Screening and treatment of cervical precancers

Organised screening programs are now making an impact on the rate of cervical cancer. By detecting disease in the preinvasive phase, we can give safe and simple treatment and prevent cancer developing in the future. This article reviews the current state of screening and treatment.

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While cervical carcinoma remains a huge problem worldwide, within Australia its incidence has decreased rapidly in the last 10 years, largely because of the intensive screening programs conducted around the country. Whereas it was formerly the commonest gynaecological cancer, it has now been surpassed by both endometrial and ovarian cancer. The NSW Cancer Registry figures for 2000 found a lifetime risk of 1:150 for cervical carcinoma, compared with 1:11 for breast cancer.[1]

The importance of detecting preinvasive disease lies in its potential for easy cure compared with carcinoma. It is vital to recognise that we are screening for precancer not cancer; once invasive disease is established, smears have no place because of a definite false-negative rate.

Preinvasive disease of the uterine cervix may be of squamous or glandular origin. Cervical intraepithelial neoplasia (CIN) denotes all precursors of squamous cervical cancer and embraces a continuous spectrum from low grade (squamous atypia to mild dysplasia) to high grade (moderate to severe dysplasia). Glandular dysplasia and adenocarcinoma *in situ* are less common.

Aetiology and natural history

The current thinking about the genesis of cervical disease is related to some subtypes of the human papillomavirus (HPV). This appears to be a very common virus in the community and, as our tests improve, the reported rates of prevalence in the population continue to rise. The virus has its effect after integration of its DNA into that of the epithelial cell, with the process of initiation and promotion taking many years before preinvasive disease is apparent. Given its high prevalence, it is likely that there are other cofactors or an immune susceptibility that allow the virus to express itself in this fashion in the few women who develop disease. Other aetiological associations are shown in the Table.

While progression from a low grade to a high grade abnormality is supposed to be slow, it may be that some disease arises as high grade *de novo*. Low grade atypia is regarded by many authorities as the earliest preneoplastic lesion and is thus part of the spectrum. Studies of these minor lesions have shown progression to a higher grade change in up to 25% of cases, but with many

IN SUMMARY

- **The rate of cervical carcinoma is decreasing.**
- **We are still not screening 100% of the recommended population.**
- **We understand some of the causative factors of cervical neoplasia.**
- **In the majority of women, colposcopy is uncomfortable but not painful.**
- **Treatment of preinvasive disease is well tolerated and effective.**
- **Recruitment by general practitioners is the most effective strategy for screening.**

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lesions regressing spontaneously. The behaviour of established CIN is similarly variable, with regression of low grade lesions in up to 70% of cases over two years. Even some high grade lesions may regress; however, few gynaecologists would manage high grade lesions conservatively because of the risk of progressive disease (40% if left untreated over five years).

The natural history of glandular lesions is poorly understood. A significant proportion of patients with adenocarcinoma *in situ* will have established invasive disease at diagnosis.

Age factors

Preinvasive disease occurs over a huge age range. Figures from the NSW Pap Test Register and the Cancer Council show high grade preinvasive disease occurring most commonly between the ages of 20 to 34, slowly decreasing from 35 but still occurring after the age of 70.[2] Invasive disease increases from the age of 20 and remains elevated until age 54, after which it slowly declines. The median age at diagnosis for cervical cancer is 51 years.

Table. Aetiological factors for cervical neoplasia

Early age at first sexual intercourse
Early age at first pregnancy
High number of partners
Regular partner having a high number of partners
High parity
Low socioeconomic class
Low level of education
Past history of genital warts
Smoking and passive smoking
Contact with seminal fluid
Uncircumcised partner
Herpes simplex virus 2 infection
Human papillomavirus infection
Immunodeficiency
Immune suppression

The Papanicolaou smear

Balancing specificity and sensitivity

When reviewing cytology tests, it is important to remember that you are dealing with a screening test, not a diagnostic test. In all such tests there is a balance of specificity against sensitivity. The more sensitive a test becomes, the less specific the outcome (i.e. more false positives). To the individual woman, sensitivity is all important – no one wishes to have a lesion missed on the cervix. However, increasing sensitivity leads to the detection of many minor lesions and true false positives, the investigation of which incurs significant cost to the health system.

