confirmed the diagnosis. 3. There is no evidence of an invasive cancer on cytology, colposcopic assessment or biopsy. 4. The entire cervical transformation zone has been visualised. 5. There is no evidence of a glandular lesion on cytology or biopsy. 	Consensus

A randomised controlled trial (Chirenje et al 2001) and case series (Anderson and Husth 1992) have shown that the overall cure rate is lower when cryotherapy is used compared to other treatments. This finding has not been confirmed by Mitchell et al (1998) in a randomised controlled trial. Treatment failure with cryotherapy has been documented to be significantly associated with higher histological grade (that is, CIN 3 versus CIN 2) (Anderson and Husth 1992).

Guideline — Cryotherapy for treatment of CIN 3	
It is advisable that women with CIN 3 are not treated with cryotherapy.	Level IV (Anderson and Husth 1992)

Excisional techniques

Excisional biopsies can be obtained using scalpel ('cold knife' cone biopsy), laser, loop electro-excisional procedure (LEEP) or other diathermy techniques. The specimen should be submitted for detailed pathological examination (McKenzie 1994). Every effort should be made to avoid fragmentation and thermal artefact at the stromal and endocervical margins, in order to allow accurate pathological assessment of the status of these margins.

Loop electro-excisional procedure

LEEPs, of which large loop excision of the cervical transformation zone (LLETZ) is one, are now commonly used for the treatment of CIN. Every effort should be made to remove the entire lesion in one specimen, and for ectocervical lesions tissue should be removed to a depth of 7 mm or greater because of possible glandular involvement (Anderson and Hartley 1979, Boonstra et al 1990). Excess diathermy artefact should be avoided in order to allow comprehensive pathological examination, including of the status of margins.

Guideline — Loop electro-excisional procedure (LEEP)	
Excess diathermy artefact should be avoided when using LEEP in order to allow comprehensive pathological examination, including margin status.	Consensus

Cone biopsy

Cone biopsy is an excisional technique in which the aim is to remove a significant length of tissue along the cervical canal (from 1.5–3 cm) and has traditionally been performed using the ‘cold-knife’ technique. The specific indications for cone biopsy are:

- failure to visualise the upper limit of the cervical TZ in a woman with a high-grade squamous abnormality on her referral cervical smear (ie unsatisfactory colposcopy)
- suspicion of an early invasive cancer on cytology, biopsy or colposcopic assessment
- the suspected presence of an additional significant glandular abnormality (ie AIS) on cytology or biopsy (ie a mixed lesion).

Careful attention should be paid to tailoring treatment to the individual woman, taking into account the size, extent, situation and severity of the lesion.

Women over 50 who have a high-grade squamous abnormality frequently require cone biopsy. Cone biopsy must be undertaken if a high-grade lesion is suspected on cervical cytology but no lesion can be seen colposcopically and the TZ is located in the endocervical canal.

While following up a cohort of 3560 women, Flannelly et al (2001) noted that treatment outcomes for women over 50 years of age suggest high rates of margin involvement despite larger excisions being undertaken, implying the presence of more extensive disease in this age group. Other cohort studies have reported that women over 50 years of age are at significantly higher risk of further high-grade disease and invasive cervical cancer, compared to younger women treated for similar lesions (Pettersson and Malke 1989, Mitchell and Hocking 2002).

Guideline — Cone biopsy	
Cone biopsy may be necessary to treat women with high-grade squamous lesions and absolute indications that include: <ol style="list-style-type: none">1. failure to visualise the upper limit of the cervical transformation zone in a woman with a high-grade squamous abnormality on her referral cervical smear (ie unsatisfactory colposcopy)2. suspicion of an early invasive cancer on cytology, biopsy or colposcopic assessment3. the suspected presence of an additional significant glandular abnormality (ie adenocarcinoma in situ) on cytology or biopsy (ie a mixed lesion).	Consensus
Careful attention should be paid to tailoring treatment to the individual woman, taking into account the size, extent, situation and severity of the lesion.	Consensus

Although laser and LLETZ can also be used to obtain a cone biopsy, this application is debated in the literature. Cone biopsies carried out by LLETZ tend to be significantly shallower than those by other methods, with high rates of positive excision margins and a degree of diathermy artefact that is unavoidable (Giacalone et al 1999, Takac and Gorinsek 1999). The average depth of LLETZ cone biopsies among studies reported ranges from 9 mm to 12 mm, compared to 15–18 mm for cold-knife cone biopsies (Girardi et al 1994, Giacalone et al 1999). Studies investigating cone volume have shown that a significantly smaller cone is commonly removed by LLETZ and laser compared to cold knife (Mathevet et al 1994). Conversely, laser and LLETZ cones, compared to cold-knife cones, facilitate the evaluation of the treated cervix (Girardi et al 1994).

Hysterectomy

Hysterectomy is not usually indicated for the management of CIN. However, there are a number of situations where hysterectomy may be advised.

- Hysterectomy may be advised in the presence of coexistent benign gynaecological disease (fibroids, prolapse, endometriosis etc).
- Following previous treatment (such as cone biopsy), the treating gynaecologist may be suspicious that high-grade disease remains because of positive apical or stromal (deep lateral) margins or further high-grade cytology. Simple hysterectomy may be appropriate, provided invasion is not suspected or has been excluded.
- When early invasive disease has been diagnosed (microinvasive squamous cancer of the cervix, FIGO⁸ stage IA1), hysterectomy may be considered if childbearing is complete. In this case, pathology review in conjunction with a gynaecological oncologist is advised.

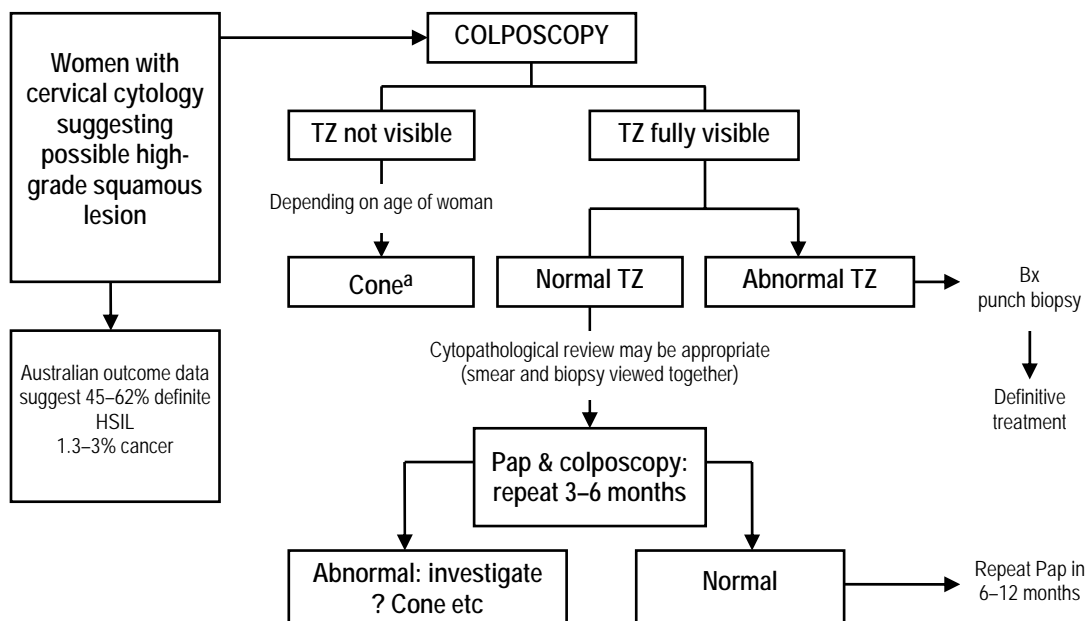
In women with high-grade cytology, hysterectomy should be undertaken only after colposcopic assessment and targeted biopsy have excluded invasive disease. When this is not possible because the cervical TZ is within the endocervical canal and therefore not assessable, invasion should be excluded by cone biopsy before proceeding to hysterectomy.

7.5 Further issues in the colposcopic assessment of women with possible high-grade squamous lesions

Women with a cytology report of possible high-grade squamous lesions have a 45–65% chance of harbouring high-grade cervical intraepithelial disease and a 1.3–3% chance of an invasive cervical cancer (Schoolland et al 1998, VCCR 2002).

If, at colposcopic assessment, the cervical TZ is either totally in the canal or is extending deeply into the canal, a cone biopsy should be considered. If the cervical TZ is fully visible, a diagnosis may be reached by colposcopically directed biopsy and treatment dictated. If the cervical TZ is fully visible and is found to be normal, then an option is to closely observe the patient (Figure 7.1).

⁸ FIGO = International Federation of Gynaecology and Obstetrics.



HSIL = high-grade squamous intraepithelial lesion; TZ = transformation zone; Bx = targeted biopsy
 a In women where fertility is an issue, repeat colposcopy

Figure 7.1 Management of women with cervical cytology predicting possible high-grade squamous lesions

7.6 Follow-up of women treated for high-grade squamous intraepithelial lesions

Several studies have shown that women who have previously been treated for CIN 2 and CIN 3 are at increased risk of further high-grade disease and cervical cancer (Pettersson and Malke 1989, Levi et al 1996, Soutter et al 1997, Nagai et al 2000, Vikki et al 2000, Mitchell and Hocking 2002). Australian data also confirm a cervical cancer rate odds ratio of 9.46 (95% CI, 1.46 to 12.22) for women with a history of CIN 3 compared to women who have no such history (Mitchell and Hocking 2002).

Recurrence may be the result of inadequately treated disease or the further development of CIN. Recurrence rates rise steeply in the initial 6–12 months following treatment but then remain constant (Flannelly et al 2001, Mitchell and Hocking 2002). There is no evidence that the risk of recurrence subsequently declines at any defined point in time (data are consistent for up to 10 years post-treatment) (Flannelly et al 2001, Mitchell and Hocking 2002). These data suggest that women should be under continued surveillance following treatment for HSIL.

Several groups of women have been shown repeatedly to be most at risk of further high-grade disease and cervical cancer. These include:

- women over 50 years of age at initial treatment (Flannelly et al 2001, Mitchell and Hocking 2002)

- women who demonstrate persistence of cervical infection with high-risk HPV types (Chua and Hjerpe 1997, Bollen et al 1999, Jain et al 2001, Lin et al 2001, Nobbenhuis et al 2001b, Paraskevaidis et al 2001)
- women who have been treated by excisional techniques and in whom excision margins of the specimen were reported as involved (Flannelly et al 2001).

It is likely that women who have combinations of the above risk factors are at the greatest risk, and closer observation of these women will allow identification of those at high risk of further disease.

Involved endocervical and stromal excision margins after LEEP are of concern, but their involvement does not in itself justify retreatment. It is noted that reported rates of endocervical involvement at LEEP may be as high as 40% depending on the surgical technique used (Flannelly et al 2001). Continued observation may be undertaken when the TZ is fully visible and cytological sampling and colposcopic assessment can be facilitated.

Data suggest that women over 50 years with involvement of excision margins are a small but high-risk group. These women have a greater than 50% chance of recurrent disease, and the combination of a high risk of further disease and the difficulties encountered with follow-up will often justify further treatment, such as hysterectomy, rather than observation (Flannelly et al 2001). In addition, follow-up in older postmenopausal women may be very difficult because the squamocolumnar junction is frequently high in the endocervical canal.

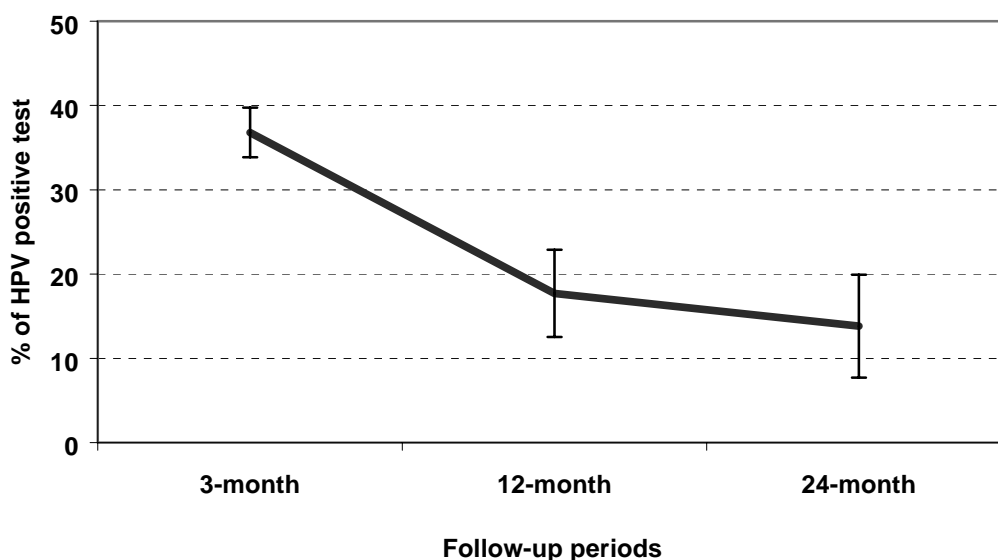
Role of colposcopy in the follow-up of women treated for a CIN 2 and 3

After treatment for a high-grade cervical lesion, women have been followed with both colposcopy and cytology. There has been debate about the value of colposcopy in this situation, especially in the older women where the TZ is no longer visible. However, cohort study reports confirm that its use can help in the diagnosis of a treatment failure and that a combination of cytology and colposcopy can identify a significant number of treatment failures sooner than cytology alone (Paraskevaidis et al 1991, Flannelly et al 1997). Higher numbers of false-positive cytology smears are observed within six months of the treatment (Shafi et al 1993).

HPV typing following treatment for CIN 2 or CIN 3

HPV typing has been shown to be as sensitive as cytology in identifying women at risk of further high-grade disease, and the specificity of HPV typing increases over time (Nobbenhuis et al 2001b). It is, however, the strong negative predictive value of HPV testing that has most clinical use. Many studies have confirmed a 98–100% negative predictive value for HPV testing (Chua and Hjerpe 1997, Bollen et al 1999, Jain et al 2001, Lin et al 2001, Nobbenhuis et al 2001b, Paraskevaidis et al 2001, Bar-Am et al 2003, Zielinski et al 2003, Chao et al 2004).

As shown in Figure 7.2, the frequency of positive HPV tests following treatment for high-grade lesions is high in the first twelve months after treatment but diminishes significantly after that. The reliable negative predictive value provides a useful clinical tool for predicting women at greatest risk of recurrence. It also emphasises the importance of not testing for HPV too soon after treatment.



Source: Nagai et al 2000, Kucera et al 2001, Nobbenhuis et al 2001b, Paraskevaidis et al 2001, Bar-Am et al 2003, Debarge et al 2003, Zielinski et al 2003, Chao et al 2004.

Figure 7.2 Frequency of positive HPV testing, by post-treatment follow-up period

In June 2004, the Australian Government Minister for Health and Ageing endorsed an MSAC recommendation ‘that on the strength of evidence pertaining to the use of high-risk HPV testing at 12 and 24 months following treatment of high-grade intraepithelial abnormalities of the cervix to monitor the effectiveness of treatment, public funding should be supported for this procedure’.

It is therefore recommended that a woman previously treated for HSIL undergo a colposcopy and cervical cytology at 4–6 months after treatment. Cervical cytology and HPV typing should then be carried out at 12 months after treatment and annually thereafter until the woman has tested negative by both tests on two consecutive occasions. At this point, the woman should continue to be screened according to the recommendation for the average population.

To monitor the safety of the recommended management of women with treated high-grade intraepithelial disease, and thus facilitate timely review of the policy as needed, a monitoring protocol has been established by the Australian Screening Advisory Committee (see Appendix 13). It is also recommended that a review of this policy should be undertaken after five years using Australian registry data.

Guidelines — Management of women previously treated for HSIL	
<p>A woman previously treated for HSIL requires a colposcopy and cervical cytology at 4–6 months after treatment. Cervical cytology and HPV typing should then be carried out at 12 months after treatment and annually thereafter until the woman has tested negative by both tests on two consecutive occasions. The woman should then be screened according to the recommendation for the average population.</p>	<p>Level IV (Chua and Hjerpe 1997, Bollen et al 1999, Jain et al 2001, Lin et al 2001, Nobbenhuis et al 2001b, Paraskevaidis et al 2001, Bar-Am et al 2003, Zielinski et al 2003, Chao et al 2004)</p>
<p>A woman already undergoing annual cytological review for follow-up of a previously treated HSIL, as advised by the previous NHMRC guidelines (1994), may be offered HPV testing as described above. Once she has tested negative by both cytology and HPV typing on two consecutive occasions, she should be screened according to the recommendation for the average population.</p>	<p>Level IV (Chua and Hjerpe 1997, Bollen et al 1999, Jain et al 2001, Lin et al 2001, Nobbenhuis et al 2001b, Paraskevaidis et al 2001, Bar-Am et al 2003, Zielinski et al 2003, Chao et al 2004)</p>

Follow-up of women who have undergone a hysterectomy

Women who have a hysterectomy for high-grade cervical abnormalities require continued screening because of their increased risk of vaginal neoplasia. The role of HPV testing in this situation requires further investigation (Daling et al 2002).

8 Management of cervical glandular abnormalities

8.1 Introduction

The Australian Modified Bethesda System (AMBS 2004) for reporting glandular abnormalities recognises four categories, based on the confidence of the cytological prediction:

- adenocarcinoma
- endocervical adenocarcinoma in situ (AIS)
- possible high-grade glandular lesion
- atypical endocervical or glandular cells of undetermined significance.

This is a major change from the previous NHMRC-endorsed Australian terminology (NHMRC 1994), which allowed for two subcategories of high-grade abnormalities:

- inconclusive, possible high-grade glandular abnormality
- high-grade epithelial abnormality (which included CIN 2, CIN 3, SCC, AIS and adenocarcinoma).

The category of ‘possible high-grade glandular lesion’ corresponds to the category of ‘atypical endocervical cells, possibly neoplastic’ in the revised Bethesda System (TBS 2001).

8.2 Frequency of cervical cytology reports of glandular abnormalities

Cervical cytology reports suggesting a glandular abnormality are rare, constituting well under 1% of all reports (see Appendix 8, Table A8.1). However, cervical screening is less effective at preventing cervical adenocarcinoma compared to squamous carcinoma (Mitchell et al 1995), and the incidence of cervical adenocarcinomas has remained stable (AIHW–AACR 2003a; see Figure 2.2). This probably results from a number of factors, including the anatomical situation of glandular lesions, sampling deficiencies at the time of smear taking and difficulties with cytological interpretation. Because of the success of cervical cancer screening in the prevention of squamous cancers, pure cervical adenocarcinomas now account for as many as 20% of all cervical cancers (AIHW–AACR 2003a).

8.3 Natural history of cervical adenocarcinoma

The natural history of invasive cervical adenocarcinoma and its pre-invasive equivalent, AIS, is less clearly defined than that of squamous disease. Infection with high-risk HPV types has been reported as associated with cervical adenocarcinomas (Iwasawa et al 1996, Skyldberg et al 1999, Pirog et al 2000) and AIS (Pirog et al 2002), and there is evidence that AIS lesions progress to adenocarcinoma (Boon et al 1981).

Table A8.5 in Appendix 8 outlines outcome data collected from Australian cervical cytology registers for women presenting with glandular abnormalities in 1999 and followed over a 24-month period (see Appendix 8). In women presenting with AIS on a Pap smear, 92% of high-grade abnormalities were diagnosed in the first six months following the index smear. For women with possible high-grade glandular lesions and atypical glandular cells of undetermined significance, the respective figures were 68% and 43%.

Table A8.7 in Appendix 8 outlines the registry histories of the women presenting with Pap tests suggesting atypical glandular cells of undetermined significance in 1999, who were subsequently diagnosed with cervical cancer.

Women with atypical glandular cells of undetermined significance on cervical cytology are far more likely to have a subsequent diagnosis of cervical cancer than those with low-grade squamous lesions (8 per 1000 and 0.53 per 1000, respectively) (see Table A8.5 and Section 6.2).

8.4 Initial evaluation and referral of women with glandular abnormalities on cervical cytology

Invasive adenocarcinoma

Cervical cytology reports suggesting a glandular malignancy fall into one of the following categories:

- endometrial adenocarcinoma
- endocervical adenocarcinoma
- adenocarcinoma of undetermined origin (when the cytopathologist is not able to specify the origin of the abnormal glandular cells)
- extrauterine adenocarcinoma (which is rare).

Cervical cytology reports suggestive of endometrial carcinoma are highly predictive for endometrial malignancy (Mitchell et al 1993). Women with these reports should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies.

Women reported to have a glandular malignancy of either endocervical, undetermined or extrauterine origin require referral to a gynaecological oncologist or a gynaecological oncology unit. Management of women with invasive carcinoma is beyond the scope of these guidelines.

Guideline — Referral of women with Pap test reports of adenocarcinoma	
A woman with a Pap test report of adenocarcinoma of endometrial origin should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist.	Level III-3 (Mitchell et al 1993)
A woman with a cytological prediction of adenocarcinoma of either endocervical, extrauterine or unspecified origin should be referred to a gynaecological oncologist or a gynaecological oncology unit.	Consensus

Endocervical adenocarcinoma in situ

Australian Pap test registry data suggest that 16.7% of women with endocervical AIS will be diagnosed with invasive cancer (90% invasive cervical carcinoma, 10% endometrial carcinoma). Over 60% of women with this report will be diagnosed with a high-grade intraepithelial lesion in the ensuing 24 months (Table A8.5); the majority of these abnormalities will be glandular. Consequently, it is recommended that women with a cytological prediction of endocervical AIS be referred for colposcopic evaluation by a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or by a gynaecological oncologist.

Guideline — Referral of women with Pap test reports of endocervical adenocarcinoma in situ (AIS)	
A woman with a Pap test report of endocervical AIS should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist.	Australian registry data

Possible high-grade glandular lesion

Australian registry data suggest that 5% of women with possible high-grade glandular lesions will be diagnosed with invasive cervical cancer and 20% with high-grade intraepithelial disease over the ensuing 24 months (Table A8.5). Consequently, it is recommended that women with possible high-grade glandular lesions be referred for colposcopic evaluation by a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or by a gynaecological oncologist.

Guideline — Referral of women with Pap test reports of possible high-grade glandular lesions	
A woman with a Pap test report of possible high-grade glandular lesions should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies or to a gynaecological oncologist.	Australian registry data

Atypical glandular or endocervical cells of undetermined significance

Both cytologists and pathologists report abnormalities in glandular cells that are insufficient to be labelled AIS. The biological behaviour and clinical significance of these minor glandular abnormalities remain undetermined (Goldstein et al 1998, Pirog et al 2002). The extremely infrequent occurrence of lesions with morphology less than AIS, coupled with an absence of cellular proliferation markers and HPV DNA in such lesions, suggests that they may not represent precursors of AIS or adenocarcinoma (Goldstein et al 1998, Lee et al 2000, Pirog et al 2002, Ioffe et al 2003).

