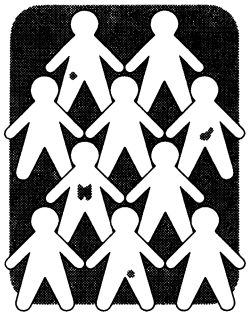
Cancer Prevention in Primary Care

Screening for cervical cancer

Joan Austoker



This is the seventh in a series of articles looking at how cancer can be prevented in general practice

Cervical screening has been shown to be effective in several countries, although not by means of randomised controlled trials. A screening programme has been in operation in the United Kingdom since 1964, but it has, in the past, been beset with problems of organisation, accountability, and commitment. The introduction in 1988 of a systematic call and recall system and the setting up of an NHS cervical screening programme national coordinating network has brought a greater sense of coherence. Coverage of the target population in England between 1989-90 and 1992-3 increased from 61% to 83%, and there is a strong indication that cervical screening is now beginning to reach those most at risk—namely, older women from lower social classes. Primary care is central to the overall success of the cervical screening programme. General practitioners are in a unique position to invite women for a smear test, to take smears, to ensure that abnormal smear test results are followed up, and to check on reasons for non-attendance. Numerous studies have looked at the involvement of general practice in cervical screening, identifying many ways in which the programme can be improved. Many practices are now running well organised and effective programmes.

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Cervical cancer: current facts

In England and Wales during 1988, 4467 new cases of invasive carcinoma of the cervix were registered (4940 in the United Kingdom as a whole), making it the eighth commonest cancer in women. Although only 15·5% of cases occur in women under 35, it is the most common cancer in this age group, accounting for 25% of all new cancers. Since the early 1970s there has been a significant increase in the incidence of both carcinoma in situ and invasive cancer in women under 45, particularly in those aged 25-34, but this may partly reflect detection by screening.

In England and Wales, 18753 women were registered in 1988 as having carcinoma in situ (including grade III cervical intraepithelial neoplasia). Most (85·5%) of these cases were registered in women under 45 (although less than 20% of deaths occur in this age group) (table I). This reflects the higher prevalence of screening among young women before 1988.

TABLE I—*Age distribution for screening, positive results on smear testing, new cases of carcinoma in situ and invasive carcinoma, and deaths from carcinoma of cervix.*[1-3] *Values are percentages*

Age (years)	Women screened, 1992-3	Positive smear, 1992-3	New cases* of carcinoma in situ or CIN3, 1988	New cases of invasive carcinoma 1988	Deaths from carcinoma of cervix, 1992
≤24	13·0	17·4	13·2	1·2	0·1
25-34	28·9	38·5	43·7	14·3	4·9
35-44	24·0	23·0	28·6	21·0	12·6
≥45	34·1	21·1	14·5	63·5	82·4

*Not true incidences as cases can be detected only by screening. Reflects a mixture of prevalence rates for women screened for the first time and cumulative incidence rates from the date of last screening for women screened previously.
CIN3=cervical intraepithelial neoplasia grade III.

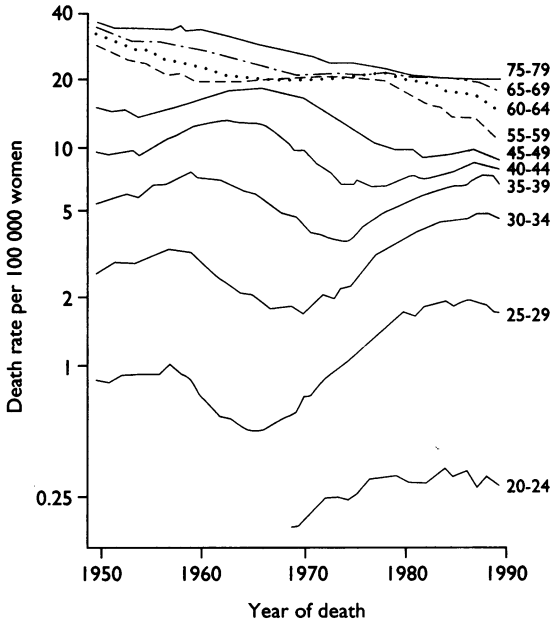

FIG 1—*Age specific death rates for cervical cancer in England and Wales, 1950-90*[4]