Screening by smear tests relies on sequential smears ultimately detecting cervical lesions while still in the preinvasive stage, because the development of carcinoma itself takes many years in the majority of patients. There have been two large meta-analyses of the Papanicolaou smear. For a specificity of around 90% (where most laboratories operate), the sensitivity for any single smear is between 20 and 50%.[3]

Smear frequency

The current recommendation is that women in the age range of 18 to 70 years have second-yearly cervical cytology examinations, with the option to commence earlier if sexually active. These ages cover the period when most lesions will develop.

Smear reporting

The current system of smear reporting is the Australian modification of the international Bethesda reporting categories. These categories were delineated in the NHMRC report of 1994[4] and are currently under review.

Lesions included in the high grade epithelial abnormalities category include both squamous and glandular invasive disease, squamous preinvasive disease (CIN 2 and 3) and glandular preinvasive disease (adenocarcinoma *in situ*).

There is an 'Inconclusive – possible high grade abnormality' category for lesions where the pathologist is uncertain but suspicious of an abnormality. A significant number of these will prove to be a high grade lesion.[5]

Low grade squamous and glandular abnormalities encompass minor atypia, HPV changes (as defined by 'stringent criteria') and CIN 1.

In addition there are smears that are technically unsatisfactory, usually because of inflammation or blood. The negative group includes those with reactive changes from an identifiable cause.

Who should be referred?

All patients with high grade abnormalities or the 'Inconclusive – possible high grade abnormality' category should be referred for colposcopic assessment.

Low grade abnormality results are usually accompanied by a recommendation for repeat cytology at three, six or 12 months. Patients with persisting low grade abnormalities after 12 months or two atypical smears should be referred for further assessment of the cervix. In practice, there are many patients who are not prepared to wait that length of time and insist upon referral immediately. It is very difficult to argue against such an approach because a proportion will have established high grade disease that has not been recognised by the cytology. However, the majority of patients will not have disease found and, while this is very reassuring for those women, it is an expensive process for the health system.

Patients for whom the cytology suggests invasion should be referred to a gynaecological oncology unit, and they will generally be seen within the week. Preinvasive disease does not need to be seen so rapidly and it will usually be assessed within several weeks. However, most gynaecologists will try to see these patients as soon as practicable, to allay the sometimes massive anxiety and stress

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the women experience on receipt of their result despite efforts by their general practitioner to reassure them.

Colposcopy, histopathology and deciding treatment

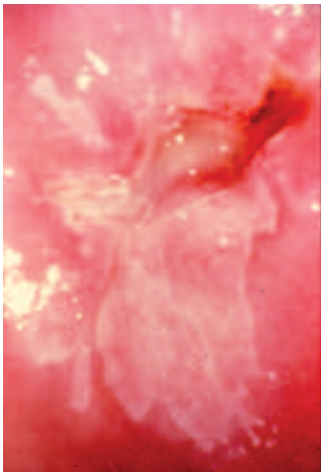
Having been referred, the patient undergoes colposcopy. In this process the cervix is washed with saline, acetic acid and iodine solutions to identify and grade lesions (Figures 1 and 2). The important features delineated are the surface contour, vascular pattern, acetowhite change, topography of the lesion and iodine uptake.

Having decided on the nature of the lesion, the gynaecologist usually takes a colposcopic biopsy from the area with the most suspicious appearance. When there is an obvious lesion, treatment may be discussed at the time or deferred until the results are available.

The recent document 'Standards in colposcopy and treatment' recommends the requirements for different treatment modes,[6] and the current standard of practice is either ablation or excision under local anaesthesia. The decision about treatment will depend on the expertise of the practitioner, the facilities available and the wishes of the patient.