Australian registry data suggest that women with atypical glandular/endocervical cells of undetermined significance on cervical cytology have a 0.8% risk of having an invasive cancer and a 9.4% risk of a high-grade intraepithelial abnormality, which is more commonly squamous than glandular (Table A8.5). In addition, there are widely varying rates of reporting of this category of cytological abnormality for women in different states and territories (see Table A8.1).

There was considerable debate within the Guidelines Review Group as to the best management of these women. It was concluded that, given the risk of invasive cancer, the small number of women with atypical endocervical cells in the screened population and the known sampling difficulties (which make cytological follow-up less reliable), it is reasonable to suggest colposcopy as an initial evaluation.

Guideline — Referral of women with Pap test reports of atypical glandular or endocervical cells of undetermined significance	
A woman with a Pap test report of atypical glandular or endocervical cells of undetermined significance should be referred to a gynaecologist with expertise in the colposcopic evaluation of suspected malignancies.	Australian registry data

8.5 Role of colposcopy, target biopsy, cone biopsy and endocervical curettage in the assessment of glandular lesions

Colposcopy is much less reliable in the assessment of glandular lesions than it is for squamous lesions. However, some colposcopic features of AIS have been identified, including subtle changes in glandular villi with villous fusion and aceto-white changes proximal to the squamocolumnar junction (SCJ) (Lickrish et al 1993). Such features cannot be relied upon (Östör et al 2000).

Despite these limitations, colposcopy is still important for the following reasons:

- to exclude clinically overt invasive carcinoma
- to identify the extent and situation of the cervical transformation zone (TZ)
- to determine the extent of any squamous disease, which is a frequent finding even though cytology may report purely glandular disease (coexistent high-grade cervical squamous abnormalities have been demonstrated in as many as 60% of women with histologic glandular abnormalities) (Östör et al 2000)
- to assess the anatomy of the cervix and the rest of the genital tract, making it easier to decide the mode and extent of treatment.

Guideline — Colposcopic assessment of glandular lesions	
Colposcopic assessment is mandatory in the presence of a cervical cytology suggesting a glandular lesion.	Consensus

Target biopsy

The only role of target biopsy is to establish the diagnosis in the presence of a frankly invasive carcinoma.

Cone biopsy

Cone biopsy is indicated for the further assessment and treatment of a woman with a cytology report predicting AIS. There are several methods of cone biopsy. These include cold-knife cone, laser cone, large loop excision of the cervical TZ (LLETZ) and Fisher cone. Cold-knife cone biopsy should be considered the ‘gold standard’. Data suggest that women treated by LLETZ tend to undergo shallower procedures with higher rates of endocervical margin involvement, and LLETZ is therefore best avoided for this purpose (Widrich et al 1996, Wolf et al 1996, Azodi et al 1999). There are very little data regarding the use of either laser or Fisher cone for the management of glandular abnormalities.

Cone biopsy should be tailored according to the colposcopic findings and the patient’s age and childbearing requirements.

Case-series data suggest that cone biopsies should be undertaken in such a way that the biopsy is submitted to the pathologist as a single specimen without excessive thermal or other damage to resection margins, permitting accurate assessment of their involvement in disease (Östör et al 2000). Attention should be paid to achieving uninvolved endocervical resection margins.

Guideline — Cone biopsy for the assessment of glandular lesions	
Cold-knife cone biopsy should be considered the ‘gold standard’ for the assessment of glandular lesions.	Consensus

Endocervical curettage

Endocervical curettage is unreliable as a diagnostic procedure when used for the initial assessment of women with AIS suggested on cytology. Endocervical curettage has a false-negative rate of over 50% in the presence of high-grade glandular pathology (Poynor et al 1995). Where there is a high likelihood of disease, it serves no useful purpose.

For women with a lower prevalence of disease (ie those with cytology suggesting possible high-grade glandular abnormalities), identification of a glandular lesion may be improved by the addition of biopsy and endocervical curettage. Therefore, these may be considered if conservative management is to be undertaken (Shin et al 2002).

8.6 Further clinical management of women with glandular abnormalities

Adenocarcinoma

Women found to have invasive adenocarcinoma on cone or punch biopsy should be referred to a gynaecological oncologist or a gynaecological oncology unit for subsequent management. Management of invasive adenocarcinoma is beyond the scope of these guidelines.

If it is logistically difficult for a woman from rural Australia to be transferred immediately to such a specialist or unit, assessment by a gynaecologist in her locality in liaison with a gynaecological oncologist may facilitate arrangements for her treatment (see Figure 8.1).

Guideline — Referral of women with adenocarcinoma on cone or punch biopsy	
Women found to have invasive adenocarcinoma on cone or punch biopsy should be referred to a gynaecological oncologist or a gynaecological oncology unit for subsequent management.	Consensus

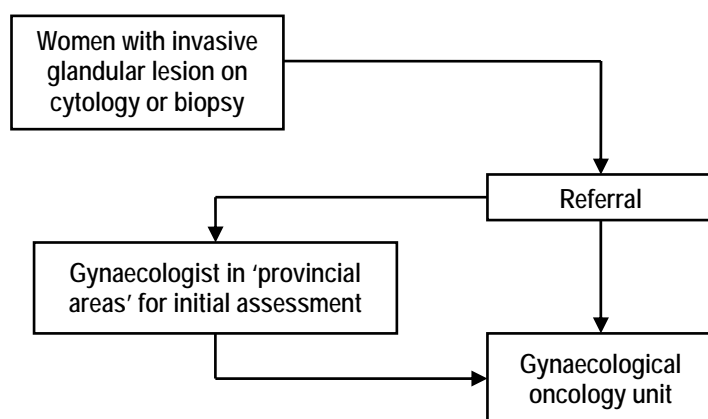


Figure 8.1 Management of women with invasive adenocarcinoma suggested on cervical cytology or biopsy

Endocervical adenocarcinoma in situ

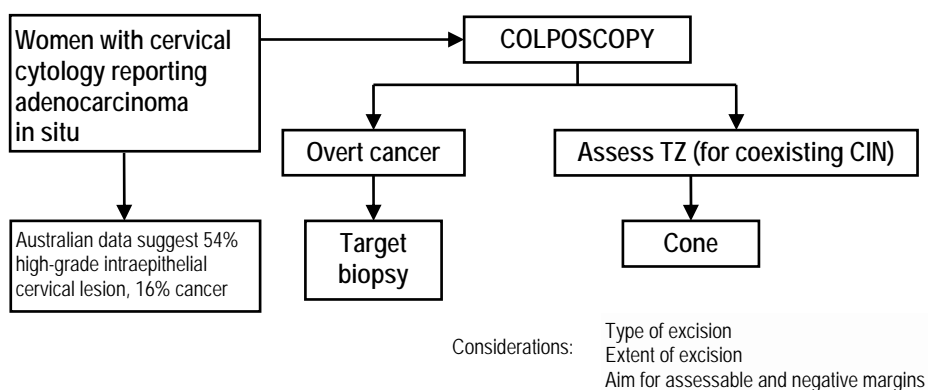
A high proportion (one in six, or 16.7%) of women with either AIS or possible high-grade glandular lesion on cytology will have an invasive carcinoma (Table A8.5). If this is not identified at colposcopy, a cone biopsy should be undertaken to exclude invasive carcinoma before further management for AIS (see Figure 8.2). Hysterectomy should not be undertaken without prior cone biopsy assessment.

Histomorphometric studies suggest that in around two-thirds of women AIS and early invasive adenocarcinoma will involve glands beneath the TZ, and that the lesions are usually contiguous with the SCJ (Bertrand et al 1987). Multifocality is reported in only

13% of cases (Bertrand et al 1987, Östör et al 2000). The deepest cervical glands are commonly involved and may be as far as 6 mm from the canal; therefore, removal of a cylindrical cone is advised (Bertrand et al 1987, Nicklin et al 1991).

Australian case-series data confirm that 85% of AIS will extend to less than 15 mm from the SCJ (Nicklin et al 1991). However, the SCJ may not always be visible and the proximal linear extent of AIS may be as far as 25 mm along the canal from the SCJ. The proximal linear extent of AIS is related to age. Women under 36 are unlikely to have disease extending more than 10 mm from the SCJ, allowing for more limited excision. Older women are likely to have more extensive lesions and require deeper excisions of at least 25–30 mm (Nicklin et al 1991).

Guideline — Management of women with a Pap test report of AIS	
<p>If invasive carcinoma is not identified at colposcopic assessment, a cone biopsy should be undertaken.</p> <p>Hysterectomy should not be undertaken without prior cone biopsy to exclude invasive carcinoma.</p>	Consensus



TZ = transformation zone; CIN = cervical intraepithelial neoplasia

Figure 8.2 Management of women with AIS on cervical cytology

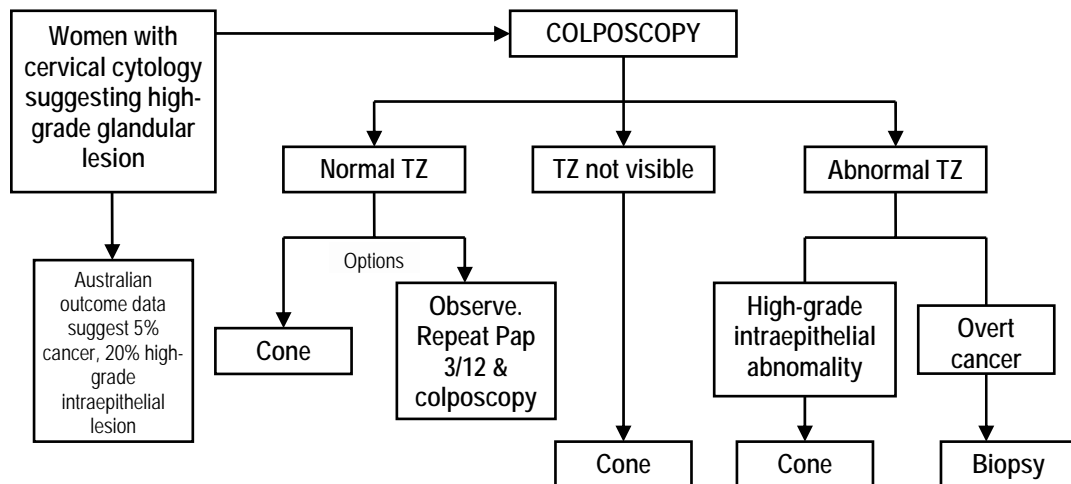
Possible high-grade glandular lesion

Colposcopic assessment must be undertaken to exclude overt invasive carcinoma. Subsequent management will depend on the colposcopic findings (Figure 8.3). If the cervical TZ is abnormal or not visualised, cone biopsy should be considered.

The need for treatment will then be determined by the presence of recurrent abnormal cytology, abnormal histology or colposcopic findings. Comprehensive sequential pathology review may be helpful in the management of these women.

Atypical glandular or endocervical cells of undetermined significance

Women with atypical glandular or endocervical cells of undetermined significance should be referred for colposcopic assessment. Subsequent management will depend on colposcopic findings, biopsy results and further cytological samples. In the presence of a normal colposcopy and a normal cervical TZ, close observation with a repeat Pap test and colposcopy at six months is an option.



TZ = transformation zone

Figure 8.3 Management of women with cervical cytology suggesting possible high-grade glandular lesions

8.7 Controversies in the management of women with histological evidence of AIS

Once the histological diagnosis of AIS has been confirmed by cone biopsy, hysterectomy is usually recommended for women who have completed childbearing, because of the difficulties of reliable cytological follow-up and the reported multifocality of the disease. There is a high incidence of residual and recurrent disease even when cone biopsy margins are reported as uninvolved (Hopkins et al 1988, Muntz et al 1992, Im et al 1995, Poyner et al 1995, Denehy et al 1997, Widrich et al 1996, Wolf et al 1996, Azodi et al 1999, Hopkins 2000, Anderson and Nielson 2002, Kennedy and Biscotti 2002, Shin et al 2002). It has been reported that only when the distance between the most proximal AIS and the endocervical margin is greater than 10 mm is there little risk of residual disease (Goldstein and Mani 1998).

International opinion (Cullimore et al 1992) has moved towards more conservative management of AIS under defined circumstances if childbearing is required. Careful counselling of the woman is essential in this situation.

Conservative fertility-sparing management may be considered only if all surgical margins of the cone biopsy are free of disease after adequate histological sampling, and if the woman understands that such management is advised only with close follow-up. If the margins of the initial cone biopsy are involved by AIS, a further cone biopsy should be undertaken because conservative management can only be safely advised when the

margins are negative. The place of hysterectomy after future childbearing should be discussed. For women managed conservatively, the cumulative risk of recurrent disease is 15% at four years (Soutter et al 2001).

Guideline — Management of women with AIS	
<p>The management of women diagnosed with AIS on cone biopsy will be dependent upon the age and fertility requirements of the women and the status of excision margins.</p> <p>Hysterectomy is recommended for women who have completed childbearing because of the difficulties of reliable cytological follow-up, a high recurrence rate and the reported multifocality of the disease.</p>	<p>Level IV (Cullimore et al 1992, Hopkins et al 1988, Muntz et al 1992, Im et al 1995, Poynor et al 1995, Denehy et al 1997, Widrich et al 1996, Wolf et al 1996, Azodi et al 1999, Hopkins 2000, Souter et al 2001, Anderson and Nielson 2002, Kennedy and Biscotti 2002, Shin et al 2002)</p>

8.8 Follow-up of women treated for AIS

Optimal follow-up of women managed without hysterectomy is yet to be defined. Follow-up cytology must include cytological sampling of the endocervical canal (Cullimore et al 1992). However, there are difficulties with cytological interpretation of glandular cells following cone biopsy. These include high scrapes resulting in endometrial sampling.

In view of the current uncertainties surrounding the conservative management of women with AIS, follow-up after treatment is best undertaken using both colposcopy and cytology. It should be acknowledged that colposcopy contributes little except by way of allowing a very accurate smear to be taken from the endocervical canal and giving the specialist gynaecologist an opportunity to reinforce to the woman the importance of ongoing follow-up.

8.9 Endometrial and other malignancies

A small number (4 of 1313) of women with AIS and possible high-grade glandular lesions reported on a conventional Pap test will be found to have an endometrial carcinoma (see Appendix 8). Cervical cytology suggestive of endometrial carcinoma is highly predictive for endometrial malignancy (Mitchell et al 1993).

Endometrial sampling and transvaginal ultrasound may be indicated if the woman complains of postmenopausal or irregular bleeding or if the atypical cells are suggestive of endometrial origin.

Should cone biopsy and endometrial sampling fail to identify significant disease in the presence of markedly abnormal glandular cells, pathology review is suggested and the presence of other neoplasms (ovarian, tubal, gastrointestinal) should be considered (Cullimore and Scurr 2000).

9 Special clinical circumstances

9.1 Pregnancy

Evaluation of an abnormal Pap test in pregnancy

Pregnancy constitutes a very special circumstance, as there are concerns for the wellbeing of the foetus and the pregnant woman. Cervical cancer complicating pregnancy is not common, occurring in about 0.05% of pregnancies (Nguyen et al 2000).

There are few studies detailing the effect of pregnancy on the progression of dysplasia to invasive cancer. A Melbourne case-series study did not find any invasive cancers in 811 women, including 103 women with high-grade lesions, attending a colposcopy clinic during pregnancy (Woodrow et al 1998). Progression from low-grade to high-grade disease during pregnancy is extremely low, but there is a high probability that a high-grade lesion will persist into the postpartum period (Coppola et al 1997, Woodrow et al 1998). Similarly, the question of regression has not been addressed, but it has been suggested that fewer than 25% of dysplastic lesions will regress during pregnancy, while the remainder persist (Coppola et al 1997).

The investigation of screen-detected abnormalities during pregnancy should follow the same guidelines as for the nonpregnant woman. In general, women who present with a low-grade abnormality should have a repeat smear in 12 months as outlined in Chapter 6.

High-grade lesions need early referral for colposcopic assessment (Figure 9.1), preferably by a colposcopist experienced in assessing the pregnant cervix. Inexperienced colposcopists may not recognise the subtle appearances of early invasive cancer in pregnancy.

Guidelines — Evaluation of an abnormal Pap test during pregnancy	
Women with low-grade cytologic lesions should be managed in the same way as for women with low-grade squamous abnormalities, with a repeat smear after 12 months.	Level IV (Coppola et al 1997, Jain et al 1997, Woodrow et al 1998, Nguyen et al 2000)
Women with high-grade lesions should be referred for colposcopic evaluation.	Level IV (Coppola et al 1997, Woodrow et al 1998, Nguyen et al 2000, Palle et al 2000)

Colposcopy during pregnancy

Colposcopy is safe during pregnancy. The colposcopic evaluation of the cervix may be more difficult due to vaginal laxity preventing the complete visualisation of the transformation zone. The increased vascularity due to pregnancy may also be difficult to interpret.

Experienced colposcopists will not usually perform a biopsy if they are confident that they have excluded an invasive cancer.

If no lesion is identified at colposcopy, it is advisable to request a review of all the cytological slides. If the diagnosis of a high-grade abnormality is confirmed, a second opinion from another colposcopist with wide experience in the colposcopic evaluation of pregnant women is recommended. In this situation it will be prudent to review the woman at approximately 20–24 weeks with cytology and colposcopy to determine as far as possible that she does not have an invasive lesion.

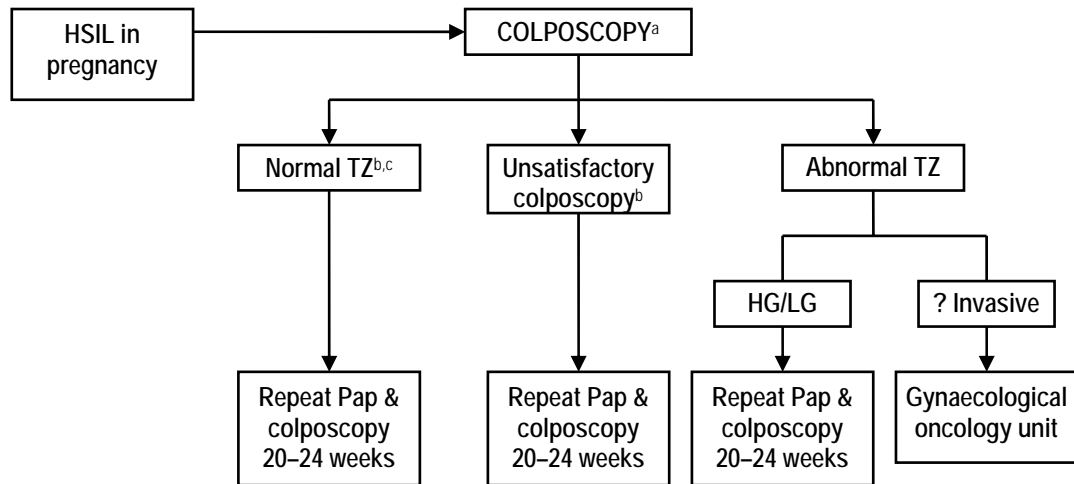
Guidelines — Colposcopy during pregnancy	
The main aim of colposcopy in the pregnant woman is to exclude the presence of invasive cancer and to reassure the woman that her pregnancy will not be affected by the presence of an abnormal Pap test.	Level IV (Woodrow et al 1998)
Biopsy of the cervix is usually unnecessary in pregnancy, unless invasion is suspected colposcopically.	Level IV (Woodrow et al 1998, Palle et al 2000)

Treatment of cervical cancer in pregnancy

The diagnosis, or suspected diagnosis, of invasive cervical cancer in pregnancy is a very worrying and difficult situation for the woman and her doctor. Referral to a gynaecological oncologist is recommended so that the woman receives expert counselling about options for investigation and treatment.

Treatment of a confirmed high-grade lesion in pregnancy is associated with an increased risk of treatment complications, abortion and persistence of the disease after treatment (Palle et al 2000). Cone biopsy or wedge biopsy of the cervix may be needed if there is a strong suspicion of invasive cancer, but these procedures carry a significant risk to the pregnancy and should only be performed by an experienced practitioner. Definitive treatment for pre-invasive disease is best deferred until after delivery. Reassessment is deferred until 6–8 weeks postpartum, when treatment can be planned. The rationale for postponing treatment is based on the disadvantages/risks of treatment during pregnancy and the extremely low rate of progression to invasive cancer (Woodrow et al 1998). If the initial colposcopic assessment was performed in the first trimester, the patient is usually reviewed later in the pregnancy, between 20 and 30 weeks. The purpose of this visit is to reassure both the pregnant woman and her obstetrician that all is well and that the high-grade lesion has not progressed to an invasive cancer.

Guideline — Treatment of a high-grade lesion during pregnancy	
Definitive treatment of a high-grade lesion, with the exception of invasive cancer, may be deferred safely until after the pregnancy.	Level IV Guerra et al (1998), Economos et al (1993)



HG/LG = high-grade / low-grade; HSIL = high-grade squamous intraepithelial lesion; TZ = transformation zone
 a No biopsy in pregnancy unless cancer is suspected; risk of progression to invasive disease is low if invasive cancer has been excluded.
 b Review all cytology slides with cytopathologist.
 c Second opinion from experienced colposcopist may be needed.

Figure 9.1 Management of a high-grade lesion in pregnancy

9.2 Immunosuppressed women

Women may be immunosuppressed because of disease such as HIV infection or because of the effects of drugs used to prevent rejection of transplanted organs or tissues, or to treat autoimmune diseases such as systemic lupus erythematosus, ulcerative colitis or asthma. Such immunosuppressed women are at increased risk of developing a persistent productive HPV infection that may lead to the development of neoplasia of the lower genital tract epithelium.

The literature on immunosuppression and cervical cancer is heavily biased to women with HIV infection: predominantly cohort studies with small numbers of women followed, no uniformity in the definition of immunosuppression, differing durations of immunosuppression and some women undergoing antiviral treatment. Some studies used cytology alone, rather than histology, for diagnosis.

Some degree of immunosuppression occurs at a CD4 count of $< 500/\text{mm}^3$, but the degree of immunosuppression does not become severe until the count is < 200 . $\text{CD4} < 40$ is very severe, but the important question is how this relates to the individual's risk of developing cervical abnormalities. Recent United States guidelines have not focused on CD4 counts but on whether the individual is HIV positive or not, and recommend that a Pap test be

performed twice in the first year after diagnosis of HIV infection and then, if normal, annually (US Public Health Service and Infectious Diseases Society of America 2001).

For the purposes of this recommendation, immunosuppression is defined as:

- CD4 count of < 400 in HIV-positive women or
- transplantation with immunosuppressive therapy > 3 years (Petry et al 1994).

From the literature reviewed, the following observations can be made.