In 1992, 1647 women died of cervical cancer in England and Wales (1860 in the United Kingdom as a whole), 95% of them aged 35 and over (table I). Over the past 20 years the mortality in women aged 45 and over has fallen noticeably (fig 1). Moreover, the rise in deaths in women aged 40-44, observed in the late 1970s and 1980s, has now reversed. For women under 40 the significant increase in mortality observed in the 1970s and 1980s now seems to be stabilising. This reversal of earlier trends may be due to an increase in screening over the past decade.

The five year relative survival rate for stage I cervical cancer is 79%, reducing to 7% for stage IV disease. Survival for precancerous lesions is almost 100%, which provides the incentive for screening.

Regional variation in the incidence of and mortality from cervical cancer is considerable in the United Kingdom. The highest risks for cervical cancer are generally in the north of the country and in Wales.

In general, women of low socioeconomic status have higher rates of cervical cancer, with a threefold difference between social classes V and I.

Evidence of effectiveness of screening

Cervical screening has been shown to be effective in several countries, although not by means of random-

ised controlled trials. In the Nordic countries, nearly complete coverage of the target population by organised cervical screening programmes in Iceland, Finland, Sweden, and parts of Denmark were soon followed by sharp falls in both incidence and mortality (table II, fig 2). Reductions in total incidence and mortality were similar in Iceland and Finland (despite the different screening intervals used) but lower in Sweden (where screening was targeted at a narrower age range), indicating that, in organised screening, achieving a wide coverage of ages is a more important determinant of risk reduction than the frequency of screening.

TABLE II—*Details of screening programmes for cervical cancer in Nordic countries*[5,6]

	Denmark	Finland	Iceland	Norway	Sweden
Extent of programme	Some counties	Nationwide	Nationwide	One county	Nationwide
Target coverage of national population (%)	40	100	100	5	100
Year in which organised screening:					
Began	1962	1963	1964	1959*	1964
Was fully developed	1975	1970	1969	—	1973
Targeted age range (years)	30-50	30-55	25-69	25-59	30-49
Screening interval (years)	4	5	2-3	3	4
% Reduction in overall world adjusted:					
Incidence rate	45	66	70	26	46
Mortality rate‡	35	60	62	18	32†

*Project 1959-77.
†National age adjusted.
‡1966/70-1981/85.

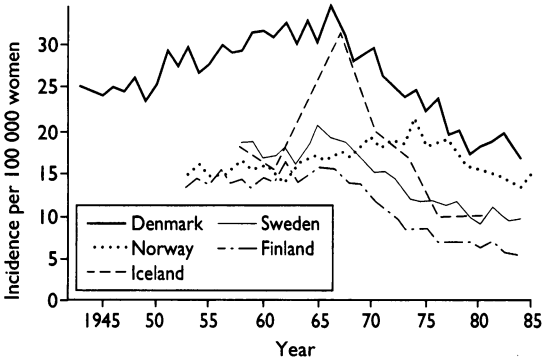

FIG 2—*Trends in annual age adjusted incidence rates of invasive carcinoma of cervix in Nordic countries*[5]

Cervical screening in the United Kingdom

A screening programme has been in operation in Britain since 1964. With the exception of a study in the north east of Scotland, screening in the United Kingdom has until recently been largely ineffective. There has been no reduction in the overall incidence of invasive cervical cancer, but a small reduction in mortality is just becoming apparent. However, any observed increases in incidence and mortality might have been much greater in the absence of screening.

Organisation of cervical screening

The reasons for the past failure of the national screening programme in the United Kingdom have been extensively examined. It is generally agreed that the problem has been not so much one of money or skill but of organisation, accountability, and commitment. The current dilemma is not whether screening should or should not be performed but how a service can be organised to greatest effect.