Subjectivity and cervical disease

While most patients and medical practitioners are aware of the shortcomings of cytology, most do not appreciate that both colposcopy and histopathology are just as subjective as cytology, with interobserver variation. The reliability of colposcopy is very dependent on the experience of the colposcopist. Histo - pathology was once considered the 'gold standard' and final answer on any lesion; however, in the last 15 years a number of studies have shown very poor inter- and intraobserver correlation, even with experienced gynaecologicalpathologists.[7] Correlations for CIN 3 are generally better than 80%, but the presence or absence of HPV is only around 40% (which must cast doubt on our 'stringent criteria'). Intraobserver correlation is only 60%. All of this indicates that we must critically review the cytology, colposcopy and histology results for every patient to determine their optimal management.



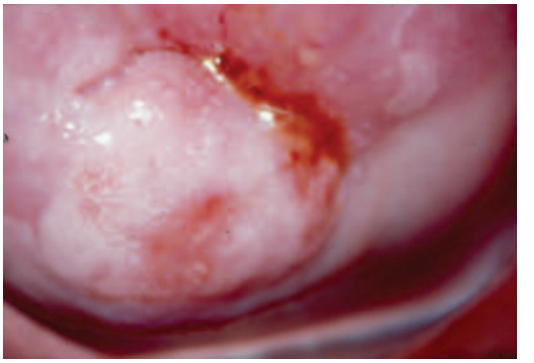


Figure 1 (left). Colposcopy showing low grade atypia.
Figure 2 (above). High grade abnormality showing a mosaic pattern on colposcopy.

Treatment

In general, high grade lesions will have treatment and low grade abnormalities may be followed conservatively. If the latter persist, then treatment may be offered at any time. The patient must be made aware that there is a recurrence rate after treatment, even for low grade atypia, so treatment does not give an absolute guarantee of disease clearance.

The current accepted standard is treatment under local anaesthesia by excision (loop or wire excision) or ablation (laser or diathermy). Such treatments require exclusion of invasive disease and for the lesion to be fully visible.

All patients are apprehensive about such procedures, but they are usually pleasantly surprised at the speed and lack of discomfort from a treatment like loop excision, where the treatment time itself is often less than one minute. The colposcopy to reveal the lesion takes most of the total examination time. The local anaesthesia does sting with the stimulation of the stretch fibres at injection, but again this is very short lived.

General anaesthesia is needed for disease extending onto the vagina or if cone biopsy is to be performed for disease that is not fully visible, for glandular lesions, where invasion is suspected, or when (sometimes) extreme anxiety mandates general anaesthetic. Hysterectomy is not indicated unless the patient is about to have this operation anyway and invasion has been excluded.

Follow up

It is vital that all patients who have had an abnormality have close follow up. Patients with low grade lesions that have been treated conservatively usually have reassessment at six months with cytology, and frequently colposcopy to rule out progression. Patients whose lesions have not progressed may then be followed up with cytology at six- to 12-monthly intervals, but they will need long term review because there is a proportion who will develop subsequent disease.[8]

After treatment of a high grade abnormality, all patients require cytology and colposcopy at three to six months, a second smear six months later and annual cytology in the long term.

A large UK study that followed treated patients found a continuing increased risk of neoplasia over many years. It was often the treated patients who defaulted

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follow up who subsequently returned with invasive disease.[8]

Overall, the rate of recurrence after treatment is 5 to 10%. Any recurrence is managed as new disease, depending on the nature of the abnormality.

Difficult situations

Pregnancy

Cytology can and should be performed during pregnancy, particularly in women who have never been screened. It is not associated with any complications, but the results are less reliable than usual because of pregnancy changes and higher rates of inflammatory and unsatisfactory smears. A Cytobrush should not be used.

Any disease identified can be assessed by colposcopy, but treatment is rarely required and only if invasive disease is strongly suspected. Even high grade disease can be followed and treated postpartum because the lesions do not progress more rapidly in pregnancy. A significant proportion of disease (30% of high grade lesions and a higher proportion of low grade lesions) will spontaneously regress with the reparative changes postpartum.