Immunosuppressed women had an increased risk of intraepithelial neoplasia of 20% (compared with less than 5% for the general population). One review showed that renal transplant patients who had iatrogenic induction of immunosuppression had a 20 times higher rate of anogenital dysplasia than the general community (Sillman et al 1997).

There were high rates of progression, recurrence and persistence of dysplastic abnormalities in severely immunocompromised women. The progression rate was not only high but also more rapid, with a median time to progression of six months. Spontaneous regression was uncommon. Cytology alone was not a very sensitive method to predict recurrence or progression, with false-negative rates between 19% and 40%. Ablative therapy was associated with a high relapse rate (Spitzer 1999). Women treated by excision had less risk of residual disease or relapse. The management of these women is complex and should be carried out in specialist centres.

Guidelines — Immunosuppressed women	
If an immunosuppressed woman has a screen-detected abnormality she should be referred for colposcopy, even if the lesion is low-grade, as cytological surveillance alone may be inadequate.	Level I/II (Sillman et al 1997, Spitzer 1999)
Assessment and treatment should be by an experienced colposcopist.	Level III-1 (Petry et al 1994)
The whole of the lower genital tract will need evaluation as the same risk factors apply for cervical, vaginal, and vulval and perianal lesions.	Level III-1 (Petry et al 1994)
Treatment of the cervix should be by excisional methods.	Level I/II (Spitzer 1999)
Follow-up after treatment should include colposcopy as well as cytology.	Level III-2 (Cordiner et al 1980)
Follow-up should be annual and indefinite.	Level III-2 (Cordiner et al 1980)

9.3 Normal endometrial cells in postmenopausal women

Normal endometrial cells in smear tests of women over the age of 45 years are commonly reported. This is based on the unproven concern that the presence of endometrial cells is associated with cancer and has led to clinicians investigating this finding. Many women undergo hysteroscopy, dilatation and curettage, or endometrial sampling, without any evidence for this intervention.

Current evidence suggests that the presence of normal endometrial cells in a Pap smear in a postmenopausal woman is of little significance, with an extremely low risk of that person having an endometrial carcinoma at the time of the Pap smear.

Six papers in the literature (Gondos and King 1977, Gomez-Fernandez et al 2000, Ashfaq et al 2001, Montz 2001, Brogi et al 2002, Chang et al 2001) considered all of the following criteria: postmenopausal women who were asymptomatic with normal endometrial cells, who had histologic endometrial assessment, and in whom atypia or endometrial carcinoma was diagnosed histologically. Pooling the data from these papers shows that of 525 women with endometrial cells found who were postmenopausal, 268 had histological follow-up of the endometrium. There was only one woman with endometrial cancer and three with atypia.

These data support the recommendation that normal endometrial cells should not be routinely reported in the Pap smear. Symptomatic postmenopausal women require investigation irrespective of the status of their Pap test (RANZCOG 2002).

Guidelines — Postmenopausal women with normal endometrial cells	
Normal endometrial cells occurring in the Pap smear of an asymptomatic postmenopausal woman should not be reported.	Level III-2 (Gondos and King 1977, Gomez-Fernandez et al 2000, Ashfaq et al 2001, Montz 2001, Chang et al 2001, Brogi et al 2002)
A symptomatic postmenopausal woman requires investigation irrespective of her Pap test status.	Level III-2 (RANZCOG 2002)

9.4 Women exposed in utero to diethylstilboestrol

Diethylstilboestrol (DES) was given to pregnant women between 1940 and 1970 to provide luteal support to those with a previous poor pregnancy outcome. In 1970, seven cases of clear cell adenocarcinoma of the vagina were reported in young women and linked to DES exposure in utero (Herbst and Scully 1970).

Although DES exposure in utero rarely leads to vaginal adenocarcinoma, vaginal adenosis occurs in 45% of these women and structural abnormalities (transverse vaginal septum, cervical collar, anterior cervical ridge, cervical hypoplasia) are present in 25% (Hacker 2000). The critical period of exposure is before 18 weeks gestation.

Clear cell adenocarcinoma of the vagina or the cervix is a rare condition and, regardless of DES exposure, appears to have two peaks of incidence — one at 26 years and one at 71 years (Hacker 2000).

DES has not been used in pregnancy for over 30 years, so the problem is diminishing because most exposed women are over 30 years old. As women reach their 70s, they may have a greater risk again (RCOG 2002). The risk to women in their later years has not yet been quantified, but will probably be low, given the risk for the younger cohort of women. In view of this uncertainty, however, if a woman thinks that she is at increased risk of developing clear cell carcinoma of the vagina, she could attend a clinician experienced in colposcopy of the lower genital tract. More information on DES is available at the NSW Health website.⁹

Guidelines — Women exposed to diethylstilboestrol (DES) in utero	
DES-exposed women should be offered annual cytological screening and colposcopic examination of both the cervix and vagina.	Level IV (Hacker 2000, RCOG 2002)
Screening should begin any time at the woman's request and continue indefinitely. A balanced perspective should be maintained.	Level IV (Hacker 2000, RCOG 2002)
DES-exposed women who have a screen-detected abnormality should be managed in a specialist centre by an experienced colposcopist.	Level IV (Hacker 2000, RCOG 2002)

9.5 Other issues

Other circumstances that were previously considered to require special consideration no longer satisfy criteria for 'special' circumstances with any evidence basis. These include the following.

Previous hysterectomy

For documented benign reasons (eg menorrhagia, fibroids)

The rate of primary vagina cancer is exceedingly low in the general population (South Australian Cancer Registry data — 3 per year); therefore, routine screening cannot be considered cost-effective.

Unknown smear history

There is no good evidence that women with an unknown Pap test history need extra surveillance once a baseline 'normal' smear has been obtained. They then fall into the category of women whose hysterectomy has been undertaken and proven to be for benign reasons.

⁹ <http://www.health.nsw.gov.au/des> (Accessed 19 July 2004)

Subtotal hysterectomy

These women still have a cervix and thus will require 'routine' surveillance, as detailed under general guidelines for surveillance.

Hysterectomy because of CIN 2 or 3

The guidelines for surveillance as detailed in the sections on high-grade abnormality surveillance will apply (see Chapter 7).

Hysterectomy for genital malignancy

These women should be under ongoing surveillance from a gynaecological oncologist. Therefore, they will be guided by this specialist about appropriate surveillance and care, and will automatically no longer be the subject of these guidelines.

It is not appropriate that they be on any reminder service for ongoing surveillance.

Smear quality**Presence or absence of endocervical cells**

This has been used as an index of the quality of the Pap smear. However, retrospective cohort studies have shown that women with smears lacking endocervical cells are not more likely to have squamous lesions on follow-up than are women whose smears have endocervical cells (Mitchell and Medley 1991).

Unsatisfactory smears

See Chapter 5.

10 Psychosocial issues

Sensitivity to a range of psychosocial issues relating to cervical screening is vital in achieving effective communication with the women involved, whether they are being actively encouraged to screen or being given an abnormal result following a Pap test. The benefits of effective communication potentially include improvements in a woman's psychological adjustment, decision making, treatment compliance and satisfaction with care.

Effective communication involves more than the provision of information. It requires a process of individually tailored explanation, problem solving and acknowledgment of the woman's feelings. Also, while it is self-evident to clinicians, many women still need to understand that cervical screening is not a test for cancer, but a method of detecting abnormalities that left untreated could lead to cancer. Explaining the viral origin of cervical pathology can also place significant demands on the clinician.

Research has found that barriers to screening can be linked to a woman's knowledge about cervical cancer and may be linked to a range of emotions including embarrassment, pain and fear of the outcome (Hennig and Knowles 1990, Cockburn et al 1990). Clinicians have a key role in effective communication; women prefer a patient-centred consulting style and look to the clinician to broach the subject of psychosocial issues (Bertakis et al 1991).

It has been recognised that many women presented with abnormal results become confused, and that breaking the news of a diagnosis can be difficult for both patient and clinician. The medium used to present information can affect both how clinicians introduce it and how consumers use it (Edwards et al 2002). Discussion of prognostic information may include discussion about risk probabilities, but statistics are not always easily understood (Doyle 1977). It has been shown that when a discussion of anticipated risks and benefits is presented statistically as natural frequencies it is more easily understood (Gigerenzer and Edwards 2003).

Although most women undergoing cervical screening are provided with some relevant information, an abnormal result usually prompts them to seek more detail, greater inclusion in the decision-making process and an understanding of the treatment rationale. Individual women require varying amounts of information with differing levels of detail (Kavanagh and Broom 1997). Treatment decisions are often stressful; explaining options clearly and providing material for later reading affects a woman's ability to recall information and to feel comfortable with the choice agreed on (Ley and Llewelyn 1992).

Women who have abnormal smear results may experience psychological consequences, including fears about cancer, sexual difficulties, changes in body image, concerns about the loss of reproductive functions and fears about treatments (Lerman et al 1991). Many women assume they have cancer when they have an abnormality detected on a smear because they do not understand that Pap smears detect precancerous lesions (Kavanagh and Broom 1997). Being aware of the role of stress when managing cervical disease increases the clinician's ability to foster effective coping strategies for women (Coker et al 2003).

These guidelines reflect the current understanding of the natural history of human papillomavirus (HPV) infection, including the fact that cervical cancer is a rare outcome

even of high-risk HPV infection. HPV infection is a sensitive issue as it is sexually transmitted, and women need ongoing education to reduce the associated stigma. They need to be informed about the prevalence of infection and about spontaneous resolution (median duration approximately eight months), and to understand that, while persisting infection of the cervix with HPV is necessary for the development of cervical cancer, it is certainly not sufficient (Walboomers et al 1999).

The International Agency for Cancer Research has recommended that educational programs about HPV be developed for health professionals and women (IARC Press Release 151, 2004).

The National Health and Medical Research Council has recently endorsed *Clinical Practice Guidelines for the Psychosocial Care of Adults with Cancer* (National Breast Cancer Centre and National Cancer Control Initiative 2003). These evidence-based guidelines have been designed for use by all health professionals who come into contact with people during the course of cancer diagnosis and treatment. Although most women with abnormal Pap tests do not have cancer, the principles outlined in the guidelines for recognising and dealing with the emotional and psychological aspects of diagnosis and treatment may provide useful and practical guidance.

11 Economic considerations

11.1 Introduction

This chapter provides an economic assessment of the changes to the management of women with screen-detected abnormalities recommended in these guidelines.

In formulating and evaluating the guidelines, Australia's commitment to a coordinated National Cervical Screening Program has been taken as given. Therefore, the economic question is not whether women with screen-detected abnormalities should be managed, but how they should be managed. The recommendations made in these guidelines involve changes motivated by an intention to improve the management of women with screen-detected abnormalities.

The existing literature on the economics of cervical screening has focused on the cost-effectiveness of alternative screening intervals and age ranges. The reason for this focus is clear: the magnitude of the resource commitment to a population cervical screening program depends largely on these two factors, along with the costs of the personnel and technology it employs. A series of recent studies have focused on the cost-effectiveness of alternative screening approaches, particularly those that incorporate tests for the human papillomavirus (HPV).

Most of the incremental changes recommended in these guidelines have not been subjected to full economic evaluations in the existing literature. Thus, there is clearly an opportunity for productive research to be done on this issue. Nevertheless, as Laupacis (whose argument was made in relation to the assessment of pharmaceuticals) has observed, sometimes the orders of magnitude of benefits and costs can be clearly discerned without a full economic evaluation (Laupacis 2002). To paraphrase Laupacis (cited in Drummond 2004), highly effective clinical guidelines will generally be cost-effective, while marginally effective clinical guidelines are unlikely to be cost-effective.

By design, the revised guidelines in their entirety have been formulated to produce incremental improvements in clinical practice, while recognising the need to maintain screening and management practices that are viable at the population level. Some of the most important changes involve removing distinctions that have been shown not to be clinically meaningful or reproducible. Changes such as these create no tension between clinical and economic objectives, because previous terminological distinctions that confer no health benefit but generate costs (eg differential reporting and clinical management costs) are unambiguously non-economic (ie they involve a net cost to society). The most substantive changes presented in these guidelines involve incremental changes of this sort. Quantifying their costs and benefits is unnecessary, because ceasing an activity that incurs costs but that does not confer benefits always improves net welfare.

Finally, it is worth noting that policy changes almost invariably impose 'switching' costs that, although typically fixed, can also be large. Important examples, in the current context, are the costs of disseminating the guidelines and educating women and practitioners about their contents and effects. In addition, pathology laboratories and registries will also incur costs from systemic changes to the Australian terminology and classification. To be balanced against these are the social benefits that may arise by

adopting a national and internationally comparable terminology. Benefits include, for example, an increase in the value of the information collected by the National Cervical Screening Program because of better national and international comparability. Such benefits are largely intangible until they are realised, and their magnitudes are difficult, if not impossible, to predict. Nevertheless, they may include an improved understanding of the epidemiology of cervical cancer and its precursors in the Australian population.

The following sections provide an economic assessment of the recommended changes, including an overview of the sources or types of costs and benefits, and a general assessment of the likelihood that each change will produce social net benefits.

11.2 Changes to terminology

An expected benefit of the Australian Modified Bethesda System (AMBS) 2004 terminology will be the national and international comparability of data collected on the screened Australian population. This benefit is intangible and its magnitude is difficult to predict, because the scientific and medical benefits of international comparability cannot easily be quantified. Also, Australian women may not be the only beneficiaries of these improvements: information has inherent characteristics that make it a public good (ie it is nonrival and nonexcludable).

The change to the terminology and recommendations for reporting may incur substantive, 'one-off' fixed costs, particularly for the laboratories and registries. The magnitudes of these costs and any private returns to the institutions are likely to vary from institution to institution. This is an important implementation issue, warranting consultation between the Australian Government and the institutions concerned.

By making clinically meaningful, evidence-based distinctions more efficient, the new terminology will also help make the management of women with screen-detected abnormalities more efficient.

11.3 Low-grade squamous abnormalities

The recommended terminology removes distinctions between the three previous low-grade epithelial abnormality subcategories (NMSC, HPV and CIN 1) because those distinctions are not supported either by evidence that the distinctions are reasonably reproducible or by significant differences in clinical outcomes (see Appendix 7, Table A7.9). The removal of the distinctions is expected to improve efficiency.

The revised management guidelines for low-grade squamous intraepithelial lesions (LSILs) will reduce the frequency of unproductive colposcopic interventions, especially in young women, in whom low-grade abnormalities are considered to reflect acute HPV infection. HPV infection is very common in young, sexually active women, commonly resolves spontaneously and, in most cases, is not associated with cytological abnormalities. Therefore, early investigations following a result of LSIL are unlikely to obviate the need for further follow-up smears. For these and other reasons, which are outlined in detail in Chapter 6, aggressive follow-up (eg with immediate colposcopy) is likely to incur substantial direct and indirect costs for additional procedures that generally produce little or no benefit. The recommendation for a repeat smear at 12 months for all women with an LSIL result on the index smear is calculated to reduce the frequency and

costs of unnecessarily aggressive early investigation while appropriately managing the risk that a woman may subsequently develop invasive cancer of the cervix.

These recommendations are not only consistent with a modern clinical understanding of cervical cancer and its precursors, but are also broadly consistent with recent American evidence about women's preferences for the management of low-grade abnormalities (Melnikow et al 2002, Birch et al 2003). Birch and colleagues used the standard gamble approach to study the preferences of women for conservative ('watchful wait/repeat smear') or aggressive ('early intervention with colposcopy') follow-ups of mildly abnormal Pap tests. The women's preferences were elicited using three different treatment outcomes (no treatment, cryotherapy and cone biopsy) for each follow-up approach, and a common health outcome (ie full health after three years) for each of the resulting six scenarios.

The authors found that, despite the common outcome, women's preferences for aggressive or conservative follow-up were sensitive to the treatment that would be required. In particular, women preferred a conservative approach when the treatment result was 'no treatment' (spontaneous resolution), but preferred a more aggressive management for the more serious pathologies. The recommendations in these guidelines are broadly consistent with such preferences.

11.4 Glandular abnormalities

One incremental change in these guidelines concerns the management of women with a cytological result of low-grade glandular abnormality. It was previously recommended that women with this diagnosis be managed with a repeat smear at six months, followed by a colposcopy in the event that the condition was persistent. The revised guidelines recommend that women be sent for immediate colposcopic investigation in the event of a diagnosis of low-grade glandular abnormality. This recommendation acknowledges that such abnormalities have a higher probability of harbouring significant cervical lesions than do LSILs, and that sampling difficulties make cytological follow-up less reliable for glandular than for squamous lesions (see Chapter 8).

The aggregate economic impact of this recommendation is likely to be very small. Cytological reports of a glandular abnormality usually make up a small proportion (less than 1%) of all Pap test reports, and reports of minor glandular atypia are a subset of this subset. Furthermore, many practitioners already initiate immediate colposcopic investigation upon a finding of minor glandular atypia, so the incremental effect of this recommendation is also likely to be small. Finally, this element of the guidelines appears to be consistent with recent evidence on women's preferences between 'watchful waiting' and immediate investigation when a procedure (eg colposcopy) is likely to be required (Birch et al 2003, Melnikow et al 2002).

11.5 HPV testing

Numerous studies of the cost-effectiveness of tests for HPV as part of a population cervical screening program have recently been published (Wright et al 1995, Lytwyn et al 2000, Shlay et al 2000, Kim et al 2002). These studies were conducted overseas, and their application in the Australian context is difficult for various reasons (differences in institutional arrangements, terminology and diagnostic categories, laboratory accuracy, relative prices, and so on).

The Medical Services Advisory Committee recently considered an application to list an HPV test for women with a minor screen-detected abnormality on the Australian Medicare Benefits Schedule, but concluded that HPV testing is not a cost-effective screening tool for such women (MSAC 2002).

Appendix 1

Guidelines Review Group membership

Guidelines Review Group membership

Professor Ian Hammond (Chairman) Gynaecological oncologist	Dr Heather Mitchell Epidemiologist (resigned Feb 2005)
Dr Annabelle Farnsworth (Deputy Chair) Cytopathologist (resigned July 2004)	Dr Ruth McNair General practitioner
Dr Alex Barratt Health communication specialist	Ms Liz Pugh (to July 2003) Ms Vicki Shaw (from August 2003) Australian Government Department of Health and Ageing representative
Ms Stephanie Bell Aboriginal and Torres Strait Islander women's health representative	Ms Maureen Ramsden Consumer representative
Dr Penny Blomfield RANZCOG representative	Dr David Roder Epidemiologist
Dr Luke Connelly Health economist	Dr Marion Saville Pathologist
Dr Margaret Culpan ACRRM representative	Dr Paul Shield Cytologist
Dr Margaret Davy Gynaecological oncologist	Dr Greg Sterrett Pathologist
Professor Ian Frazer Virologist	Ms Sheena Thornton Consumer representative
Dr Elizabeth Hindmarsh RACGP representative	Dr Gerry Wain Gynaecological oncologist
Dr Chris Hunter ASCCP representative	Professor Richard Williams RCPA representative

Terminology Working Group

Dr Marion Saville (Chair)
Dr Gerry Wain
Dr Paul Shield
Dr Greg Sterrett
Dr Elizabeth Hindmarsh
Ms Sheena Thornton
Dr Richard Williams

High-Grade Working Group

Dr Penny Blomfield (Chair)
Dr Heather Mitchell
Dr Luke Connelly
Prof. Ian Frazer
Dr Greg Sterrett
Dr Ruth McNair
Professor Ian Hammond

Low-Grade Working Group

Dr Gerry Wain (Chair)

Dr Chris Hunter

Prof. Ian Frazer

Dr Annabelle Farnsworth

Dr Luke Connelly

Dr Heather Mitchell

Dr Margaret Culpan

Dr Marion Saville

Implementation Working Group

Ms Liz Pugh (Chair) (to July 2003)

Ms Vicki Shaw (from August 2003)

Dr Annabelle Farnsworth

Ms Stephanie Bell

Ms Maureen Ramsden

Dr Ruth McNair

Professor Ian Hammond

Dr Alex Barratt

Ms Sheena Thornton

Dr David Roder

Dr Richard Williams

Special Clinical Circumstances Working Group

Dr Margaret Davy (Chair)

Dr Elizabeth Hindmarsh

Professor Ian Hammond

Ms Liz Pugh

Dr Marion Saville

Secretariat

Ms Jayne Ross (Secretary)

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Ms Jackie O'Callaghan

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Technical editing

Dr Janet Salisbury, Biotext

Research

Mr Stephen Morrell

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Ms Clare Banks

IT support

Ms Amanda Niciak

Appendix 2

Process for development of guidelines

The NHMRC *Screening to Prevent Cervical Cancer: Guidelines for the Management of Women with Screen Detected Abnormalities* (NHMRC 1994) were originally developed by an expert group convened by the NHMRC, and were endorsed by the NHMRC in December 1993. While the guidelines were based on the latest available literature at that time and provided effective guidance to practitioners, they were not formulated in line with more recent NHMRC standards for clinical practice guidelines.

In 2001, the National Advisory Committee to the National Cervical Screening Program requested that the guidelines be reviewed and updated. The NSW Cervical Screening Program undertook to manage this review under the auspices of the Australian Government Department of Health and Ageing. The review has been undertaken in accordance with the NHMRC's *A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines* (NHMRC 1999).

Terms of reference

The terms of reference for the Guidelines Review Group were to:

1. gain agreement on the terminology to be used for cervical cytology reporting
2. review the scope and coverage of the current guidelines to identify the areas that need revision
3. revise the current guidelines consistent with the terminology, best scientific evidence and practice, and with regard to cost implications
4. develop an implementation plan, including a plan for the production of a consumer version of the revised guidelines.

Composition of Guidelines Review Group

The NHMRC recommends that guidelines be developed by a multidisciplinary group that is representative of all stakeholders. The composition of such groups has an impact on the effectiveness of implementation.

The composition of the Guidelines Review Group reflected those groups involved in the cervical screening pathway. Membership included representation from the following stakeholders:

- cytologists
- general practitioners
- gynaecological oncologists
- gynaecologists
- pathologists

- virologists
- epidemiologists
- health communication specialists
- health economists
- consumers
- Aboriginal and Torres Strait Islander people.

The professional bodies formally represented in the group were the Royal Australian and New Zealand College of Obstetricians and Gynaecologists (RANZCOG), the Australian College of Rural and Remote Medicine (ACRRM), the Royal Australian College of General Practitioners (RACGP), the Australian Society of Colposcopy and Cervical Pathology (ASCCP) and the Royal College of Pathologists of Australasia (RCPA).

The Australian Government Department of Health and Ageing (DoHA) was also represented.

Process followed

The first meeting of the Guidelines Review Group was held on 26 November 2001 and identified the following key tasks:

- agreement on terminology
- review of literature and development of recommendations on low-grade abnormalities, high-grade abnormalities and special clinical circumstances
- development of a process for implementation and evaluation of the guidelines.