Box 1 shows the factors needed to improve the effectiveness of cervical screening. The target in the *Health of the Nation* is to reduce the incidence of invasive cervical cancer by at least 20% by the year 2000, from 15 per 100 000 population to no more than 12 per 100 000. If uniform acceptance rates of 80% can be achieved, a reduction in mortality of 65% to 70% can then be expected in the long term.

The introduction in 1988 of a systematic call-recall system and the setting up of an NHS cervical screening programme national coordinating network have brought a greater sense of coherence. A more uniform approach is being formulated for deciding who should be screened and how often, for classifying smears according to the degree of nuclear abnormality, for standardising terminology, for interpreting results and following up abnormalities, and for evaluating the effectiveness of the programme. Steps being taken locally by health authorities, the appointment of a national coordinator, the development of a quality assurance programme, and measures to improve the training of the relevant health professionals should all help to improve the effectiveness of the programme.

Improving population coverage: impact of targets

To be most effective screening must concentrate on a wide age range, with every effort being made to reach those at higher risk of developing invasive cancer—namely, older women of lower social classes. Before 1988 at least two thirds of patients with invasive cancer had never been screened at all and in women over the age of 40 (among whom over 70% of cases of invasive disease occur) the proportion who had never been screened was over 90%. In Aberdeen, where a large percentage of the population have had a smear taken, only 2% of women with invasive cervical cancer had had a negative result on smear testing within the preceeding five years, while 90% had never had a smear tested.

Primary care can exert a major influence on coverage. The 1990 general practitioner contract set targets on which payment for cervical screening depends. Payments are triggered on reaching 50% or 80% coverage of the target population over the preceding 5·5 years, with a differential of 3:1 in favour of the latter. This has led to a considerable increase in screening activity. Between April 1990 and October 1993 the percentage of general practitioners reaching the 80% target increased from 53% to 83%, while the percentage achieving neither target decreased over the same period from 15% to 3%. Coverage of the target population between 1989-90 and 1992-3 increased from 61% to 83%. The range between regional health authorities in England in 1992-3 was 70·3-88·8%, with lowest coverage achieved in the Thames regions. Nine district health authorities in inner London achieved a coverage of less than 60%. There is a strong indication that cervical screening is now beginning to reach those most at risk. Coverage in the age groups 55-59 and 60-64 improved between 1988-9 and 1992-3 by 128% and 225% respectively (from 37% and 25% to 84·3% and 81·3% respectively). At least one survey in 1992 has shown that the social class differential in screening that was apparent in an earlier survey in 1988 has almost disappeared. However, differential uptake is still likely to be a problem in inner city areas, where there is a higher proportion of women in social classes

Box 1—Factors necessary to improve effectiveness of cervical screening

- Spread screening evenly across a wide age range
- Ensure a high participation rate of the target population by making the service acceptable to women
- Repeat the tests at a suitable interval, not exceeding five years
- Ensure adequate facilities and quality control for taking and interpreting smears
- Ensure a reliable fail safe mechanism for the prompt follow up of abnormal results
- Ensure adequate facilities for appropriate treatment
- Ensure systematic evaluation and monitoring

IV and V, a higher population mobility, inaccurate registers, and a lower overall coverage than that achieved in other parts of the country.

The setting of targets has clearly provided a great stimulus to many practices. It remains a matter of concern that it is a disincentive to those for whom any target or the higher target seems impossible to achieve and has resulted in very little interest in either providing or improving the cervical screening programme in these practices.

Cervical screening in primary care: organisational issues

Primary care is central to the overall success of the screening programme. General practitioners are in a unique position to invite women for a smear test, to take smears, to ensure abnormal results are followed up, and to check on reasons for non-acceptance of screening. Box 2 gives the objectives for primary care teams in cervical screening. The main obstacle to the success of cervical screening in primary care relates to organisation.