The inflammatory smear

The inflammatory smear is always a difficult situation because not only can inflammation make a smear unsatisfactory, it may also mask true dysplasia. Conversely, longstanding inflammation will make epithelial cells look abnormal and give false positive results. Inflammation has been found to be a contributing factor with 'Inconclusive – …' results.

If any infective element can be identified, it should be treated and the smear repeated six weeks later. Commonly, it is nonspecific inflammation, which will settle spontaneously, allowing the smear to be repeated eight to 12 weeks later.

If the cervix looks at all abnormal in the presence of an inflammatory smear, the patient should be referred immediately to exclude invasive disease. With inflammatory smears, consideration should be given to performing liquid based cytology, which filters out inflammatory cells and may give a definite result compared with the standard smear.

New technology

Liquid based cytology

Liquid based cytology has now been available in Australia for several years. It filters away inflammatory and blood cells and gives a monolayer preparation of good quality. It is very useful in decreasing inflammatory smears and unsatisfactory results. Initial studies indicated a better sensitivity, although there has been one review showing no improvement in sensitivity for laboratories with a high quality cytology service.

HPV testing

Testing for HPV is being actively promoted as a possible replacement for standard cytology. There is much confusion, both in some medical practitioners and the general public, that a positive HPV test equates to disease. The very great majority of women who carry the virus will never develop any disease, and it is no more than a transient colonisation. HPV can be transmitted by sexual contact, but there is also research showing vertical transmission from mother to daughter at birth. Other studies have shown easy transmission through non-sexual contact and even from inanimate objects, and a large study of viral subtypes in patients and partners attending the Colposcopy Clinic at Royal Prince Alfred Hospital showed that there was a very poor correlation for viral subtypes between couples.[9]

HPV testing may be useful in trying to predict which women with low grade disease may be more at risk of progression, but while our knowledge of how the disease truly evolves is incomplete it is impossible to be dogmatic. Sadly, I have seen more than one patient whose cervix has been treated on the strength of the HPV test alone, after smear, colposcopy and biopsy were all normal. These patients were referred for a second opinion on where the disease lay and what further treatment was necessary to remove it – no treatment was ever necessary. An as yet unknown variable is how the insurance industry will treat a positive HPV test.

Other screening methods

Noncytological screening methods have their proponents. Most involve some method of staining the cervix to identify disease for referral. To date, none have come into common practice within Australia. A new device that measures the optoelectric properties of normal and abnormal cells has recently been released overseas. Initial results show sensitivity better than 90% when combined with cytology. It appears to be acceptable to patients and gives an immediate result. [I have been involved in the development of this device.]

Patient information

Useful patient information resources can be obtained from the NSW Cervical Screening Program. Examples are:

- 'A guide to understanding your abnormal Pap test result' – a brochure providing a simplified, brief explanation of abnormal results
- 'Pap smear test results: a guide for women with an abnormal Pap smear test' – a booklet produced by the Commonwealth Department of Health and Family Services.

Both are available free from the NSW Cervical Screening Program (phone toll-free number 131 556 or download from www.csp.nsw.gov.au/women/womens_resources.html).

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Psychological effects

We must not forget the psychological trauma that a positive smear will cause. Most patients still consider cervical carcinoma a sexually transmitted disease because of women's magazines headlines such as 'sexually transmitted cancer epidemic'. Depression, anxiety, psychosexual sequelae and relationship difficulties are well documented in the literature.

It is not possible to determine how any individual patient came into contact with the viral elements, so definite sexual transmission cannot be proven. Telling patients about other transmission methods does much to allay these problems. Reassurance that treatment is simple and effective and that any abnormality is extremely unlikely to be cancer is appreciated by the patient. There is literature available to help patients understand what the disease and its treatment entails (see the box on page 46).

Conclusion

Organised screening has gone far in our efforts to overcome cervical cancer. However, there still remains a population of unscreened women who have a potentially preventable disease and whom we need to encourage to attend for screening. The single most effective recruitment strategy for each of these women is her general practitioner asking her 'When did you have your last Pap smear?'. MT

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