The Guidelines Review Group set up a series of working groups to address the above tasks:

- the terminology working group
- the low-grade squamous abnormalities working group
- the high-grade squamous abnormalities and glandular abnormalities working group
- the special clinical circumstances working group
- the implementation working group.

The chairs of the working groups, along with the chair and deputy chair of the Guidelines Review Group, formed an executive for ongoing oversight of the process.

The full Guidelines Review Group met five times at face-to-face meetings over a period of two years. The executive met, mainly by teleconference, frequently over the course of the review.

The working groups met, mainly by teleconference, an average of four times each. Considerable work on the preparation of documents was done electronically.

Consultation

The primary vehicle for consultation and wide access to the guidelines development process was through a special website (www.csp.nsw.gov.au/nhmrc), which enabled access to all documents produced and provided a facility to make comments and register to be part of the consultation process.

In addition, at the outset, advertisements were placed to advise of the guideline development process and to invite comment. Advertisements appeared in:

- the Australian Divisions of General Practice newsletter
- ACRRM newsletter
- Australian Society of Cytology newsletter and website
- RACGP website
- RANZCOG journal and website
- RCPA newsletter
- *Australian Physician*.

In addition, letters were sent to all members of RANZCOG by the RANZCOG representative, advising them of the process and the availability of the guideline website for their comments.

The question of revised terminology was also the subject of a presentation to the 2002 annual scientific meeting of the Australian Society of Cytology. This society also formed a working group to consider the matter. Their consultations included a web-based discussion through the society's own website. This process resulted in widespread endorsement of the proposed changes in terminology.

Following the completion of the first draft of the guidelines by the Guidelines Review Group in August 2003, an advertisement was placed in *The Australian* newspaper (11 October 2003) advising of the availability of the draft for formal comment in accordance with NHMRC requirements.

Formal consultation on the draft guidelines was also undertaken at meetings of the following bodies:

- Australian Society of Gynaecological Oncology
- Australian Society of Cytology
- RACGP
- RANZCOG
- ASCCP
- NSW Cervical Screening GP Task Force
- state cervical screening programs
- Australian Divisions of General Practice

Consultation with consumers was undertaken through a series of meetings with women, held under the auspices of the state and territory cervical screening programs across Australia.

Submissions received

Ms Andriana Koukari	Director, Population Screening Department of Health and Ageing
A/Prof Michael Quinn Dr Alistair Lochhead	Cytopathology Advisory Committee MSAC, Committee member RCPA Anatomical Pathology Advisory nominee for the National Association of Testing Authorities
Dr RG Wright JA Halford	Queensland Medical Laboratory
Dr Elizabeth Hindmarsh	NSW Cervical Screening Program General Practice Taskforce Chairperson Royal Australian College of General Practitioners
Mr Ron Bowditch	
Dr Jane Twin	Capital Pathology, ACT
Dr Gloria Armellin	Capital Pathology, ACT
Dr Ian Clark	Capital Pathology, ACT
Dr Nicole Sides	Capital Pathology, ACT
Dr Clare Biro	Mayne Health Lavery Pathology
Dr Suzanne Hyne	Mayne Health Lavery Pathology
Dr Jennifer Roberts	Mayne Health Lavery Pathology
Dr Kate Williams	Mayne Health Lavery Pathology
Dr Ibrahim Zardawi	Mayne Health Lavery Pathology
Mr Mark Van Asten	Diagnostic Technology
Dr Caroline Harvey	Medical Director, Family Planning Queensland
Dr John Scott	Acting General Manager, Queensland Health
Professor Christopher Fairley	Professor of Sexual Health, School of Population Health, The University of Melbourne Director, Melbourne Sexual Health Centre
Dr Gabrielle Medley	
Dr Robert Rome	Australian Society of Colposcopy and Cervical Pathology
Associate Professor Jane Gunn	Department of General Practice The University of Melbourne

Dr Jennifer Reath	Royal Australian College of General Practitioners, Indigenous Health Projects Manager
Ms Carol Devine	Coordinator, DES Action Australia
Dr Stella Heley	Victorian Cytology Service, Liaison Physician
Ms Bethany Jones	Consumer
Professor Doreen Rosenthal	Key Centre for Women's Health in Society The University of Melbourne
Gynaecological Cancer Society	
Tasmanian Cervical Cancer Prevention Program	
Adverse Drug Reactions Unit Therapeutic Goods Administration	

Further consultations in November and December 2004

The Guidelines Review Group gave full consideration to comments received during the consultations described above and amended the guidelines as appropriate for submission to the NHMRC in September 2004.

However, the Guidelines Review Group withdrew the guidelines from the NHMRC Council meeting in September 2004 in order to consider claims that the recommendations for women with low-grade abnormalities were unsafe, and to review the underpinning evidence and methodology for these claims.

Epidemiology meeting

The Australian Government Department of Health and Ageing (DoHA) convened a meeting of independent epidemiologists with expertise in cervical screening in November 2004 to discuss the epidemiological basis and safety of the recommendations for women with LSIL cytology, as proposed in the draft guidelines. Attendees at the meeting included representatives from the Guidelines Review Group, the Screening Section of DoHA and a number of independent epidemiologists with expertise in this field.

The participants at the meeting unanimously dismissed the claims made against the recommendations and agreed that the methodology to support the recommendations for women with LSIL cytology as put forward by the Guidelines Review Group were sound, logical and appropriate for the Australian population. The Guidelines Review Group demonstrated that the impact of the LSIL management recommendations was likely to be neutral in terms of additional cancers after taking account of the cervical cancers that would have their diagnosis brought forward by following the proposed recommendations (see Appendix 10).

Clinicians' meeting

DoHA convened a further meeting of clinicians in December 2004 to discuss the guideline recommendations, clarify data and consider issues relating to implementation of the guidelines. Attendees at the meeting included representatives from the Guidelines Review Group, DoHA, RCPA, RACGP, RANZCOG, Australian Society of Cytology,

National Pathology Accreditation Advisory Council, Australian Medical Association, and ASCCP. Discussion at the meeting covered a range of issues, including consideration of practical implementation processes for clinicians.

Three submissions were received subsequent to this meeting from Mr Ron Bowditch, the RCPA and Mr Robert Rome on behalf of the ASCCP. The RCPA, Mr R Bowditch and the ASCCP have advised that they are not in agreement with the recommended management of asymptomatic women with low-grade cervical cytology reports. These submissions were circulated to the Guidelines Review Group for comment and comments received were considered by the executive of the group.

Consumer forum

On 14 March 2005, the DoHA Screening Section hosted Cervical Screening — Future Directions — A Women's Forum in Canberra to provide key women's organisations with information on the revised guideline recommendations and to provide an opportunity for clarification and discussion.

The 72 participants at the forum included representatives from a range of national women's organisations, state and territory governments and the Australian Government. The forum provided an opportunity for discussion about how the guideline recommendations might impact on women, the best mechanisms for monitoring the impacts over time and how the revised guidelines, once approved, can be communicated to women and medical professionals. On noting the evidence presented at the forum, the majority of participants indicated support of the guideline recommendations.

Literature review

Key questions to be answered from the literature were developed by the low-grade, high-grade and glandular, and special clinical circumstances working groups during the preparation of their chapters.

The following data sources were searched for all questions under review:

- the specialised trials register maintained by the Cochrane Gynaecological Cancer Group
- the Cochrane Database of Systematic Reviews and the Cochrane Library, including the Database of Abstracts (DARE)
- MEDLINE, EMBASE, Cancerlit, HealthSTAR and CINAHL
- unpublished studies sought from review group members.

To identify systematic reviews and randomised controlled trials, a series of specified codes were used. Individual MeSH terms and a few non-MeSH words were also used to identify literature of interest. Overall, a large number of search terms were used (see below), reflecting the field of cervical abnormality, cytology and management.

Where the above search strategy failed to produce any relevant literature, the cross-reference and ‘snowball’ method was also used. In many instances, because of the incompatibility of international nomenclature for cervical abnormality classification (such as the ‘inconclusive’ category in Australia), the text search included non-MeSH words.

Terminology

Question 1:

What is the reproducibility of different levels of abnormality identified in Pap smears by scientists and/or pathologists?

Search terms used:

Pap smear
diagnostic test
abnormality
CIN — cervical intraepithelial neoplasia
reproducibility
HSIL, HGSIL
LGSIL, LSIL
screening test

Low-grade lesions

Questions:

What are the advantages and disadvantages of either repeating the Pap test or of immediate colposcopy for the various categories of low-grade cytology report and do these options differ for age groups, for example, more or less than 30 years of age?

What is the cost–benefit of repeating the Pap test versus immediate colposcopy for the various types of low-grade cytology reports, and does the cost–benefit differ for different age groups, for example, more or less than 30 years of age?

What is the value of Digene Hybrid Capture II (HC-II or HC2) in detecting histologically confirmed high-grade lesions in women with the various categories of low-grade cytology report and does this vary with age, such as more or less than 30 years of age?

What are the sensitivity, specificity, positive and negative predictive value of HPV testing using Digene HC-II in detecting histologically confirmed high-grade lesions among women with the various types of low-grade cytology reports?

Search terms used:

Pap smear
colposcopy
low-grade abnormality
LGSIL
LSIL
follow-up
age
Digene
HC 2
sensitivity
specificity
positive predictive value
negative predictive value
histology
high-grade abnormality
HGSIL
HSIL
cervix uteri
malignancy
benign hyperplasia
neoplasia

High-grade lesions

Question 1:

In women with inconclusive (possible high-grade abnormality) Pap test results, what are the sensitivity, specificity, positive and negative predictive value of HPV testing with Digene Hybrid Capture II (HC-II) in identifying women who actually have high-grade cervical pathology?

Objective: To assess the specificity, sensitivity of HPV testing with Digene HC-II to reclassify an inconclusive result as being a high-grade abnormality.

Types of outcome measures: Number (%) women with inconclusive cytology classified as high-grade by histology / number (%) of women with inconclusive cytology classified as high-grade using Digene testing.

Search terms used:

epithelial abnormality
cervical intraepithelial neoplasia, CIN
inconclusive
cytology
high grade
HPV
Digene
hybrid capture test
specificity
sensitivity
positive
negative
predictive value
pathology
HSIL, HGSIL

Where the above search strategy failed to produce any relevant literature, the cross-reference and snowball method was also used. In many instances, because of the incompatibility of international nomenclature for cervical abnormality classification (such as the 'inconclusive' category in Australia), the text search included non-MeSH words.

Question 2:

In women previously treated for CIN 2 and CIN 3, what is the positive and negative predictive value of HPV testing in relation to the detection of further high-grade disease?

Do the predictive values of an HPV test alter depending upon the timing of HPV testing from initial treatment?

Is there a time point at which a negative test for HPV (using Digene) can be used to predict the absence of future risk for high-grade disease in women previously treated for CIN 2 and 3?

Does age of patient have an influence upon the predictive value of HPV testing in this setting?

Objectives: To assess the accuracy of HPV DNA testing in detecting a high-grade abnormality in women who have cytology suggesting atypical glandular cells. To assess the negative predictive value of HPV testing.

Types of outcome measures: Number (%) women with inconclusive cytology not confirmed as high grade. Number (%) of women with inconclusive cytology confirmed as high grade. Number (%) of women with HPV testing confirming result.

Search terms used:

epithelial abnormality
cervical intraepithelial neoplasia, CIN
inconclusive
cytology

high grade
HPV
Digene
predictive value
pathology
HSIL, HGSIL
HC2, HCII, HC-2, HC-II

Question 3:

In women previously treated for a high-grade abnormality, does colposcopy improve the identification of further disease and over what time period (ie first 12 months, or first 24 months) should it be utilised?

Objectives: To assess the use of colposcopy for women with previous treatment for CIN 2 and 3 to predict risk of further abnormalities and to determine whether any time period (ie first 12 months or first 24 months) affects the predictive value of colposcopy.

Search terms used:

epithelial abnormality
cervical intraepithelial neoplasia, CIN II, III, CIN2, CIN3
positive HPV (present)
high grade
negative HPV
colposcopy
predictive value
HSIL, HGSIL
treatment
management
follow up
monitor

Special clinical circumstances

Question 1:

For any cervical abnormality (either low or high grade), what is the likelihood of developing an invasive cancer during pregnancy, and does pregnancy accelerate this potential progression?

Search terms used:

pregnant, pregnancy
epithelial abnormality
cervical intraepithelial neoplasia, CIN
mild squamous atypia
cytology
high grade
low grade
progress\$
develop\$
low-grade squamous intraepithelial lesion, LSIL, LGSIL
high-grade squamous intraepithelial lesion, HSIL, HGSIL
criteria of HPV effect
nonspecific minor changes

Question 2:

In a postmenopausal woman with no history of vaginal bleeding and with normal endometrial cells on a Pap smear, is there any increased risk of cancer or precancer of the endometrium?

Search terms used:

post menopausal
vagina
bleeding
endometrial cells
uterine cervix
Pap smear
cervical intraepithelial neoplasia
CIN
abnormality
LGSIL
LSIL
HGSIL
HSIL
cancer
endometrium
history
follow-up

Question 3:

For a woman already immunocompromised, or who is embarking on a protracted immunosuppression regimen, what is the optimal screening interval?

For immunocompromised women, what is the likelihood of persistence, progression and recurrence of any existing cervical abnormality?

Search terms used:

uterine cervix
Pap smear
cervical intraepithelial neoplasia
CIN
abnormality
LGSIL
LSIL
HGSIL
HSIL
cancer
immunosuppressed
immunocompromised
immune deficient
persistence of disease
progression
recurrence
history
follow-up

Table A2.1 Search protocols for identifying systematic reviews and randomised controlled trials

For systematic reviews	Randomised controlled trials
1. Systematic Review	1. Randomised controlled trial IN PT
2. Meta-analysis (pt)	2. Controlled IN PT
3. Meta-anal: (tw)	3. Randomised controlled trials
4. Metaanal: (tw)	4. Random allocation
5. Quantitative: review: OR quantitative: overview: (tw)	5. Double blind method
6. Systematic: review: OR systematic: overview:(tw)	6. Single blind method
7. Methodologic: review: OR methodologic: overview: (tw) review (pt) AND medline (tw)	7. 1 OR 2 OR 3 OR 4 OR 5 OR 6
1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7	8. TG=Animal NOT (TG=Human AND TG+ Animal)
	9. 7 not 8
	10. Clinical-Trial IN PT
	11. explode Clinical-Trials
	12. (Clin*near trial*) IN TI
	13. (Clin*near trial*) IN AB
	14. (Singl* OR doubl* OR trebl*) near (blind* or mask*)
	15. (#14 IN TI) OR (#14 in AB)
	16. Placebos
	17. Placebo* IN TI
	18. Placebo* IN AB
	19. Random* IN TI
	20. Random* IN AB
	21. Research-design
	22. 10 OR 11 OR 12 OR 13 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21
	23. TG=Animal NOT (TG=Human AND TG = Animal)
	24. 22 NOT 23
	25. 24 NOT 9
	26. TG = comparative study
	27. explode Evaluation studies
	28. Follow-up studies
	29. Prospective studies
	30. control* OR prospective* OR volunteer*
	31. (30 IN TI) OR (30 IN AB)
	32. 26 OR 27 OR 28 OR 29 OR 31
	33. TG = Animal NOT (TG = Human AND TG = Animal)
	34. 32 NOT 33
	35. 34 NOT (9 OR 25)
	36. 9 OR 25 OR 35

pt = publication type; tw = text word; ab = abstract

Source: NHMRC 2000a

Analysis of national Pap test registry data

The advent of Pap test registers in Australia gave the Guidelines Review Group the opportunity to review the outcome data of the entire Australian population. This unique and complete dataset (or census), provided the Guidelines Review Group with information on the relevant outcomes of all women who received cytological predictions of low-grade epithelial or glandular abnormalities during 1999. These data were provided by state and territory Pap test registries according to specifications drawn up by Dr Heather Mitchell. The data were subsequently analysed by Dr Mitchell. The data on outcomes after low-grade cytology are presented in Appendix 7, and the data regarding glandular abnormalities appear in Appendix 8.

Appendix 4

Dissemination, implementation, monitoring and review of guidelines

Introduction of new terminology

The review of the *Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen-Detected Abnormalities* has been based on a change in the terminology used in Australia for reporting cervical abnormalities. While the terminology remains peculiarly Australian in some aspects, it does bring Australia into line with the United States Bethesda 2001 terminology to the extent that in future, the data in large international studies will be able to be extrapolated to the Australian environment.

However, the change to the new terminology, designated as the Australian Modified Bethesda System (AMBS 2004), will need to be properly managed and coordinated.

The change to the new terminology will affect:

- National Pathology Accreditation Advisory Committee reporting standards
- laboratory reporting categories
- cervical cytology registers and other systems for collecting and analysing data
- external quality assurance programs for laboratories.

In order to have consistency in reporting and standards, the old terminology will cease to be recorded and the new terminology introduced on 1 July 2006. The Australian Government Department of Health and Ageing will need to confirm this date after consultation with key stakeholders.

Dissemination and implementation strategy

The dissemination and implementation strategies for the guidelines are based on the recommendations of the National Health and Medical Research Council (NHMRC 1999, 2000c).

Dissemination

It is well established that the development of guidelines without an effective dissemination and distribution plan is a waste of effort. Dissemination strategies are based on the identified needs of each stakeholder group. Strategies include:

- articles in journals and professional magazines
- advice to each target audience of guidelines accessibility and availability
- mailout to general practitioners (GPs) and specialists

- website
- state programs
- GP professional development programs.

Educational resources

Resource development will reflect the different levels of information required by the identified groups and will be pilot and/or focus tested as appropriate:

- guideline book
- consumer book
- GP resource
- brochure.

Implementation

Strategies to encourage the uptake of the guidelines include:

- use of champions in clinical and nonclinical fields to promote guidelines
- endorsement by professional bodies
- education of women
- development of educational material
- educational seminars (eg peer education seminars)
- reminder systems incorporated into clinicians' daily work
- quality assurance/quality improvement
- local adaptation
- incentives
- use of information technology.

Monitoring

The Screening Section of the Australian Government Department of Health and Ageing (through the Australian Screening Advisory Committee) will assume responsibility for the monitoring of the safety of the recommended management of women with low-grade cytology (see Appendix 12) and treated high-grade intraepithelial disease (see Appendix 13). This will facilitate timely review of the policy as needed.

Close monitoring of women with cervical cancer should also be undertaken and will be the responsibility of the National Cervical Screening Program using a national coding set and data monitoring through the Australian Institute of Health and Welfare.

Evaluation

The evaluation process is intended to assess the uptake of the guidelines and the effectiveness of their dissemination. Adhering to the NHMRC framework (NHMRC 1999), the evaluation will include:

- an assessment of guideline dissemination
- an assessment of whether or not clinical practice is moving towards the guidelines' recommendations
- an assessment of whether or not the guidelines have contributed to any changes in clinical practice or health outcomes
- an assessment of the guidelines' impact on consumers' knowledge and understanding

Next update

When guidelines are developed, a date and strategy should be set for their revision. The NHMRC recommends that this occur every three to five years and more often where the subject matter or circumstances are prone to rapid change (*A Guide to the Development, Implementation and Evaluation of Clinical Practice Guidelines*, NHMRC 1999). In accordance with this recommendation, the Australian Screening Advisory Committee will be responsible for revising these guidelines before 2010.

Appendix 5

Examples of reports conforming to the terminology requirements

GYNAECOLOGICAL CYTOLOGY	
<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	NEGATIVE FOR INTRAEPITHELIAL LESION OR MALIGNANCY
<u>SPECIFIC DIAGNOSIS</u>	No cellular evidence of neoplasia. An endocervical component is present.
<u>RECOMMENDATION</u>	Please repeat the smear in two years.

GYNAECOLOGICAL CYTOLOGY	
<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	POSSIBLE LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION
<u>SPECIFIC DIAGNOSIS</u>	There are minor nonspecific changes in squamous cells. An endocervical component is present.
<u>RECOMMENDATION</u>	Please repeat the smear in one year.

GYNAECOLOGICAL CYTOLOGY	
<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	POSSIBLE HIGH-GRADE SQUAMOUS LESION
<u>SPECIFIC DIAGNOSIS</u>	The specimen contains atypical squamous cells, suspicious for, but not diagnostic of, a high-grade squamous intraepithelial lesion (CIN 2 or 3). An endocervical component is present.
<u>RECOMMENDATION</u>	Colposcopy is recommended.

GYNAECOLOGICAL CYTOLOGY

<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	POSSIBLE HIGH-GRADE GLANDULAR LESION
<u>SPECIFIC DIAGNOSIS</u>	The specimen contains atypical endocervical cells, suspicious for, but not diagnostic of, adenocarcinoma in situ (AIS). An endocervical component is present.
<u>RECOMMENDATION</u>	Colposcopy is recommended.

GYNAECOLOGICAL CYTOLOGY

<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	POSSIBLE HIGH-GRADE GLANDULAR LESION
<u>SPECIFIC DIAGNOSIS</u>	The specimen contains atypical endocervical cells, suspicious for, but not diagnostic of, endocervical adenocarcinoma. An endocervical component is present.
<u>RECOMMENDATION</u>	Colposcopy is recommended.

GYNAECOLOGICAL CYTOLOGY

<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	POSSIBLE HIGH-GRADE GLANDULAR LESION
<u>SPECIFIC DIAGNOSIS</u>	The specimen contains atypical glandular cells, suspicious for, but not diagnostic of, adenocarcinoma. It is not certain whether the cells are endocervical or endometrial in origin. An endocervical component is present.
<u>RECOMMENDATION</u>	Further investigation is recommended.

GYNAECOLOGICAL CYTOLOGY

<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	POSSIBLE HIGH-GRADE GLANDULAR LESION
<u>SPECIFIC DIAGNOSIS</u>	The specimen contains high endocervical cellular material displaying atypia of undetermined significance. The possibility that this material represents adenocarcinoma in situ cannot be excluded.
<u>RECOMMENDATION</u>	Further investigation is recommended.

GYNAECOLOGICAL CYTOLOGY

<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	LOW-GRADE SQUAMOUS INTRAEPITHELIAL LESION
<u>SPECIFIC DIAGNOSIS</u>	The specimen contains squamous cells with changes consistent with HPV effect.
<u>RECOMMENDATION</u>	Please repeat the smear in 12 months.

GYNAECOLOGICAL CYTOLOGY

<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	HIGH-GRADE SQUAMOUS INTRAEPITHELIAL LESION
<u>SPECIFIC DIAGNOSIS</u>	The specimen contains squamous cells with changes consistent with CIN 2.
<u>RECOMMENDATION</u>	Referral for colposcopic evaluation is recommended.

GYNAECOLOGICAL CYTOLOGY

<u>SPECIMEN</u>	Cervix — Conventional Smear
<u>RESULT</u>	UNSATISFACTORY
<u>SPECIFIC DIAGNOSIS</u>	There is extensive obscuring inflammation.
<u>RECOMMENDATION</u>	Please repeat the smear in 6–12 weeks.