Box 2—Cervical screening: objectives for primary care teams

- To run a systematic call and recall system
- To improve the coverage of the target population
- To follow up women who did not respond to the invitation
- To improve the quality of the smears taken
- To communicate with the laboratory
- To deal with normal results
- To deal with abnormal results
- To improve the follow up of smears that are not normal
- To reduce patients' anxiety and dissatisfaction
- To run an effective fail safe system
- To monitor and evaluate the effectiveness of the screening programme in the practice

NEED FOR SYSTEMATIC METHOD OF CALL-RECALL

The effectiveness of a systematic method of call-recall over an opportunistic approach in encouraging women to have a smear test has been shown in a randomised controlled trial. Other studies have confirmed that a call-recall system increases overall uptake, particularly among older women and those from lower social classes who have never been screened.

There is a wide range of methods of organising cervical screening in primary care. A study has shown that a younger age of general practitioner, a more rural practice, larger practice size, employment of a practice nurse, a belief in the efficacy of cervical screening, and a positive attitude to the time spent on cervical screening were all strong predictors of an organised approach to cervical screening within a practice.

Organisation of cervical screening varies between health authorities and between practices. The call-recall system can be administered either by the local health authority or family health services authority or from within the practice itself. Figure 3 shows a protocol for a practice call system. A coordinated system at a local level could improve the programme substantially. There is strong evidence that most practices are capable of providing well organised systematic programmes and the majority are now achieving high population coverage. When this is not the case, practices may need help and advice from a primary care cervical screening facilitator (box 3).

Box 3—Cervical screening: what can a facilitator offer?

- Provide support and liaison
- Offer a strategy for improving cervical screening within the practice
- Advise on organisation of resources, planning, and integration into the local call-recall scheme
- Provide ideas and suggestions for administration of the scheme—for example, specimen invitation and results letters, ideas on record keeping, flags and stickers for notes
- Provide posters, leaflets, and educational materials for patients and members of primary care teams
- Provide details of training for practice nurses and receptionists
- When there is no practice nurse, encourage and facilitate employment of a suitable person
- Provide ongoing study and updating sessions for primary care team members
- Offer practices advice on audit

PRACTICE REGISTERS

A key issue influencing overall uptake and thereby the success of the screening programme is the adequacy of the population register. Studies in inner London and Manchester have found that between 30% and 60% of invitations were sent to wrong addresses. Even in a small, stable general practice population a study found that 2% to 4% of eligible women could not be traced.

LETTER OF INVITATION

The style, tone, presentation, and contents of the letter of invitation are important. There is more likelihood of a woman accepting an invitation for screening if the potential benefits of the test are properly explained (box 4). The availability of a female doctor or nurse should also be mentioned. One survey

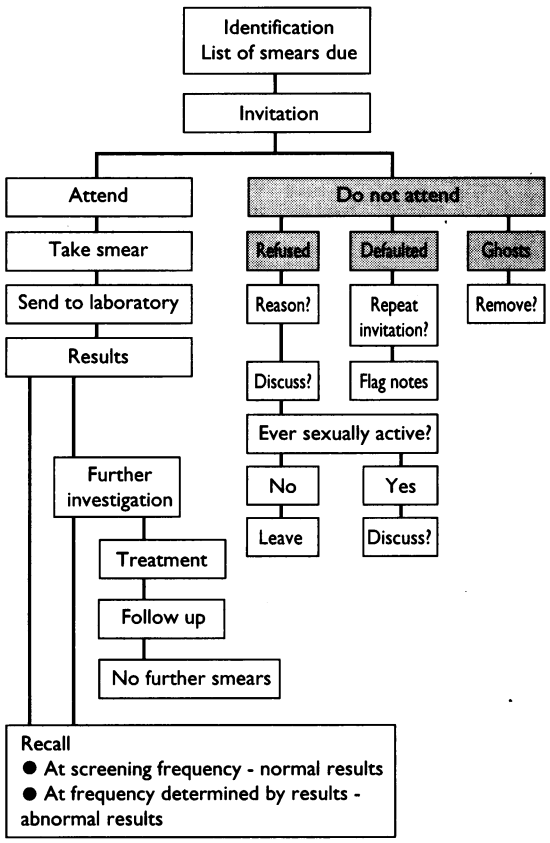

FIG 3—*Protocol for call-recall system for cervical screening in general practice*[7]

Box 4—Invitation letters

- The purpose of the test should be clearly stated
- The applicability of the test to the women should be stated—that is, the letter should answer the question "Why me?"
- A fixed appointment should be given if possible. This results in better uptake rates than asking the patient to make her own appointment
- A reply slip helps practice organisation
- The availability of a woman doctor or nurse to take the smear should be mentioned
- A statement should be made on how results will be communicated
- The letter should if possible be signed by a doctor the woman knows
- A leaflet should be included

showed that 41% of women would prefer a female doctor to take the smear, and the proportion was higher among older women and women from lower socioeconomic groups.