Appendix 6

Principles of screening

Population screening is the systematic application of a suitable screening test to identify individuals at risk of a specific condition/disorder that warrants direct preventive action. It is undertaken amongst asymptomatic individuals. Importantly, population screening is an organised process that involves call and recall of the population to regular screening, as an aid to early detection and appropriate follow-up of people requiring further treatment.

As such, population screening differs significantly from dealing with symptomatic patients, or even individual case finding in asymptomatic patients with certain risk factors.

The World Health Organization has developed a set of principles that govern the implementation of screening programs at the population level (Wilson and Junger 1968). The principles are:

- The condition should be an important health problem.
- There should be a recognisable latent or early symptomatic stage.
- The natural history of the condition, including the development from latent to declared disease, should be adequately understood.
- There should be an accepted treatment for patients with recognised disease.
- There should be a suitable test or examination.
- The test should be acceptable to the population.
- There should be an agreed policy on whom to treat as patients.
- Facilities for diagnosis and treatment should be available.
- The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
- Case finding should be a continuing process, and not a once-and-for-all project.

Appendix 7

Outcome after a cytological prediction of low-grade abnormality in 1999

A report to the Low-Grade Working Group for the Review of *Screening to Prevent Cervical Cancer: Guidelines for the Management of Women with Screen Detected Abnormalities* (NHMRC 1994)

Dr Heather Mitchell
Victorian Cervical Cytology Registry

Data provided by the Australian Pap test registries

1. Aim

To describe the outcome, over a 24-month period, for the following three groups of women with cytological predictions of a low-grade epithelial abnormality (LGEA) during 1999:

- i) nonspecific minor change (NSMC).
- ii) HPV effect.
- iii) CIN 1, possible CIN 1, and equivocal CIN.

2. Method

A specification for the study was developed and the Australian Pap test registries (PTRs) were approached to participate.

The allocation of women to the three groups was based on the woman's first cytology report as known to the registry in 1999. As none of the PTRs separates cytology reports of definite CIN 1 from possible CIN 1 or equivocal CIN, in this report the CIN 1 group comprises all of these.

The outcome of most interest was that which would incur a definite detrimental effect to the woman if the diagnosis was delayed. This was considered to be a 'true' disease state of microinvasive cervical cancer (Stage 1a). Where cytology fails to predict this degree of abnormality in an asymptomatic woman and the recommended management is for repeat cytology, there is a risk of the woman suffering an adverse outcome in the interim. This is because during the time period to the repeat cytology, the abnormality may progress and subsequently require more extensive surgery with a poorer prognosis.

A 'true' disease state of invasive cervical cancer (Stage 1b or worse) was not accorded equal status to microinvasive cervical cancer because of the substantial probability that women with invasive cervical cancer would have signs and/or symptoms of the malignancy, and the investigation of these signs and/or symptoms would proceed despite the LGEA cytology report.

Also, a biopsy finding of high-grade intraepithelial abnormality (CIN 2, CIN 2/3, CIN 3, AIS) was not accorded similar status to microinvasive cervical cancer because of the high probability of regression of these intraepithelial lesions.

While the main outcome of interest was disease of the cervix, information on uterine malignancies was also sought. Information on other uterine histology was not requested.

The outcome of women was subdivided into two time periods: cross-sectional information (describing the profile of cervical histology reports in the 6-month period after the index cytology report¹⁰) and longitudinal information which, for women who did not have a cervical biopsy in the first six months, describes the outcome over a 24-month period. If a cervical biopsy was performed in the six to 24 month period, this took precedence over cytology.

Where a woman had multiple possible endpoints of interest within a time period (eg two cervical biopsies within six months of the cytology report), the worst outcome was used. If a woman had a cervical biopsy in the first six months reported as less than cancer but had malignant histology in the 6–24 months, the outcome for this woman was based on the malignant biopsy performed during the 6–24 month period.

All age-stratified information in this report uses the age of the woman at the time of the index cytology. Separate information was sought for women aged <30 years at the time of the index cytology, and women aged 30+ years at the time of the index cytology. No upper or lower age limits were specified.

¹⁰ The index cytology report is defined as the first cytology report for the woman in 1999.

3. Results

Seven PTRs provided data, being the Australian Capital Territory, New South Wales, Queensland¹¹, South Australia, Tasmania, Victoria and Western Australia. The willing cooperation of the staff from these registries, particularly Belinda Seeto, Nerida Steel, Penny Iosifidis, Nathan Dunn, Paul Chandler and Peter Couvee, in providing the raw data is most gratefully acknowledged.

Thus the information in this report essentially relates to an Australia-wide picture; only the Northern Territory, which screens on an annual basis <20,000 women or <1% of all screening performed in Australia (AIHW 2002), is not included. For ease of expression, the data in this report will be referred to as Australian.

3.1 Frequency of use

During 1999, a total of 2,000,896 women were screened in Australia. Of these, 90,566 (4.5%) had an LGEA as their first cytology report during the year.

The distribution by age group and degree of LGEA is shown in Table A7.1.

Table A7.1 Proportion of women with LGEA cytology reports, by age and type of LGEA report, 1999

Age group	Number and percentage of women with index cytology in 1999 of:						
	NSMC		HPV		CIN 1		Total
< 30 yrs	22,587	(39%)	8473	(60%)	10,787	(58%)	
30+ yrs	35,267	(61%)	5670	(40%)	7782	(42%)	48,719
Total	57,854	(100%)	14,143	(100%)	18,569	(100%)	90,566

Nonspecific minor change was the most common type of LGEA, accounting for 64% (57,854/90,566) of all LGEA reports. HPV accounted for 16% of the LGEA reports, and CIN 1 for 21%.

As shown in Table A7.1, women aged 30+ years comprised 61% (35,267/57,854) of the NSMC reports, but only around 40% of the HPV and CIN 1 reports.

3.2 Geographic variation

There was substantial variation between the states and territories in the frequency of use of LGEA cytology reports, as shown in Table A7.2.

¹¹ As the Queensland Registry only commenced operation in February 1999, the selection of women for the study was made over the 12-month period February 1999 to February 2000.

Table A7.2 Proportion of women with LGEA cytology reports, by region and type of LGEA report, 1999

Geographical area	Percentage of women with index cytology in 1999 reported as:			Total
	NSMC	HPV	CIN 1	
Region 1	1.84	0.63	1.30	3.78
Region 2	2.48	0.87	0.60	3.95
Region 3	2.50	0.76	0.70	3.97
Region 4	3.15	0.82	0.71	4.68
Region 5	2.92	0.79	1.17	4.88
Region 6	3.46	0.62	1.01	5.10
Region 7	4.37	0.56	0.66	5.59
Australia	2.89	0.71	0.93	4.53

The wide variation in the prevalence of use of the various LGEA cytology reports is consistent with differing criteria being applied by cytopathologists, particularly as to what constitutes NSMC and CIN 1.

If the prevalence of Region 1 were applied to all of Australia, then 75,634 screened women would receive LGEA cytology reports each year. If the prevalence of Region 7 were applied to all of Australia, then 111,850 screened women would receive LGEA cytology reports each year.

3.3 Women with no further information

Some women had no further cervical cytology or histology known to the local PTR during the 24 months of follow-up. Women whose only cytology and histology during the 24 months of follow-up was reported as unsatisfactory are considered to have no further information.

The number and proportion of these women are shown in Table A7.3.

Table A7.3 Proportion of women with no further information, by age and type of LGEA report

Age group	Index cytology reported as		
	NSMC	HPV	CIN 1
<30 yrs	22% (4895 / 22,587)	22% (1822 / 8473)	11% (1216 / 10,787)
30+ yrs	13% (4414 / 35,267)	13% (719 / 5670)	10% (791 / 7782)
Total	16% (9309 / 57,854)	18% (2541 / 14,143)	11% (2007 / 18,569)

It is considered unlikely that cervical cancer was diagnosed among the 13,857 women with no further information during the 24 months of follow-up. If cervical cancer had been diagnosed on cytology or histology, this information should have been provided by the pathology laboratory to the local PTR under the usual method of notification.

All remaining analyses in this report use the 76,709 women with further information as the denominator. This represents 48,545 women with NSMC, 11,602 women with HPV, and 16,562 women with CIN 1.

3.4 Cross-sectional information

Table A7.4 shows the percentage of women undergoing a cervical biopsy within six months of the index cytology.

Table A7.4 Proportion of women undergoing cervical biopsy within six months, by age and type of LGEA report

Age group	Index cytology reported as:		
	NSMC	HPV	CIN 1
<30 yrs	16% (2905 / 17,692)	22% (1477 / 6651)	57% (5461 / 9571)
30+ yrs	14% (4359 / 30,853)	20% (1005 / 4951)	52% (3600 / 6991)
Total	15% (7264 / 48,545)	21% (2482 / 11,602)	55% (9061 / 16,562)

Fifteen per cent of women with NSMC as their index cytology had a biopsy within six months of this report. The current management recommended by NHMRC for women with this degree of abnormality on their Pap smear is to repeat the cytology every 12 months until it either returns to normal or becomes more abnormal. The data in Table A7.4 suggest substantial noncompliance with the current NHMRC recommendation.

The NHMRC guidelines recommend colposcopy after three HPV cytology reports over a 12-month interval. Twenty-one per cent of the women with HPV cytology in this study had a biopsy within six months of the smear. This could be consistent with the NHMRC guidelines.

The NHMRC guidelines recommend colposcopy and, if indicated, directed biopsy after a cytology report of definite CIN 1. As the PTRs do not distinguish between possible and definite CIN 1 in their coding, it is difficult to comment as to whether the data in Table A7.4 are consistent with the management recommended by the NHMRC guidelines. Anecdotal feedback would suggest that more than 55% of all CIN 1 reports are of definite CIN 1; if this impression is correct, then the above figures may indicate undercompliance with the NHMRC guidelines. Alternatively, all women with cytology of definite CIN 1 may have undergone a colposcopy, but in the absence of an abnormality being confirmed, a biopsy may not have been taken. The PTRs do not collect comprehensive colposcopy information, and information on known colposcopy findings was not sought as part of this study.

Because a similar proportion of the women in each of the three groups did not undergo a biopsy within six months of the index cytology, a detection bias is operating. It is not possible to reduce or eliminate this bias by statistical adjustment. In effect, the three groups did not undergo the same intervention (a colposcopy and directed biopsy to detect asymptomatic disease).

The only outcome that is not subjected to this detection bias is that of invasive cancer. This is because invasive cancer is typically a disease state manifest by symptoms and/or signs which share an approximately equal probability of being investigated in each of the three groups.

Table A7.5 shows the results of cervical biopsies performed within six months of the index cytology.

Table A7.5 Profile of histology results within six months, by age and type of LGEA report

Age group	Histology results within 6 months of index cytology	No. of women, after cytology prediction on index smear of			Total
		NSMC	HPV	CIN 1	
<30 yrs	High-grade disease — endometrial cancer	–	–	–	– (0.0%)
	High-grade disease — cervical cancer				
	– microinvasive squamous	1	–	–	1 (<0.1%)
	– microinvasive adenocarcinoma	–	–	–	– (0.0%)
	– invasive squamous	1	–	1	2 (<0.1%)
	– invasive adenocarcinoma	1	1	2	4 (<0.1%)
	High-grade intraepithelial disease ^a	577	245	1611	2433 (25%)
	Abnormal but less than high-grade disease ^b	1664	971	3079	5714 (58%)
Normal or benign	661	260	768	1689 (17%)	
Total	2905	1477	5461	9843 (100%)	
30+ yrs	High-grade disease — endometrial cancer	8	–	–	8 (<0.1%)
	High-grade disease — cervical cancer				
	– microinvasive squamous	1	–	1	2 (<0.1%)
	– microinvasive adenocarcinoma	–	–	1	1 (<0.1%)
	– invasive squamous	2	–	4	6 (<0.1%)
	– invasive adenocarcinoma	4	–	–	4 (<0.1%)
	High-grade intraepithelial disease	444	124	824	1392 (16%)
	Abnormal but less than high-grade disease	2160	611	1981	4752 (53%)
Normal or benign	1,740	270	789	2799 (31%)	
Total	4359	1005	3600	8964 (100%)	

^a Includes CIN 2, CIN 2/3, CIN 3, adenocarcinoma in situ.

^b Includes equivocal dysplasia, endocervical dysplasia not otherwise specified, mild dysplasia, CIN 1, atypia, HPV, equivocal HPV, mild nuclear changes, possible low-grade glandular abnormality, low-grade glandular abnormality.

The high proportion of women with abnormal cervical biopsies performed within six months of the index cytology is not surprising, given that a biopsy is only taken if the colposcopy shows an area of abnormality. Nevertheless, it is noted that almost one-third of the biopsies taken from women aged 30+ were not reported as showing an abnormality.

The detection bias described previously precludes a direct comparison of outcomes relating to asymptomatic disease states¹² for the three groups of LGEA within six months of the index cytology.

Four women were diagnosed with microinvasive cancer of the cervix within six months of their index cytology report. This represents one woman in 4702 who had a cervical biopsy, or one woman in 19,177 from the combined cohort of 76,709 women for whom further information over the 24 months was available. The LGEA cytology may have under-represented the ‘true’ disease state of these women, either because the most abnormal cervical cells were not present on the smear, or because the cytopathologist undergraded the degree of abnormality.

¹² Asymptomatic disease states would particularly include ‘high-grade intraepithelial abnormality,’ ‘abnormal but less than high-grade disease’ and ‘microinvasive cancer’.

3.5 Longitudinal information

Separate information was requested for histology and cervical cytology during the 6–24-month period, with histology being given precedence over cytology. Table A7.6 shows the results of cervical biopsies performed within 6–24 months of the index cytology.

Table A7.6 Profile of histology results within 6–24 months, by age and type of LGEA report

Age group	Histology results within 6–24 months of index cytology	No. of women, after cytology prediction on index smear of			Total
		NSMC	HPV	CIN 1	
<30 yrs	High-grade disease — endometrial cancer	–	–	–	– (0.0%)
	High-grade disease — cervical cancer				
	– microinvasive squamous	1	–	1	2 (<0.1%)
	– microinvasive adenocarcinoma	–	–	–	– (0.0%)
	– invasive squamous	1	2	1	4 (0.2%)
	– invasive adenocarcinoma	1	1	–	2 (<0.1%)
	High-grade intraepithelial disease	923	275	386	1584 (32%)
	Abnormal but less than high-grade disease	1241	665	519	2425 (49%)
Normal or benign	497	226	200	923 (19%)	
Total	2664	1169	1107	4940 (100%)	
30+ yrs	High-grade disease — endometrial cancer	1	–	–	1 (<0.1%)
	High-grade disease — cervical cancer				
	– microinvasive squamous	2	–	1	3 (0.1%)
	– microinvasive adenocarcinoma	1	–	–	1 (<0.1%)
	– invasive squamous	6	–	–	6 (0.2%)
	– invasive adenocarcinoma	3	–	–	3 (0.1%)
	High-grade intraepithelial disease	601	137	207	945 (20%)
	Abnormal but less than high-grade disease	1531	431	335	2297 (48%)
Normal or benign	1,171	203	175	1,549 (32%)	
Total	3,316	771	718	4,805 (100%)	

Six women were diagnosed with microinvasive cancer of the cervix within 6–24 months of their index cytology report. This represents one in 1624 women who were biopsied in the 6–24-month period, or one woman in 12,785 from the combined cohort of 76,709 women for whom further information over the 24 months was available.

In addition to the reasons previously proposed as to why cytology in women with a ‘true’ disease state of microinvasive carcinoma may be reported as only LGEA (namely, sampling difficulties or undergrading), there is one further reason that could explain a later diagnosis of cancer. This is that the disease may have progressed in the interval since the index cytology was collected.

Endometrial cancer was diagnosed histologically in nine women, all of whom had an index cytology report of NSMC and all of who were aged 30+ years. Eight women were within six months of an NSMC cytology report (Table A7.5), and one woman was in the 6–24-month period (Table A7.6). It is probable that the eight women in Table A7.5 were symptomatic around the time of the index cytology, and that investigation of the symptoms led to the diagnosis of endometrial malignancy. Cervical cytology is known to have a low sensitivity for predicting endometrial malignancy (Mitchell et al 1993).

No cases of endometrial cancer occurred in the women who had HPV and CIN 1 as their index cytology.

Table A7.7 shows the profile of the worst cytology results performed within 24 months by degree of cytological abnormality on the index smear. Women appear in Table A7.7 only if there was no cervical biopsy during the 24 months (ie they do not appear in Table A7.5 or A7.6).

Table A7.7 Profile of worst cytology results within 0–24 months, by age and type of LGEA report

Age group	Worst cytology result within 6–24 months of index cytology	No. of women, after cytology prediction on index smear of			Total
		NSMC	HPV	CIN 1	
<30 yrs	High-grade disease — cancer	–	–	–	– (0.0%)
	High-grade disease — intraepithelial	87	44	92	223 (1%)
	Possible high-grade disease ('inconclusive')	115	23	40	178 (<1%)
	Low-grade disease				
	– CIN 1	404	239	548	1191 (6%)
	– HPV effect	485	558	247	1290 (7%)
	– NSMC	1609	553	421	2583 (14%)
	– other	104	32	6	142 (<1%)
	Negative	9319	2556	1649	13,524 (71%)
Total	12,123	4005	3003	19,131 (100%)	
30+ yrs	High-grade disease — cancer	1 ^a	–	–	1 (<0.1%)
	High-grade disease — intraepithelial	92	33	65	190 (0.7%)
	Possible high-grade disease ('inconclusive')	128	20	55	203 (0.7%)
	Low-grade disease				
	– CIN 1	387	179	515	1081 (4%)
	– HPV effect	439	574	135	1148 (4%)
	– NSMC	3589	425	393	4407 (15%)
	– other	149	20	6	175 (0.6%)
	Negative	18,393	1924	1504	21,821 (75%)
Total	23,178	3175	2673	29,026 (100%)	

^a The cytology predicted an endometrial malignancy.

The profile of cytology results in Table A7.7 indicates that the dominant feature in the women who were not biopsied was a return to negative cytology. The very low proportion of women having high-grade cytology (1%–2%) is explained by the fact that most women with high-grade cytology would be referred for colposcopy and, if indicated, directed biopsy and would therefore appear in Table A7.5 or A7.6.

3.6 Composite results over the 24-month period

Table A7.8 combines the information in Tables A7.5–A7.7 and represents a summary outcome over the 24 months of the study for the women.

Table A7.8 Composite results over the 24-month period (number and proportion)

Age group	Summary outcome over a 24-month period after the index cytology	Number (%) of women, after cytology prediction on index smear of		
		NSMC	HPV	CIN 1
<30 yrs	High-grade disease — endometrial cancer	–	–	–
	High-grade disease — cervical cancer	6 (<0.1%)	4 (<0.1%)	5 (<0.1%)
	High-grade disease — intraepithelial ^a	1702 (10%)	587 (9%)	2129 (22%)
	Low-grade disease	5507 (31%)	3018 (45%)	4820 (50%)
	Normal or benign	10,477 (59%)	3042 (46%)	2617 (27%)
	Total	17,692 (100%)	6651 (100%)	9571 (100%)
30+ yrs	High-grade disease — endometrial cancer	10 (<0.1%)	–	–
	High-grade disease — cervical cancer	19 (<0.1%)	–	7 (0.1%)
	High-grade disease — intraepithelial	1265 (4%)	314 (6%)	1151 (16%)
	Low-grade disease	8255 (27%)	2240 (45%)	3365 (48%)
	Normal or benign	21,304 (69%)	2397 (48%)	2468 (35%)
	Total	30,853 (100%)	4951 (100%)	6991 (100%)

^a Includes cytology reports of possible high-grade abnormality ('inconclusive')

The higher proportion of women having high-grade intraepithelial disease in the CIN 1 group than in the NSMC or HPV groups is consistent with the detection bias described previously (see Section 3.4 of this appendix) or with these women having a more severe degree of LGEA.

Nevertheless, in all three groups and in both age groups the dominant outcome state (accounting for 80%–95% of the outcomes) was of no abnormality or only low-grade disease.

Table A7.9 presents the information displayed in Table A7.8 as rates per 1000 women. This facilitates comparison between the three types of LGEA cytology.

Table A7.9 Composite results over the 24-month period (rates per 1000 women)

Age group	Outcome over a 24-month period after the index cytology	Rate per 1000 women, after cytology prediction on index smear of		
		NSMC	HPV	CIN 1
<30 yrs	High-grade disease — endometrial cancer	0.0	0.0	0.0
	High-grade disease — cervical cancer	0.3	0.6	0.5
	High-grade disease — intraepithelial	95.0	88.3	222.4
	Low-grade disease	307.3	453.8	503.6
	Negative	584.7	457.4	273.4
30+ yrs	High-grade disease — endometrial cancer	0.3	0.0	0.0
	High-grade disease — cervical cancer	0.6	0.0	1.0
	High-grade disease — intraepithelial	41.0	63.4	164.6
	Low-grade disease	267.6	452.4	481.3
	Negative	690.5	484.1	353.0

3.7 Known history of women diagnosed with microinvasive cervical cancer

Table A7.10 describes the information that is known about the histories of the women who were diagnosed with microinvasive cancer during the study.

With the exception of case 6, all information in Table A7.10 came from PTRs that had been in operation for more than 4 years at the time of the index LGEA cytology.

Table A7.10 Screening history of women diagnosed with microinvasive cancer after an LGEA report

Case	Age at index cytology	Interval from index cytology	History
1	23 yrs	22 months	2/98 Cytology: negative 8/99 Cytology: NSMC 4/00 Cytology: inconclusive 5/00 Punch biopsy: CIN 1+HPV 12/00 Cytology: CIN 3 2/01 Punch biopsy: CIN 3 5/01 LEEP biopsy: CIN 3 6/01 Cone biopsy: microinvasive squamous carcinoma
2	25 yrs	23 months	8/94 Cytology: negative 6/99 Cytology: CIN 1 3/00 Cytology: CIN 3 4/00 Punch biopsy: HPV 4/01 Cytology: CIN 3 4/01 Target biopsy: CIN 3 5/01 Cone biopsy: microinvasive squamous carcinoma
3	26 yrs	3 months	8/94 Cytology: negative 11/96 Cytology: negative 3/98 Cytology: negative 12/99 Cytology: NSMC 2/00 Punch biopsy: CIN 3 3/00 LLETZ: microinvasive squamous carcinoma
4	30 yrs	7 months	9/96 Cytology: negative 1/99 Cytology: CIN 1 2/99 Punch biopsy: CIN 3 3/99 LLETZ/LEEP 7/99 Cytology: CIN 2 8/99 Cone biopsy: microinvasive squamous carcinoma
5	32 yrs	9 months	5/95 Cytology: negative 3/97 Cytology: negative 2/99 Cytology: NSMC 8/99 Cytology: inconclusive 11/99 Cone biopsy: microinvasive squamous carcinoma
6	33 yrs	21 months	5/99 Cytology: NSMC 12/00 Cytology: CIN 3 2/01 Cone biopsy: microinvasive squamous carcinoma
7	40 yrs	2 months	8/94 Cytology: NSMC 6/95 Cytology: negative 1/99 Cytology: CIN 1 2/99 Punch biopsy: CIN 3 + HPV 3/99 Cone biopsy: microinvasive adenocarcinoma
8	41 yrs	<1 month	4/96 Cytology: negative 3/99 Cytology: CIN 1 + HPV 3/99 Cone biopsy: microinvasive squamous carcinoma

Table A7.10 Screening history of women diagnosed with microinvasive cancer after an LGEA report (continued)

Case	Age at index cytology	Interval from index cytology	History
9	47 yrs	5 months	6/93 Cytology: negative
			4/94 Cytology: NSMC
			1/95 Cytology: negative
			3/96 Cytology: NSMC
			5/96 Cytology: negative
			3/98 Cytology: negative
			4/99 Cytology: NSMC
			8/99 Cytology: inconclusive
			9/99 Cone biopsy: microinvasive squamous carcinoma
10	65 yrs	22 months	4/94 Cytology: negative
			1/95 Cytology: negative
			3/96 Cytology: inconclusive
			4/96 Cytology: NSMC
			4/96 Punch biopsy: CIN 2 + HPV
			4/96 LLETZ: CIN 1 + HPV
			7/96 Cytology: inconclusive
			12/96 Cytology: negative
			5/97 Cytology: negative
			6/98 Cytology: NSMC
			12/98 Cytology: negative
			11/99 Cytology: NSMC
			5/00 Cytology: NSMC
			11/00 Cytology: inconclusive
			3/01 LLETZ: negative
			7/01 Cytology: inconclusive (glandular)
9/01 Hysterectomy: microinvasive adenocarcinoma			

Multiple biopsies were required for cases 1, 2, 4 and 10 before the diagnosis of microinvasive malignancy was made, with abnormal cytology persisting after the earlier biopsies.

Four women with microinvasive cancer were close to two years after the initial LGEA cytology when the malignancy was diagnosed, being cases 1, 2, 6 and 10. All four of these women had more abnormal cytology in the intervening period, three having cytology predictions of CIN 3, and one of inconclusive — possible high-grade disease.

4. Outcome of cervical cancer

It is difficult to make an exact comparison between the findings of this Australian study and the published literature because of the international variations in the terminology used to report cervical cytology. In relation to The Bethesda System for reporting cervical cytology, our combined HPV and CIN 1 groups broadly equate to low-grade SIL (squamous intraepithelial lesion). Our NSMC group is probably encompassed as a part of ASCUS (atypical squamous cells of undetermined significance) group; however, there is no exact correlation, as ASCUS probably also encompasses the Australian 'inconclusive' category.

This Australian study documented 20 cases of cervical cancer during the first six months after the index cytology, representing one woman in 3835. By contrast, five cancers were present at inception in the LSIL arm of the ALTS study, representing one woman in 314 (Sherman et al 2003b).

An outcome of cervical cancer was experienced by 0.05% (95% CI, 0.03 to 0.07) of the women with NSMC index cytology, 0.03% (95% CI, 0.00 to 0.07) of the women with HPV index cytology, and 0.07% (95% CI, 0.03 to 0.11) of the women with CIN 1 cytology. The confidence intervals provide an indication of the precision of these statistics. If this study were repeated using women screened in a different year (eg 2001), it is likely that there would be some variation in the figures; the variation should be within the 95% confidence intervals.

As this is an observational study with unequal investigation and management of the women within the three subgroups of LGEA cytology, it is difficult to further interpret the findings. It is possible that treatment of a larger proportion of the women with CIN cytology may have differentially reduced the chance of some of these women developing cervical cancer during the period of interest.

5. Conclusions

1. A total of 90,566 women received an LGEA report on their first Pap test in 1999, representing 4.5% of all women screened in Australia in that year.
2. Overall, NSMC accounted for 64% of the LGEA reports, HPV accounted for 16%, and CIN 1 accounted for 21%. There was substantial age variation in these proportions.
3. There was substantial variation between states and territories in the frequency of use of the three types of LGEA, consistent with poor repeatability in the use of these cytological reports.
4. The proportion of women with no further information during the 24-month period of follow-up was 16% for index cytology of NSMC, 18% for HPV and 11% for CIN 1.
5. During the first six months of follow-up, a detection bias existed for the CIN 1 group due to the high frequency of cervical biopsy in this group of women. This detection bias cannot be reduced or eliminated by statistical adjustment. A direct comparison of outcomes relating to asymptomatic disease states for the three groups of LGEA within six months of the index cytology is therefore invalid.
6. Among women whose index cytology was reported as NSMC, 15% had a cervical biopsy within six months. This suggests that the current management recommended by NHMRC for these women (repeat cytology in 12 months) is not well adhered to.
7. Microinvasive cancer (stage 1a) was an infrequent outcome for all three types of LGEA on cytology. Over the subsequent 24 months, six women out of the 48,545 women with NSMC cytology were diagnosed with microinvasive cancer, as were four women out of the 16,562 women with CIN 1 cytology. None of the 11,602 women with HPV cytology were diagnosed with microinvasive cancer during the 24 months.
8. Four women were diagnosed with microinvasive cervical cancer (Stage 1a) within six months of their index cytology report. This represents one woman in 4702 who had a cervical biopsy, or one woman in 19,177 from the combined cohort of 76,709 women for whom further information was available during the 24 months.
9. Thirty-one women were diagnosed with invasive cervical cancer (Stage 1b or worse) during the 24 months after the LGEA cytology. Nineteen of these followed an index cytology report of NSMC, four followed an HPV report, and eight followed a CIN 1 report. Thirteen (42%) of the 31 invasive cervical cancers were adenocarcinomas, and 18 (58%) were squamous.
10. The dominant outcome state (accounting for 80%–95% of the outcomes) for both age groups (<30 yrs, 30+ yrs) and for the three types of LGEA cytology was of no abnormality or only low-grade disease during the 24 months of follow-up.
11. The risk of an outcome of cervical cancer (microinvasive and invasive) over a 24-month period was very low.
12. The information in this report could be used to better inform women and practitioners about the significance of a LGEA cytology report.

Table A7.11 Criteria for the selection of women for each registry

State/territory	Nonspecific minor change (NSMC)	HPV	CIN 1 ± HPV
Australian Capital Territory	S3 and W1 or W2 or W99 and E0 or E1 or E2 or E99 and O1 or O99	S1 or S2 or S3 or S99 and W3 and E0 or E1 or E2 or E99 and O1 or O99	S5 and W1 or W2 or W3 or W99 and E0 or E1 or E2 or E99 and O1 or O99
New South Wales	S3 and W1 or W2 and E0 or E1 or E2 and O1	S1 or S2 or S3 and W3 and E0 or E1 or E2 and O1	S5 and W1 or W2 or W3 and E0 or E1 or E2 and O1
Northern Territory	S3 and W0 or W1 and E0 or E1 or E2 and M- or M0 or M1 or M2 and O0	S1 or S2 or S3 and W2 and E0 or E1 or E2 and M- or M0 or M1 or M2 and O0	S5 and W0 or W1 or W2 and E0 or E1 or E2 and M- or M0 or M1 or M2 and O0
Queensland	S3 and W1 or W2 and E0 or E1 or E2 and O1	S1 or S2 or S3 and W3 and E0 or E1 or E2 and O1	S5 and W1 or W2 or W3 and E0 or E1 or E2 and O1
South Australia	S3 and W0 or W1 and E0 or E1 or E2 or E9 and M- or M0 or M1 or M2 and O0	S1 or S2 or S3 and W2 and E0 or E1 or E2 or E9 and M- or M0 or M1 or M2 and O0	S5 and W0 or W1 or W2 and E0 or E1 or E2 or E9 and M- or M0 or M1 or M2 and O0
Tasmania	S3 and W1 or W2 and E1 or E2 or E3 and O1	S1 or S2 or S3 and W3 and E1 or E2 or E3 and O1	S5 and W1 or W2 or W3 and E1 or E2 or E3 and O1
Victoria	S3 and W- or W1 or W2 and E- or E0 or E1 or E2 and O- or O1	S1 or S2 or S3 and W3 and E- or E0 or E1 or E2 and O- or O1	S5 and W- or W1 or W2 or W3 and E- or E0 or E1 or E2 and O- or O1
Western Australia	S2 and W1 or W2 and E- or E0 or E1 and M1 or M2 and O1	S1 or S2 and W3 and E- or E0 or E1 and M1 or M2 and O1	S3 and W1 or W2 or W3 and E- or E0 or E1 and M1 or M2 and O1

Note: The code displayed in bold is an essential prerequisite for selection into the group.

Appendix 8

Outcome after a cytological prediction of glandular abnormality in 1999

A report to the Low-Grade Working Group for the Review of *Screening to Prevent Cervical Cancer: Guidelines for the Management of Women with Screen Detected Abnormalities* (NHMRC 1994)

Dr Heather Mitchell
Victorian Cervical Cytology Registry

Data provided by the Australian Pap test registries

1. Aim

To describe the outcome over a 24-month period for the following three groups of women with cytological predictions of glandular abnormality during 1999:

- i) Atypical endocervical cells — minor atypia
- ii) Atypical endocervical cells — possible adenocarcinoma in situ (AIS). Note that this type of cytology report may have been referred to as ‘inconclusive — possible high-grade lesion.’
- iii) Atypical endocervical cells — AIS.

2. Method

A specification for the study was developed and the Australian Pap test registries (PTRs) were approached to participate.

The allocation of women to the three groups was based on the woman’s first cytology report as known to each registry in 1999. The criteria for the identification of the three groups of women from each registry are shown in Table A8.8. For the ‘minor atypia’ category in Table A8.8, the nominated criteria represent a best approximation. The nominated criteria for minor atypia encompass codes with descriptors such as atypia, abnormal endocervical cells not specifically described as a high-grade lesion, minor nonspecific changes, and mild/moderate dysplasia. Minor reactive and inflammatory changes in endocervical cells were excluded, these being considered to not represent changes with a premalignant potential.

Information was sought only on the outcome after a cytological prediction of pure glandular abnormality. Cytological predictions of mixed disease (ie those having both a squamous and glandular component) were considered easier to investigate and were excluded from the study.

The outcome of women was subdivided into two time periods: cross-sectional information (describing the profile of cervical histology reports in the 6-month period after the index cytology report¹³), and longitudinal information which, for women who did not have a cervical biopsy in the first six months, describes the outcome over a 24-month period. If a cervical biopsy was performed in the 6–24-month period, this took precedence over cytology.

The outcome event of interest was a subsequent diagnosis of high-grade disease (glandular, squamous or mixed), encompassing cancer (cervical or endometrial), AIS, CIN 2, CIN 2/3 and CIN 3. While the main outcome of interest was disease of the cervix, uterine malignancy was included as an outcome event; no other uterine histology was included as an outcome.

Where a woman had multiple possible endpoints of interest within a time period (eg two cervical biopsies within six months of the cytology report), the worst outcome was used. For example, a biopsy of AIS took precedence over a negative biopsy. If a woman had a cervical biopsy in the first six months that was reported as less than cancer or high-grade disease and also had a biopsy in the 6–24-month period that was reported as cancer or high-grade disease, the outcome of this woman was based on the more abnormal biopsy performed during the 6–24-month period.

All age-stratified information in this report uses the age of the woman at the time of the index cytology. Separate information was sought for women aged <30 years at the time of the index cytology, and women aged 30+ years at the time of the index cytology. No upper or lower age limits were specified.

¹³ The index cytology report is defined as the first cytology report for the woman in 1999.

3. Results

Seven PTRs provided data, being the Australian Capital Territory, New South Wales, Queensland¹⁴, South Australia, Tasmania, Victoria and Western Australia. The willing cooperation of the staff from these registries, particularly Belinda Seeto, Nerida Steel, Penny Iosifidis, Nathan Dunn, Paul Chandler and Peter Couvee, in providing the raw data is most gratefully acknowledged.

Thus the information in this report essentially relates to an Australia-wide picture; only the Northern Territory, which screens on an annual basis <20,000 women or <1% of all screening performed in Australia (AIHW 2002), is not included. For ease of expression, the data in this report will be referred to as Australian.

3.1 Frequency of use

A total of 877 women were reported as receiving cytology reports of minor atypia, 307 women with possible AIS, and 129 women with AIS. The ratio of these counts is 6.8:2.4:1.

There was substantial variation between the states and territories in the frequency of use of the three types of reports, as shown in Table A8.1. States and territories have been given the same region number as in the low-grade report (see Appendix 7).

Table A8.1 Proportion of women with glandular abnormalities on cytology, by region of Australia, 1999

Geographical area	Percentage of women with index cytology in 1999 reported as			Total
	Minor atypia	Possible AIS	AIS	
Region 1	0.002	0.033	0.007	0.042
Region 2	0.130	0.014	0.007	0.150
Region 3	0.040	0.029	0.011	0.080
Region 4	0.053	0.005	0.003	0.060
Region 5	0.000	0.024	0.002	0.026
Region 6	0.030	0.006	0.011	0.046
Region 7	0.100	0.013	0.007	0.120
Australia	0.044	0.015	0.006	0.066

No further information was known during the 24-month follow-up period for 85 (9.7%) women with minor atypia, nine (2.9%) women with possible AIS, and three (2.3%) women with AIS.

3.2 Cross-sectional information

Information about histology performed within six months of the index cytology was available for 82% (106/129) of the women with cytology reports of AIS, 40% (124/307) of the women with cytology reports of possible AIS, and 14% (125/877) of the women with cytology reports of minor atypia.

Table A8.2 shows the results of cervical biopsies performed within six months of the index cytology.

¹⁴ As the Queensland PTR only commenced operation in February 1999, the selection of women for the study was made over the 12-month period February 1999 to February 2000.

Table A8.2 Profile of histology results performed within six months, by degree of cytological abnormality

Histology results within 6 months of index cytology	Cytology prediction on index smear		
	Minor atypia	Possible AIS	AIS
High-grade disease — cervical or endometrial cancer	3	13	19
High-grade disease — AIS or mixed adenosquamous high-grade intraepithelial disease	4	17	51
High-grade disease — CIN 2, CIN 2/3 and CIN 3 (ie pure squamous intraepithelial disease)	28	21	11
Abnormal but less than high-grade disease ^a	49	25	11
Normal or benign	41	48	14
Total	125	124	106

^a Includes equivocal dysplasia, endocervical dysplasia NOS, mild dysplasia, CIN 1, atypia, HPV, equivocal HPV, mild nuclear changes, possible low-grade glandular abnormality, low-grade glandular abnormality.

Among the 167 women in Table A8.2 who had a histologic diagnosis of high-grade disease, 35 (21%) had a diagnosis of cancer, 72 (43%) had a diagnosis of AIS or mixed adenosquamous high-grade intraepithelial disease, and 60 (36%) had a diagnosis of purely squamous high-grade intraepithelial disease.

3.3 Longitudinal information

Separate information was requested for histology and cervical cytology during the 6–24-month period, with histology being given precedence over cytology. Table A8.3 shows the results of cervical histology performed within 6–24 months of the index cytology.

Table A8.3 Profile of histology results performed within 6–24 months of the index smear, by degree of cytological abnormality

Histology results within 6–24 months of index cytology	Cytology prediction on index smear		
	Minor atypia	Possible AIS	AIS
High-grade disease — cervical or uterine cancer	2	2	1
High-grade disease — AIS or mixed adenosquamous high-grade intraepithelial disease	7	6	1
High-grade disease — CIN 2, CIN 2/3 and CIN 3 (ie pure squamous intraepithelial disease)	22	3	0
Abnormal but less than high-grade disease	12	5	1
Normal or benign	17	7	0
Total	60	23	3

The data in Table A8.3 shows that among women who were biopsied between six and 24 months after the index cytology report and who were found to have high-grade disease, the dominant morphology was squamous.

Table A8.4 shows the profile of the worst cytology results performed within 24 months by the degree of cytological abnormality on the index smear. Women appear in Table A8.4 only if there was no cervical histology during the 24 months (ie they do not appear in Table A8.2 or A8.3).

Table A8.4 Profile of worst cytology results performed within 0–24 months of the index smear, by degree of cytological abnormality

Worst cytology result within 0–24 months	Cytology prediction on index smear		
	Minor atypia	Possible AIS	AIS
Atypical endocervical cells: glandular cancer	1	0	0
Atypical endocervical cells: AIS	1	0	0
Other abnormality: high-grade ^a	12	7	5
Atypical endocervical cells: possible AIS	1	6	0
Atypical endocervical cells: minor atypia	25	1	2
Other abnormality: low-grade	42	12	1
Normal or benign	525	125	9
Total	607	151	17

^a Includes cytology reports of possible squamous high-grade abnormality ('inconclusive') as well as cytology reports of CIN 2 or CIN 3.

The data in Table A8.4 show that most women who did not have a biopsy had only normal cytology during the 24-month period.

3.4 Composite results over the 24-month period

Table A8.5 combines the information in Tables A8.2–A8.4.

Table A8.5 Composite results over the 24-month period

Outcome over a 24-month period after the index cytology	Cytology prediction on index smear		
	Minor atypia	Possible AIS	AIS
High-grade disease — cancer	6 (<1%)	15 (5%)	20 (16%)
High-grade disease — intraepithelial	75 (9%)	60 (20%)	68 (54%)
Low-grade disease	128 (16%)	43 (15%)	15 (12%)
Normal or benign	583 (74%)	180 (60%)	23 (18%)
Total	792 (100%)	298 (100%)	126 (100%)

Overall, 70% of the women with cytology reports of AIS were confirmed as having high-grade disease. However, this proportion was very much less for women with cytology reports of possible AIS (25% confirmed as high-grade disease) and for women with reports of minor atypia (10% confirmed as high-grade disease).

Table A8.5 shows that 16% of the women with cytology reports of AIS were diagnosed on histology with cancer. This is high in comparison to cytology reports of squamous in situ disease, where the proportion diagnosed with cancer is more typically 3%–4% (VCCR 2001).

3.5 Additional information about women diagnosed with cervical cancer

Table A8.6 provides additional information about 36 women from Tables A8.2 and A8.3 who were diagnosed on histology with cervical cancer.

Table A8.6 Profile of cervical cancers diagnosed among women in the study

Index cytology	Age at index cytology (yrs)	Type of cancer				
		Adeno — microinvasive	Adeno — invasive	Squamous — microinvasive	Squamous — invasive	Other
Minor atypia	20–29	–	2	1	–	–
	30–39	–	1	–	–	–
	40–49	–	–	–	–	–
	50–59	–	–	–	–	–
	60–69	–	–	–	1	–
Possible AIS	20–29	–	1	–	–	–
	30–39	–	2	–	–	1 ^a
	40–49	1	4	2	–	–
	50–59	–	–	2	–	–
	60–69	–	–	–	–	–
AIS	20–29	–	3	–	–	–
	30–39	1	6	1	1	–
	40–49	1	2	–	1	–
	50–59	–	–	–	–	–
	60–69	1	1	–	–	–
Total		4	22	6	3	1

a This cancer was recorded as 'carcinoma — not otherwise specified'

The data in the above table show that 56% (20/36) of the women diagnosed with cervical cancer after a cytological prediction of glandular intraepithelial abnormality were aged <40 years at the time of the cytology report. This is similar to the age distribution of all women who are screened; during 1999, 52% of the women who were screened in Australia were <40 years of age at the time of screening (AIHW 2002).

In addition to the women described in Table A8.6, one woman with an index cytology report of minor atypia had a later malignant cytology report but no biopsy. Endometrial carcinoma was diagnosed in two women (aged 68 and 70) with cytology reports of possible AIS, and in two women (aged 61 and 80) with cytology of AIS.

Table A8.7 provides additional details of the screening history of women diagnosed with cervical cancer after a minor (glandular) atypia report.

Table A8.7 Screening history of women diagnosed with cervical cancer after a minor (glandular) atypia report

Case	Age at index cytology	Region	Interval from index cytology	History
1	29 yrs	7	6 months	8/96 Cytology: negative 7/99 Cytology: minor (glandular) atypia 1/00 Cytology: adenocarcinoma 1/00 Punch biopsy: invasive adenocarcinoma
2	25 yrs	7	2 months	5/94 Cytology: negative 10/95 Cytology: negative 5/96 Cytology: negative 7/98 Cytology: negative 7/99 Cytology: minor (glandular) atypia 8/99 Punch biopsy: CIN 3 9/99 LLETZ: microinvasive squamous carcinoma
3	21 yrs	4	1 month	10/98 Punch biopsy: negative 1/99 Cytology: minor (glandular) atypia 2/99 Biopsy: adenocarcinoma in situ 2/99 Biopsy: invasive adenocarcinoma
4	33 yrs	4	18 months	6/97 Cytology: negative 5/99 Cytology: minor (glandular) atypia 11/00 Cytology: adenocarcinoma in situ 11/00 Biopsy: invasive adenocarcinoma
5	60 yrs	4	1 month	11/99 Cytology: minor (glandular) atypia 12/99 Biopsy: invasive squamous carcinoma
6	86 yrs	2	18 months	12/98 Cytology: CIN 3 12/98 Cytology: invasive adenocarcinoma 1/99 Biopsy: invasive adenocarcinoma 3/99 Biopsy: mild atypia 5/99 Cytology: minor (glandular) atypia 11/00 Cytology: invasive adenocarcinoma

4. Comparison with published literature

Three relevant Australian publications were identified in the refereed literature.

Schoolland et al (1998) reported outcome data on nine cases of 'Inconclusive — possible high-grade epithelial abnormality of glandular type' from a laboratory in Western Australia between January and June 1995. Six of the nine cases had follow-up biopsy information. Five of the six biopsies confirmed high-grade disease.

A further publication from Western Australia (Sparkes et al 2000) gives positive predictive values of 87% (20/23) and 33% (15/45) for cytology reports of AIS and possible high-grade abnormality of endocervical glandular cells respectively for the years 1995–1997. The analysis of biopsy findings was made over periods of one to four years.

Roberts et al (2000) reported biopsy findings for cytology reports of AIS and possible AIS made over a 10-year period (1989–1998) from a laboratory in New South Wales. Because of the large number of reports of low-grade endocervical smears, only data for 1996 were included.

Among cases where biopsy information was known, the histology was reported as high-grade disease for 96% (157/164) of the cytology reports of AIS, and 71% (69/97) for the cytology reports of possible AIS. Only 7% (15/211) of the cytology reports of low-grade endocervical abnormality were followed by biopsy evidence of high-grade disease.

The data published by Roberts et al (2000) are substantially different from the national data presented in this report. This illustrates the problem associated with developing policy on the basis of publications in the refereed literature. Articles from single-site facilities in the refereed literature can overemphasise either very good or very poor results (in this case, very good results). By contrast, nationally compiled data such as that derived from the PTRs present a census of results found 'in the field' and allow for more realistic policy formation.

5. Conclusions

1. Cytology reports of glandular intraepithelial abnormalities were infrequent in Australia in 1999. Cytology reports of possible AIS were more than twice as common as reports of AIS. Cytology reports of minor atypia were seven times as frequent as reports of AIS.
2. When outcome was measured over a 24-month period after the abnormal cytology report, 70% of women with cytology reports of AIS were confirmed as having high-grade disease. For cytology reports of possible AIS, the proportion was 25%. For cytology reports of minor atypia, the proportion was 10%.
3. Cervical or uterine malignancy was diagnosed on histology in 16% (20/129) of the women with AIS cytology reports, in 5% (15/306) of the women with possible AIS cytology, and in <1% (5/877) of the women with cytology reported as minor atypia.
4. Most of the women with cytology reports of AIS or possible AIS who were confirmed as having histologic high-grade disease had this confirmatory investigation performed in the 6 months after the cytology report.
5. Squamous disease was the dominant morphology found in women with histologic high-grade disease during the 6–24 months after a cytology report of minor atypia or possible AIS.
6. The age distribution of the women with cervical cancer in this study was similar to the age distribution of all women screened in 1999.
7. The data in this report could be used to better inform women and practitioners about the significance of an abnormal glandular cytology report.

Table A8.8 Criteria for the selection of women for each registry

State/ territory	Minor atypia	Possible AIS	AIS
Australian Capital Territory	S1 or S2 or S99 <u>and</u> W1 or W99 <u>and</u> E3 <u>and</u> O1 or O99	S1 or S2 or S99 <u>and</u> W1 or W99 <u>and</u> E4 <u>and</u> O1 or O99	S1 or S2 or S99 <u>and</u> W1 or W99 <u>and</u> E5 <u>and</u> O1 or O99
New South Wales	SN or S1 or S2 <u>and</u> W1 <u>and</u> E4 <u>and</u> O1	SN or S1 or S2 <u>and</u> W1 <u>and</u> E3 <u>and</u> O1	SN or S1 or S2 <u>and</u> W1 <u>and</u> E5 <u>and</u> O1
Northern Territory	S1 or S2 <u>and</u> W0 <u>and</u> E2 <u>and</u> M- or M0 or M1 or M2 <u>and</u> O0	S1 or S2 <u>and</u> W0 <u>and</u> E3 <u>and</u> M- or M0 or M1 or M2 <u>and</u> O0	S1 or S2 <u>and</u> W0 <u>and</u> E4 <u>and</u> M- or M0 or M1 or M2 <u>and</u> O0
Queensland	SN or S1 or S2 <u>and</u> W1 <u>and</u> E4 <u>and</u> O1	SN or S1 or S2 <u>and</u> W1 <u>and</u> E3 <u>and</u> O1	SN or S1 or S2 <u>and</u> W1 <u>and</u> E5 <u>and</u> O1
South Australia	S1 or S2 <u>and</u> W0 <u>and</u> E2 <u>and</u> M- or M0 or M1 or M2 <u>and</u> O0	S1 or S2 <u>and</u> W1 <u>and</u> E3 <u>and</u> M- or M0 or M1 or M2 <u>and</u> O0	S1 or S2 <u>and</u> W1 <u>and</u> E4 <u>and</u> M- or M0 or M1 or M2 <u>and</u> O0
Tasmania	n/a	S1 or S2 <u>and</u> W1 <u>and</u> E4 <u>and</u> O1	S1 or S2 <u>and</u> W1 <u>and</u> E5 <u>and</u> O1
Victoria	S1 or S2 <u>and</u> W- or W1 <u>and</u> E4 <u>and</u> O- or O1	S1 or S2 <u>and</u> W- or W1 <u>and</u> E3 <u>and</u> O- or O1	S1 or S2 <u>and</u> W- or W1 <u>and</u> E5 <u>and</u> O- or O1
Western Australia	S1 <u>and</u> W1 <u>and</u> E2 <u>and</u> M1 or M2 <u>and</u> O1	S1 <u>and</u> W1 <u>and</u> E3 <u>and</u> M1 or M2 <u>and</u> O1	S1 <u>and</u> W1 <u>and</u> E4 <u>and</u> M1 or M2 <u>and</u> O1

Appendix 9

RANZCOG guidelines for referral for investigation of intermenstrual and postcoital bleeding

Title	Guidelines for referral for investigations of intermenstrual and postcoital bleeding
Statement No.	C-Gyn 6
Date of this document	July 2002
First endorsed by Council	1995

Background

These guidelines were first developed in 1995 by the Royal Australian College of Obstetricians and Gynaecologists, the Royal Australian College of General Practitioners, the Australian Society for Colposcopy and Cervical Pathology and the Commonwealth Department of Human Services and Health.

The purpose of the guidelines is to assist general practitioners to decide when it is necessary to refer women with intermenstrual or postcoital bleeding (IMB, PCB) for further tests or to a specialist gynaecologist, and to assist gynaecologists in formulating management plans.

Genital tract malignancy is an uncommon cause of bleeding at any age and is rare in younger women. Nevertheless it is a possible cause. Since intermenstrual and postcoital bleeding are common, especially in women using hormonal contraception or on hormonal therapies, it is obviously impractical, unreasonably worrying and inappropriate to refer every case for immediate investigation. These guidelines recommend appropriate management of women presenting complaining of IMB or PCB and referral indications.

1. Careful history

Take a careful history noting:

- Patient's age
- Nature, frequency and clinical associations of the bleeding
- Hormonal therapy and contraceptive history
- Past history of bleeding
- Previous abnormal Pap tests
- Cigarette smoking
- Sexual history and relevant symptoms in a partner

2. Examination

Conduct abdominal examination, speculum examination (with a good light) and bimanual pelvic examination.

Check:

- Complete normality of ectocervix
- Contact bleeding and cervical tenderness
- Friability of tissue, ulceration or cervical polyp
- Other possible sites of bleeding
- Signs of vaginal discharge, foreign body or IUCD tail

Practitioners must always bear in mind the need to re-examine a patient if particular symptoms recur at a future stage.

3. Investigations

If the patient has not had a Pap test within the previous three months, take a Pap smear using speculum carefully in order not to provoke further bleeding. These diagnostic (rather than screening) Pap smears (Medicare item no. 73055) should be sent to laboratories using appropriate quality control procedures. Cervical swabs should be taken for *Chlamydia trachomatis* if appropriate.

Cervical ectopy is a common finding in premenopausal women, especially in combined oral contraceptive users and pregnant women, and contact bleeding from the cervix is relatively common when taking a smear, particularly from the endocervix using a cytobrush. A thin prep sample should also be sent if bleeding is likely to obscure the cells on the slide.

The occurrence of contact bleeding or abnormal bleeding in the case history should be noted on the request form. Contact bleeding or ectopy should not prompt referral unless other features are present or IMB or PCB has been persistent. In women with PCB or IMB a negative smear does not rule out the possibility of pathology. IMB and PCB are, by nature, intermittent, and duration, volume and frequency need to be taken into account in determining whether symptoms are 'persistent'. It is not possible to give a simple and all encompassing definition of 'persistent', but, for example, several minor episodes over a three month period or 2 episodes of heavy bleeding should generally prompt referral.

4. Management and referral

The following patients should be referred.

- **Women with persistent IMB and/or PCB without any unusual features**

These women should be referred for specialist opinion. In general, hysteroscopy/D&C by a specialist should be the primary imaging procedure in women with persistent IMB, while colposcopy should be the primary procedure with persistent PCB or if a suspicious lesion is present on the cervix. Both investigations may be required. In some instances high resolution transvaginal ultrasound scanning may provide additional information, but this skilled and expensive technology should not usually be the primary or the sole investigation. Saline infusion sonohysterography may also be useful.

- **Women with a friable cervix**

Where this is causing persistent symptoms, women should be referred for assessment and possible treatment. After careful exclusion of significant pathology by colposcopy, a variety of ablative methods may be used. Generally the problem will resolve without treatment.

- **Women with IMB/PCB and an abnormal Pap smear**

These women should be referred for colposcopy if:

- a) The smear contains abnormal cells suggestive of CIN 1 or worse, or high grade of glandular abnormalities
- b) On repeated diagnostic Pap smear testing 2–3 times over a 12-month period, the smear contains cells suggestive of an underlying low-grade squamous lesion less than CIN 1 (eg minor atypia, HPV atypia)

Practitioners in remote areas should consider telephone consultation with a specialist if the circumstances are unclear.

5. Women on hormonal therapy

Women with IMB who are on the progestogen-only minipill or in the first 6 months of Depo-Provera treatment (often called breakthrough bleeding) should generally not be referred in the first instance unless bleeding is excessively frequent or prolonged, and provided Pap smears are normal and up-to-date. Low oestrogen-dose combined pills and IUCDs are also frequent causes of IMB.

6. Documentation

Brief documentation as outlined above must be maintained on:

- Type of abnormal bleeding
- Hormonal therapy
- Past history of bleeding and previous investigations
- Date and report of last Pap test
- Examination findings
- Action taken for investigation and treatment
- Follow-up recommended

7. Information for women

Consideration should be given to the following points when informing women who present with symptoms of IMB or PCB:

- The most likely cause or causes
- Either that serious causes like cancer are so rare, or other causes so likely, that further investigation is not indicated OR that the cause needs to be investigated
- Instructions about investigations, if indicated
- When to return for routine review if symptoms persist
- That a Pap test is a screening test, and is only 80–90% sensitive and may therefore not detect underlying pathology in 10–20% of affected women

Companion documents (or references): none available

Links to other related College Statements: none

Patient resources: none provided

Disclaimer: This college statement has been prepared having regard to general circumstances, and it is the responsibility of the practitioner to have express regard to the particular circumstances of each case, and the application of this statement in each case. In particular, clinical management must always be responsive to the needs of individual patients, resources, and limitations unique to the institutions or type of practice. College statements have been prepared having regard to the information available at the time of their preparation, and the practitioner should therefore have regard to any information, research or material which may have been published or become available subsequently. Whilst the college endeavours to ensure that college statements are as current as possible at the time of their preparation, it takes no responsibility for matters arising from changed circumstances or information or material which may have become available subsequently.

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Appendix 10

Analysis of cancer outcomes from recommended management of women with LSIL/possible LSIL cytology

The following analysis was conducted by the Guidelines Review Group to assess the possible impact on cancer incidence following the adoption of the guidelines for the recommended management of women with LSIL/possible LSIL cytology.

- The 1999 Australian low-grade cohort study (see Appendix 7) documented 6354 women who had a biopsy reported as high-grade intraepithelial abnormality (ie CIN 2, CIN 3 or AIS) over the 24 months of follow-up. This is the group of women who might progress to cancer if a period of cytological surveillance after a low-grade Pap test report was recommended (based on the assumption that the biopsy and any associated treatment may have altered the natural history and prevented cancers that would have been additional to the 41 that were observed in the cohort).

The breakdown of these women by age and time period from the low-grade Pap test report until the high-grade intraepithelial abnormality was diagnosed is as follows:

0–6 months	<30 years	2433 women
6–24 months	<30 years	1584 women
Total (<30 years)		4017 women
0–6 months	30+ years	1392 women
6–24 months	30+ years	945 women
Total (30+ years)		2337 women
TOTAL		6354 women

- The draft guidelines propose repeat cytology at 12 months. Therefore, we need an estimate of how many of these high-grade intraepithelial abnormalities were diagnosed during the first 12 months.

If we assume that half of the biopsies during the 6–24 month period were done in the 6–12 month period (which makes allowance for women who may have a biopsy shortly after 12 months), the numbers are:

0–6 months	<30 years	2433 women
6–12 months	<30 years	792 women
Total (<30 years)		3225 women
0–6 months	30+ years	1392 women
6–12 months	30+ years	473 women
Total (30+ years)		1865 women
TOTALS		5090 women

3. Based on the known natural history of cervical neoplasia (see Chapter 3), we make the assumption that only CIN 3 lesions will progress to cancer over a 12-month period.
4. The exact breakdown of these 5090 cases into CIN 2 versus CIN 3 is unknown because most Pap test registers do not record histology to this level of detail. From the published statistical reports of the Victorian Cervical Cytology Registry (VCCR), we know that when the cytology is reported as low-grade, 80% of HSIL biopsies are CIN 2 (VCCR 2003, section 5, p 14). The remaining 20% are CIN 3 (including AIS). Using this breakdown, the number of CIN 3 cases diagnosed in the 90,000 women within 12 months of their low-grade Pap test is:

0–12 months	< 30 years	645 CIN 3
0–12 months	30+ years	373 CIN 3
TOTAL		1018 CIN 3

5. The draft guidelines exclude symptomatic women from the 12-month repeat cytology testing. National information on what proportion of women this will affect is not available. Based on the clinical information provided to the Victorian Cytology Service on the request forms of women with LSIL/possible LSIL cytology reports during 2003, we estimate the proportion as at least 6%. Assuming these women are no more likely to have CIN 3 diagnosed in the next 12 months than asymptomatic women with a low-grade Pap test report, the number of asymptomatic women who had CIN 3 diagnosed within 12 months of their low-grade Pap test is:

0–12 months	<30 years	606 CIN 3
0–12 months	30+ years	351 CIN 3
TOTAL		957 CIN 3

6. The revised guidelines also exclude women aged 30+ years who do not have negative cytology in the two to three years before the 12-month repeat cytology testing. National information on what proportion of women this will affect is not available. Based on the VCCR records of women with LSIL/possible LSIL cytology in 2003, we estimate the proportion as 29%. This includes women without negative cytology in the preceding three years plus women whose last Pap test before the LSIL/possible LSIL cytology report was abnormal; the latter group may have had negative cytology earlier in the three-year period.

Assuming these women are at the same risk of developing CIN 3 during the succeeding 12 months as those with a negative Pap test preceding their low-grade result reduces the number of women who will develop CIN 3 within 12 months and who are recommended for 12-month repeat cytology testing to:

0–12 months	< 30 years	606 CIN 3
0–12 months	30+ years	249 CIN 3
TOTAL		855 CIN 3

7. If we assume the progression rate from CIN 3 to cancer is 1% per year (Canfell et al 2004) among women aged 30+ years, and 0.5% per year among women aged <30 years (McIndoe et al 1984), these 855 women would have 5.5 extra cancers develop during a 12-month surveillance period.

8. We regard this estimate of 5.5 extra cancers as likely to be an overestimate because the progression rate quoted is predominantly derived from studies where the initial cytology was CIN 3, whereas we are applying it to women whose initial cytology was LSIL or possible LSIL, albeit probably harbouring undetected CIN 3. Because of this low-grade finding on cytology, the area of any underlying CIN 3 would be expected to be very much smaller (Tidbury et al 1992, Sherman et al 2003b). This would reduce the risk of progression to cancer over such a short time period by an uncertain but probably substantial amount.
9. The guidelines open up the potential for prevention or earlier diagnosis of some of the 41 women who had cancer as their endpoint in the 1999 Australian low-grade cohort study.

The potential for earlier diagnosis of microinvasive cancer at the intraepithelial stage exists. Data provided in Appendix 11 indicate that four of the eight women (50%) diagnosed with microinvasive cervical cancer in Victoria during 1999–2001 who had low-grade cytology in the preceding 24 months would have been recommended for earlier intervention under the 2004 guidelines than they would have been under previous guidelines (cases V2, V5, V6, V8). Victorian data are used for two reasons. First, a complete enumeration of cancers had occurred because of reconciliation between the Victorian Cancer Registry and the VCCR. Second, as the VCCR had been in operation for a minimum of 10 years before the date of diagnosis of cancer, this facilitates a more complete screening history for the women in comparison to other states and territories.

Thus, the guidelines, if followed, would reduce the number of cancers currently seen within 24 months of low-grade cytology. Applying the Victorian data to the 10 women diagnosed with microinvasive cancer in the Australian cohort suggests that five cancers would be diagnosed earlier, possibly at the intraepithelial stage of disease, as a result of application of the guidelines.

The remaining 31 cancers in the 1999 Australian low-grade cohort study were diagnosed at the invasive stage. We assume most were symptomatic and therefore excluded from the 12-month period of cytological surveillance. While the dominant reason for women being diagnosed with invasive cervical cancer is a lack of regular screening, the guidelines may result in earlier diagnosis of some of these cases. Data provided in Appendix 11 indicate that two of the three women diagnosed with invasive cervical cancer in Victoria during 1999–2001 who had low-grade cytology in the preceding 24 months would have been recommended for earlier intervention under the 2004 guidelines than they were under the previous arrangements (cases V9, V10). Because it is unclear whether the guidelines would bring the diagnosis back to the intraepithelial stage, we have not included them as potentially avoidable cases.

10. We conclude that the likely net effect of the proposed management of LSIL/possible LSIL cytology is no change in the number of cancers. This conclusion is necessarily predicated on a number of assumptions, including maintaining the quality of cytology and the continued participation of women in the National Cervical Screening Program at least at current levels.
11. A sensitivity analysis is included as Table A10.1. A sensitivity analysis involves exploring the impact of altering an assumption or variable in the model by a meaningful amount within a plausible range. It is useful where a model involves assumptions and variables with a degree of uncertainty in their measurement.

A one-way sensitivity analysis involves changing each critical assumption or variable by a meaningful amount while holding all other parameters constant at their baseline value. In a two-way sensitivity analysis, two critical assumptions or variables are altered simultaneously while holding all other parameters constant at their baseline values.

The one-way and two-way sensitivity analyses in Table A10.1 have a net effect varying from -2.2 cancers to $+4.5$ cancers.

An extreme scenario analysis (whereby each variable that increases the number of potential additional cancers is altered to its most pessimistic value in order to generate the worst-case scenario) gave a net effect of $+5.7$ cancers. An extreme scenario analysis (whereby each variable that decreases the number of potential additional cancers is altered to its most optimistic value in order to generate the best-case scenario) gave a net effect of -3.1 cancers.

13. Finally, if there were any additional cancers due to transition from CIN 3 to cancer over the 12 months of cytological surveillance, we assume most would be microinvasive in nature. Microinvasive cancer is frequently treated by cone biopsy in premenopausal women. It has an excellent prognosis.

Table A10.1 Sensitivity analysis

Analysis	Change	Year 1 potential additional cases	Potential reduction in microinvasive cases	Estimated change in the number of cancers
Base case		+5.5	-5.0	+0.5
One-way analysis	Proportion of histologic HSIL due to CIN 3 reduced to 15%	+4.1	-5.0	-0.9
	Proportion of histologic HSIL due to CIN 3 increased to 25%	+6.9	-5.0	+1.9
	Proportion asymptomatic reduced to 85%	+5.0	-5.0	+0.0
	Proportion asymptomatic increased to 97%	+5.7	-5.0	+0.7
	Rate of progression to cancer decreased to 0.25% and 0.5% per year in women aged <30 and 30+ years respectively	+2.8	-5.0	-2.2
	Rate of progression to cancer increased to 0.75% and 1.5% per year in women aged <30 and 30+ years respectively	+8.3	-5.0	+3.3
	Rate of progression from CIN 2 to cancer occurs at 0.0195% and 0.106% per year in women aged <30 and 30+ years respectively ^a	+7.0	-5.0	+2.0
	Proportion of existing cases of microinvasive cancer with earlier diagnosis reduced from 50% to 30%	+5.5	-3.0	+2.5
	Proportion of existing cases of microinvasive cancer with earlier diagnosis reduced from 50% to 10%	+5.5	-1.0	+4.5
	Two-way analysis	Proportion of histologic HSIL due to CIN 3 increased to 25% <u>and</u> rate of progression to cancer decreased to 0.25% and 0.5% per year in women aged <30 and 30+ years respectively	+3.5	-5.0
Proportion asymptomatic reduced to 85% <u>and</u> rate of progression to cancer increased to 0.75% and 1.5% per year in women aged <30 and 30+ years respectively		+7.5	-5.0	+2.5
Extreme scenarios	Proportion of histologic HSIL due to CIN 3 increased to 25% <u>and</u> proportion asymptomatic increased to 97% <u>and</u> rate of progression to cancer increased to 0.75% and 1.5% per year in women aged <30 and 30+ years respectively	+10.7	-5.0	+5.7
	Proportion of histologic HSIL due to CIN 3 decreased to 15% <u>and</u> proportion asymptomatic decreased to 85% <u>and</u> rate of progression to cancer decreased to 0.25% and 0.5% per year in women aged <30 and 30+ years respectively	+1.9	-5.0	-

a From Canfell et al (2004), rate of progression from CIN 2 to CIN 3 per year among women aged 16–34 years is 0.0389. Applying this value to women aged <30 years gives a rate of progression from CIN 2 to cancer of 0.0195% per year (0.0389 x 0.005). Canfell estimates progression rates from CIN 2 to CIN 3 per year among women aged 35–44 years and 45+ years at 0.0797 and 0.1062, respectively. Applying the latter value to women aged 30+ years gives a rate of progression from CIN 2 to cancer of 0.106% per year (0.1062 x 0.01). This is a worst-case scenario for women aged 30+ years.

Appendix 11

Evaluation of low-grade guidelines against historical data from Victoria

The management policy for women with low-grade cytology has been evaluated against women diagnosed with cervical cancer in Victoria. Limitations to such an evaluation are twofold. First, the Victorian Cervical Cytology Registry (VCCR) does not record the symptom status of women, and the guidelines apply only to asymptomatic women. Second, treatment of intraepithelial lesions diagnosed after the investigation of LSIL/possible LSIL cytology may have prevented some cancers; this is considered a rare outcome given current knowledge about the natural history of cervical neoplasia and the fact that the guidelines are proposing to defer colposcopy for only 12 months for some women while their cytology remains in the LSIL phase.

Following an amendment to the *Victorian Cancer Act 1958* and with the approval of a human research ethics committee, a reconciliation of incident cases of cervical cancer now occurs between the Victorian Cancer Registry and the VCCR. The Victorian Cancer Registry recorded 472 new cases of cervical cancer during the three-year period from 1999 to 2001. Reconciliation between the two registries has occurred for each of these years.

Women with cervical cancer diagnosed in 1999–2001 were identified within the records of the VCCR. The Victorian registry had been operating for a minimum of 10 years prior to these diagnoses of cancer. The screening history of the women was ascertained, with particular emphasis being given to women who had LSIL/possible LSIL cytology in the 24 months (30 months if <30 years) before the cancer diagnosis. Whether or not the woman received a hysterectomy as part of the treatment of the cancer was determined from histology records and the site of origin of later cytology (ie cervical or vaginal vault). The investigation and management of the women as known to the registry was compared against the 2004 guidelines.

The findings of the evaluation are shown in Table A11.1. Major points are as follows:

- The frequency of women being diagnosed with cancer after LSIL/possible LSIL cytology was very low. Of the 472 women diagnosed with cervical cancer in this three-year period, 11 (2.3%) were diagnosed after LSIL/possible LSIL cytology (8 microinvasive, 3 invasive). Six of the eight women with microinvasive cancer did not have a hysterectomy, thus preserving fertility (if relevant). Microinvasive carcinoma has an excellent prognosis.
- Only one woman (case V10) had a substantive history of repeated negative cytology. This woman was diagnosed with adenocarcinoma, against which cervical cytology is known to offer less protection (Mitchell et al 2003).
- Two women (cases V5 and V8) had a long history of cervical abnormality.
- Three women (cases V1, V3 and V10) had intervening surgery between the LSIL/possible LSIL cytology and the cancer. In these women, the intervening surgery either failed to identify the cancer or failed to prevent its development. This finding was also observed in the 1999 Australian low-grade cohort study.
- Seven women (cases V2, V5, V6, V8, V9, V10 and V11) would have been recommended for earlier intervention or different management under the 2004

guidelines than they received. Importantly, this would have included all three women who were diagnosed with invasive cancer.

These findings suggest that low-grade cytology currently plays only a very small role among women diagnosed with cervical cancer. These 11 women comprised 2.3% of incident cases diagnosed in Victoria between 1999 and 2001. In many of these women, the cancer was multifactorial in origin and not solely attributable to low-grade cytology.

These 11 cancers occurred in the setting of at least 60,000 cytology reports of LSIL/possible LSIL. More intensive management of all women with LSIL/possible LSIL (eg by colposcopy or repeat cytology at 6 months) will contribute very little to the prevention of cervical cancer.

Table A11.1 Evaluation of 2004 guidelines against women diagnosed with cervical cancer in Victoria during 1999, 2000 and 2001

Case ID	Type of cancer	Age group at cancer	Hysterectomy	Screening history (all times calculated back from date of cancer)	Negative cytology in 3 years preceding LSIL cytology	Other comments
V1	Microinvasive squamous carcinoma	20–29	No	0 mth Cone biopsy: microinvasive squamous carcinoma -1 mth Punch biopsy: CIN 3 -1 mth Cytology: HSIL -13 mths Punch biopsy: HPV effect -14 mths Cytology: HSIL -23 mths Cytology: LSIL (CIN 1) -82 mths Cytology: negative	No	Intervening surgical intervention with probable underdiagnosis.
V2	Microinvasive squamous carcinoma	30–39	No	0 mth Biopsy: microinvasive squamous carcinoma 0 mth Cytology: LSIL (CIN 1) -3 mths Cytology: LSIL (CIN 1) -8 mths Cytology: LSIL (CIN 1) -30 mths Cytology: LSIL (HPV)	No	Under guidelines (and under 1994 guidelines), intervention would be recommended earlier than it was received.
V3	Microinvasive squamous carcinoma	30–39	No	0 mth Biopsy: microinvasive squamous carcinoma -1 mth Cytology: HSIL -6 mths Punch biopsy: CIN 3; treated by LLETZ -8 mths Cytology: LSIL (CIN 1) -36 mths Cytology: negative	Yes	Intervening surgical intervention with possible underdiagnosis.
V4	Microinvasive squamous carcinoma	30–39	No	0 mth Biopsy: microinvasive squamous carcinoma 0 mth Cytology: negative -2 mths Cytology: Possible LSIL (NSMC) -9 mths Cytology: negative -11 mths Cytology: Possible LSIL (NSMC) -36 mths Cytology: negative -65 mths Cytology: negative	Yes	
V5	Microinvasive squamous carcinoma	40–49	Yes	0 mth Biopsy: microinvasive squamous carcinoma -2 mths Cytology: HSIL -6 mths Cytology: Possible cancer -10 mths Cytology: HSIL -14 mths Cytology: Possible LSIL (NSMC) NB 4 prev. biopsies of CIN 3 & 1 prev. CIN 1 biopsy: multiple earlier cytology reports of HSIL and cancer	No	Long history of cervical disease. Delayed investigation of HSIL/cancer cytology.

Case ID	Type of cancer	Age group at cancer	Hysterectomy	Screening history (all times calculated back from date of cancer)	Negative cytology in 3 years preceding LSIL cytology	Other comments
V6	Microinvasive squamous carcinoma	50–59	No	0 mth Biopsy: microinvasive squamous carcinoma 0 mth Cytology: HSIL –2 mths Cytology: LSIL (CIN 1) –24 mths Cytology: negative –33 mths Cytology: Possible LSIL (NSMC)	No	Subsequently had a hysterectomy after continuing abnormal cytology post management of the microinvasive carcinoma.
V7	Microinvasive squamous carcinoma	50–59	No	0 mth Biopsy: microinvasive squamous carcinoma –1 mth Cytology: Possible high-grade glandular abnormality –2 mths Cytology: Possible HSIL/glandular abnormality. –4 mths Cytology: Possible LSIL (NSMC) –31 mths Cytology: negative	Yes	
V8	Microinvasive squamous carcinoma	70–79	Yes	0 mth Cone biopsy: microinvasive squamous carcinoma –1 mth Punch biopsy: CIN 2 –1 mth Cytology: LSIL (CIN 1) –2 mths Cytology: Possible HSIL –10 mths Cytology: Negative NB 8 earlier cytology reports of LSIL & possible LSIL interspersed by an HPV biopsy treated with diathermy	Yes	Long history of abnormal cytology. Under guidelines, would have been recommended for earlier intervention.
V9	Invasive squamous carcinoma	30–39	Yes	0 mth Biopsy: invasive squamous carcinoma 0 mth Cytology: Cancer –17 mths Cytology: LSIL (CIN 1) –87 mths Cytology: negative	No	Earlier intervention under guidelines due to lack of preceding negative cytology.
V10	Invasive adenocarcinoma	30–39	Yes	0 mth Biopsy: invasive adenocarcinoma –1 mth Cytology: AIS –8 mths Cytology: Negative –11 mths Punch biopsy: Negative –12 mths Cytology: AIS –15 mths Cytology: LSIL (CIN 1) –21 mths Cytology: LSIL (HPV) –36 mths Cytology: Possible LSIL (NSMC) NB 6 preceding negative cytology reports	Yes	Under guidelines, would have received earlier intervention after second LSIL cytology and would have been recommended for a cone biopsy rather than a punch biopsy. Probable under-diagnosis on punch biopsy.

Case ID	Type of cancer	Age group at cancer	Hysterectomy	Screening history (all times calculated back from date of cancer)	Negative cytology in 3 years preceding LSIL cytology	Other comments
V11	Invasive squamous carcinoma	40–49	Yes	0 mth Biopsy: invasive squamous carcinoma -1 mth Cytology: HSIL -3 mths Cytology: LSIL (CIN 1) -18 mths Cytology: Negative -25 mths Cytology: Negative -28 mths Cytology: Negative -31 mths Biopsy: CIN 3 -32 mths Cytology: HSIL	Yes	Under guidelines, the high risk status of this woman may have been ascertained by HPV typing tests performed after the management of the CIN 3 biopsy. Post CIN 3 treatment colposcopy status unknown.

Appendix 12

Safety monitoring of the recommended management for women with low-grade cervical cytology

Note: As the Guidelines Review Group will cease to exist when the NHMRC makes its decision about these guidelines, it will not have ongoing responsibility for the safety monitoring. Accordingly, this appendix presents only a high-level overview of the recommended approach. Further development of the safety monitoring approach will be under the auspices of the Australian Screening Advisory Committee.

Aim

To monitor the safety of the recommended management of women with low-grade cervical cytology reports, and thus facilitate timely review of the policy as needed.

Background

Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen-Detected Abnormalities encompasses a new management approach for women with low-grade cervical cytology reports.

In recommending the new approach, the Guidelines Review Group made a commitment to monitor the safety of the new approach.

Key management features under the 1994 guidelines for women with low-grade cervical cytology included:

Nonspecific minor change	Annual cytology until cytology returns to normal.
HPV effect	Repeat cytology at 6 and 12 months. If HPV effect still present at 12 months, colposcopy and directed biopsy (where indicated).
CIN 1	Colposcopy and biopsy (where indicated).

Key management features under these revised 2004 guidelines for all women with low-grade or possible low-grade cervical cytology include:

Repeat cytology at 12 months.	If low-grade abnormality still present, colposcopy and directed biopsy (where indicated).
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Australia is extremely fortunate to already have in place the Australian Pap test registries. Information routinely collected by the registries will allow regular monitoring of the safety of the new approach. Baseline information on the number of women diagnosed with cervical cancer after a low-grade cytology report is available and can be used for comparison purposes.

Responsibility

The Screening Section of the Australian Government Department of Health and Ageing will take responsibility for ensuring that timely monitoring takes place and is reported to the Australian Screening Advisory Committee.

The composition and modus operandi of the safety monitoring committee will be determined by the Australian Screening Advisory Committee.

Approach

1. Collection and reporting of data

The coding schedule used by the Pap test registries to record the cervical cytology reports issued by pathology laboratories is being modified to reflect the AMBS 2004 terminology described in Chapter 4. The management recommendation made by the laboratory (eg repeat cytology in 12 months, referral for colposcopy etc) is routinely stored within the Pap test register database.

It is proposed that one of the options for recording the management recommendation become 'symptomatic — clinical management required'. In addition to emphasising that symptomatic women are not within the scope of these guidelines, this data would also allow stratification of the cancers that are diagnosed after low-grade cytology into symptomatic versus asymptomatic women.

On a half-yearly basis, each Pap test registry will be asked to provide de-identified information about any woman with a histologic diagnosis of cervical cancer (microinvasive or invasive) within 24 months of a low-grade cervical cytology report.

The following information will be required from the Pap test registry:

- age of the woman at the time of the diagnosis of cancer
- summary of the known screening history before the diagnosis of cancer
- symptom status (yes/no) at time of low-grade cytology
- stage and morphologic details of the cancer (microinvasive or invasive, squamous or adeno- or other).

The Pap test registers can also provide information on an annual basis about the number of women who receive a low-grade cytology report.

From the provided information, a summary of the screening histories of women diagnosed with cervical cancer will be compiled (similar to Table A7.10 in Appendix 7 of these guidelines) and presented on a half-yearly basis to the Australian Screening Advisory Committee.

2. Comparison with baseline information

The audit of outcome after a low-grade cervical cytology report during 1999 documented that 41 cases of cervical cancer were diagnosed over the following 24 months. This provides a useful baseline for comparison.

If considered necessary, further baseline data could be collected.

3. Policy review

At any time, a review of the safety of the policy can be initiated by the Australian Screening Advisory Committee.

If the guidelines have an implementation date of 1 July 2006, the safety of the low-grade management recommendations should be capable of being assessed progressively from 1 January 2007. The full impact of the recommended management should be assessable during the first half of 2008.

Appendix 13

Safety monitoring of the recommended management of women with treated high-grade intraepithelial abnormalities

Note: As the Guidelines Review Group will cease to exist when the NHMRC makes its decision about these guidelines, it will not have ongoing responsibility for the safety monitoring. Accordingly, this appendix presents only a high-level overview of the recommended approach. Further development of the safety monitoring approach will be under the auspices of the Australian Screening Advisory Committee.

Aim

To monitor the safety of the recommended management of women with treated high-grade intraepithelial disease, and thus facilitate timely review of the policy as needed.

Background

Screening to Prevent Cervical Cancer: Guidelines for the Management of Asymptomatic Women with Screen-detected Abnormalities encompasses a new management approach for women who have been treated for high-grade intraepithelial disease.

The revised approach has utilised the improved understanding of cervical neoplasia that has evolved over the past decade. Most particularly, this involves evidence of the pivotal role of persistent infection with high-risk HPV subtypes as a necessary cause for cervical malignancy to occur.

As there were no published Australian studies, policy development in this area relied on overseas studies. The Guidelines Review Group considered that overseas studies were generalisable to Australia, as there are no major differences in terminology or the treatment modalities in the area of high-grade disease.

Key management features under the 1994 guidelines for women with treated high-grade intraepithelial abnormalities included:

- | | |
|-----------------------------|----------------------------------|
| 2–6 months after treatment: | Cytology and colposcopy |
| 12 months after treatment: | Cytology and optional colposcopy |

If the above three (or four) tests using two modalities are normal, then annual cytology for life.

Key management features under these revised 2004 guidelines for women with treated high-grade intraepithelial abnormalities include:

- | | |
|-----------------------------|---------------------------------|
| 4–6 months after treatment: | Cytology and colposcopy |
| 12 months after treatment: | Cytology and high-risk HPV test |
| 24 months post-treatment: | Cytology and high-risk HPV test |

If the above six tests using three modalities are normal, then return to usual screening interval.

In June 2004, the Minister for Health and Ageing endorsed a recommendation from the Medical Services Advisory Committee that high-risk HPV testing be listed on the Medicare Benefits Schedule for monitoring, as a 'test of cure', the status of women who have been treated for high-grade intraepithelial disease of the cervix.

In recommending the new approach, the Guidelines Review Group made a commitment to monitor the safety of the approach.

Australia is extremely fortunate to already have in place the Australian Pap test registries. Information routinely collected by the registries will allow regular monitoring of the safety of the new approach. Baseline information on the rate of cervical cancer diagnosis after treatment of high-grade intraepithelial disease in Victoria has been published and this can be used for comparison purposes.

Responsibility

The Screening Section of the Department of Health and Ageing will take responsibility for ensuring that timely monitoring takes place and is reported to the Australian Screening Advisory Committee.

The composition and modus operandi of the safety monitoring committee will be determined by the Australian Screening Advisory Committee.

Approach

1. Collection and reporting of data

In the first instance, monitoring will occur on an incident basis.

On a half-yearly basis, each Australian Pap test registry will be asked to provide de-identified information about any woman with a first-ever histologic diagnosis of cervical cancer (microinvasive or invasive) occurring 12 or more months after treatment of high-grade intraepithelial disease. Information about cases diagnosed within one year of the original intraepithelial disease will not be requested, as these may be considered to be underdiagnosed disease at the time of treating the intraepithelial disease, rather than incident cases of cancer. Furthermore, their diagnosis is not directly related to the new aspects of the proposed management of women with treated intraepithelial disease.

The following information will be requested from the Pap test registries:

- age of the woman at the time of the diagnosis of cancer
- summary of the known screening and management history (including dates and results of cytology, colposcopy, histology, high-risk HPV status, treatment modality) prior to the diagnosis of cancer
- stage and morphologic details of the cancer (microinvasive or invasive, squamous or adeno- or other).

The Pap test registers can also provide information about the number of women treated for high-grade intraepithelial disease who retain a cervix.

From the provided information, a report will be compiled and presented on a half-yearly basis to the Australian Screening Advisory Committee. Particular interest will be given to the time interval between the intraepithelial disease and the later diagnosis of cancer, the screening and management history, and whether or not the woman had returned to the usual screening interval.

Depending on the results of the incident monitoring, a more formal cohort study of all treated women may be considered appropriate.

2. Comparison with baseline information

Baseline data is available from Victoria (Mitchell and Hocking 2002). A summary of the main findings is as follows:

- Among 6849 women treated for high-grade intraepithelial abnormality (squamous or glandular) during 1990–92 who had further cervical cytology or histology before 31 December 2000, 15 cases of cervical cancer were diagnosed (excluding cases diagnosed within one year of the original intraepithelial disease).
- The types of cancer were:
 - 4 microinvasive squamous carcinomas
 - 9 invasive squamous carcinomas
 - 1 invasive adenocarcinoma
 - 1 invasive adenosquamous carcinoma.
- The crude rate of cervical cancer in the cohort of women treated for high-grade intraepithelial disease was 0.35 per 1000 person-years (95% CI, 0.21 to 0.59).
- The cumulative rates of cervical cancer in the cohort of women treated for high-grade intraepithelial disease after 5 and 10 years study duration were 2.10 and 3.71 per 1000 person-years.
- The crude rate of cervical cancer in a separate cohort of women who had negative cytology ('average-risk' women) was 0.08 per 1000 person-years (95% CI, 0.03 to 0.21).

3. Policy review

At any time, a review of the safety of the policy can be initiated by the Australian Screening Advisory Committee.

If the guidelines have an implementation date of 1 July 2006, the safety of the proposed management of women treated for high-grade intraepithelial disease should be capable of being assessed progressively from 1 July 2008. A two-year time lapse is inevitable, as the revised management approach does not involve significant variation from the 1994 guidelines until beyond 24 months.

Abbreviations

AACR	Australasian Association of Cancer Registries
ACRRM	Australian College of Rural and Remote Medicine
AGUS	atypical glandular cells of undetermined significance
AIHW	Australian Institute of Health and Welfare
AIS	adenocarcinoma in situ
ALTS	Atypical Squamous Cells of Undetermined Significance and Low-Grade Squamous Intraepithelial Lesions Triage Study
AMBS 2004	Australian Modified Bethesda System 2004
ASCCP	Australian Society of Colposcopy and Cervical Pathology
ASCUS	atypical squamous cells of undetermined significance
CCR	cervical cancer registry
CI	confidence interval
CIN	cervical intraepithelial neoplasia
DARE	Database of Abstracts of Reviews of Effectiveness
D&C	dilatation and curettage
DES	Diethylstilboestrol
DNA	deoxyribonucleic acid
GP	general practitioner
HC-II	Hybrid Capture II test (Digene)
HGEA	high-grade epithelial abnormality
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
IMB	intermenstrual bleeding
IUCD	intrauterine contraceptive device
LEEP	loop electro-excisional procedure
LGEA	low-grade epithelial abnormality
LLETZ	large loop excision of the cervical transformation zone
LSIL	low-grade squamous intraepithelial lesion
LYS	life-years saved
MSAC	Medical Services Advisory Committee
NCI	National Cancer Institute (United States)
NCSP	National Cervical Screening Program
NHMRC	National Health and Medical Research Council (Australia)

NHS	National Health Service (United Kingdom)
NSMC	nonspecific minor change
PCB	postcoital bleeding
PTR	Pap test registry
RACGP	Royal Australian College of General Practitioners
RACOG	Royal Australian College of Obstetrics and Gynaecologists
RANZCOG	Royal Australian and New Zealand College of Obstetricians and Gynaecologists
rb	Retinoblastoma
RCPA	Royal College of Pathologists of Australasia
ROD	rate of discount
SCC	squamous cell carcinoma
SCJ	squamocolumnar junction
SIL	squamous intraepithelial lesion
SNOMED	systematised nomenclature of medicine
TBS	The Bethesda System
TDS	total dimension score
TZ	transformation zone
VCCR	Victorian Cervical Cytology Registry

Glossary

Adenocarcinoma	A rare cancer affecting the cervix, but involving the columnar cells rather than the squamous cells. The columnar cells are involved in glandular activity. Adenocarcinoma has a different type and rate of progression and is not so often picked up in Pap test
Atypia	Slight changes in cells of the cervix
Benign	Not malignant. In a condition that is called benign, the cells may be different, but they are not malignant
Biopsy of the cervix	Removal of a small piece of the cervix for examination under a microscope
Carcinoma in situ	Cancer cells that are restricted to the surface epithelium. The abnormal cells are evident throughout each of the layers of the epithelium but they have not extended into other, deeper tissue or surrounding areas
Cells	The smallest unit of the body capable of independent life. Body tissues and organs are made up of millions of cells. Each cell is usually invisible to the naked eye
Cervical intraepithelial neoplasia	Abnormal changes or growth in the surface layers of the cervix. These changes are not cancer but warn that cancer may develop over future years. CIN is graded CIN 1, 2 or 3; CIN 3 involves the most severe changes
Cervix	The neck of the uterus (womb), located at the top of the vagina
Colposcopy	Examination of the cervix and vagina with a magnifying instrument called a colposcope to check for abnormalities
Cone biopsy	The removal, under general anaesthetic, of a cone-shaped section of the cervix so that tissue can be examined in a laboratory. The same procedure is used as a treatment in some cases
Cytology	The study of cells taken as samples during procedures such as Pap tests
Dysplasia	An older term used to describe abnormal changes in the cervix. Dysplasia is graded mild, moderate or severe. Mild dysplasia corresponds to CIN 1 and so on
Ectocervix	The outer surface layer of the cervix
Endocervical	Inside the canal of the cervix
Glandular lesion	Lesion involving the columnar cells of the cervix, which produce mucus and have both a different appearance and a different function from the squamous cells
Human papillomavirus	Group of viruses that can cause infection in the skin surface of different areas of the body, including the genital area. The virus can cause visible warts of the skin or may only cause microscopic changes in the cells of the skin

Hysterectomy	Removal of the uterus (womb)
Index smear	Initial reference smear to which a subsequent sequence of follow-up management, including repeat smears, relates. Term is usually applied to the first abnormal cytology report in a sequence, which might not be the first-ever abnormal smear. Results of the index smear determine subsequent treatment. Many women have multiple episodes of abnormality during their adult years, typically interspersed with long periods when their cytology is normal either because of treatment or because the abnormality regresses spontaneously.
Intraepithelial lesion	Lesion confined to the surface layer of the cervix
Invasive cancer	Cancerous cells that have spread to deeper tissue
Koilocytes	Cytologic abnormality correlated with productive HPV infection
Lesion	Alteration of surface tissue, caused by injury or disease
Malignancy	Disease which, if not treated, will become serious or life threatening
Microinvasive	Lesion in which the cancer cells have invaded just below the surface of the cervix, but have not developed any potential to spread to other tissues
National Cervical Screening Program	Australia-wide systematic approach to cervical screening based on sound international scientific evidence, the aim of which is to reduce the incidence and mortality rates for cervical cancer
Oncology	The study of cancer
Opportunistic screening	Taking Pap smears when a woman visits her GP for another reason
Os	Opening of the cervix leading to the endocervical canal
Pap test (or smear)	Simple procedure in which a number of cells are collected from the cervix, smeared onto a microscope slide and sent to a laboratory for cytological examination to look for changes that might lead to cervical cancer. Up to 90% accurate and the best way to prevent squamous cervical cancer. Named after the test's inventor, Dr Papanicolaou
Pathology	Laboratory-based study of disease, as opposed to clinical examination of systems
Precancerous	Sometimes used to describe a condition that, if left untreated, may go on to become cancerous
Precursor	An early form of an object that changes to become the next stage in a developmental process
Prognosis	Prediction of the course or outcome of a disease or abnormality
Screening	Testing of all people at risk of developing a certain disease, even if they have no symptoms. Screening tests can predict the likelihood of someone having or developing a particular disease

Speculum	Instrument (like a duck bill with handles) used to hold open the sides of the vagina
Squamous cells	Thin and flat cells, shaped like soft fish scales. Layers of squamous cells make up skin-like epithelium. In the cervix they form the skin on the outer surface of the cervix (ectocervix)
Vault smear	Like a Pap smear but taken from the top of the vagina in women who have had their cervix removed during a hysterectomy

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