Some studies have suggested that women who have not had a smear test before are more likely to accept an invitation if they are offered a specific appointment rather than an open invitation. Sending times of appointments is, however, administratively more complex than sending each patient an identical letter, especially if the letters of invitation are dispatched from the family health services authority. Offering a wide range of times when smears can be taken at the surgery should improve response rate.

Reminders by telephone are more effective than standard letters. Personal approaches from practice staff may help overcome anxiety about the test and the disease, but care must be taken not to coerce women against their will.

A leaflet should accompany the invitation letter. This offers the opportunity not only to address women's attitudes and beliefs about cervical screening but also to consider organisational and administrative barriers that can deter women from attending for a smear test.

NON-ATTENDERS

Improving population coverage requires to some extent an understanding of the reasons why women do or do not attend for cervical screening. Factors affecting uptake of cervical screening include the influence of age and social class on perceptions of vulnerability and the costs and benefits of screening. Many studies have shown that attendance can be inhibited by a high level of anxiety about the test and fear about cervical cancer, by erroneous beliefs about the relevance of the test, by concurrent family difficulties, and a low priority being accorded to cervical screening.

Studies have shown that flagging the notes of non-attenders and offering them screening on an opportunistic basis increases uptake.

Taking a smear

Of the 4·5 million smears taken in 1991-2 in England, 77·6% were taken in primary care. Evidence suggests that most were taken by practice nurses.

Women's anxiety about cervical screening can be reduced by providing adequate information before taking the smear (box 5).

A key factor determining the effectiveness of cervical screening programmes is the quality of smear taking. Poor smear taking can miss 20% or more of precancerous abnormalities. Ideally, smears should contain endocervical cells, metaplastic cells, endocervical mucus, and squamous cells. Adequate smears contain squamous cells and at least two of the remaining three elements. The person who takes the smear has the responsibility of ensuring that the cervix has been adequately sampled. In England in 1991-2, 6·3% of smears taken were inadequate (table III). Box 6 shows some of the reasons why smears may be reported as inadequate. Any infection or atrophy should be treated before repeating the smear. Repeat the smear at a minimum interval of four weeks. If smears are persistently inadequate, assessment by colposcopy should be considered.

Recent guidelines from the Department of Health emphasise the importance of appropriate training for all those who take smears.

Table III also shows the estimated national percentages of adequate smear test results for women of all ages in England in 1991-2. Borderline results and mild, moderate, and severe dyskaryosis occurred more often in the younger age groups, while suspicion of invasive carcinoma and suspicion of glandular neoplasia occurred more often in the older age groups.

TABLE III—*Results of smear tests for all age groups in England, 1991-2.*[8] *Values are percentages*

Result of test	Mean
Inadequate	6·3
Adequate:	
Negative	92·9
Borderline changes	3·4
Dyskaryosis	
Mild	2·1
Moderate	0·9
Severe	0·6
?Invasive carcinoma	0·1
?Glandular neoplasia	0·1

Box 5—What every woman should know before having a smear test

- The condition cervical screening can detect—that is, precancerous lesions
- Likelihood of a negative result (about 93%)
- Meaning of a negative result: low risk, not no risk
- Meaning of being recalled:
  An inadequate or unsatisfactory smear
  A positive or abnormal smear—most women do not have cancer, any disease detected is treatable
- When and how results will be made available: each woman should receive a written result, whether it is negative or positive

Interpreting and managing results of smear tests

A smear may have negative results in that there is no nuclear abnormality, but other incidental comments may also be made about the smear (table IV). When a smear is reported with some abnormal cells, the action required will depend on many factors, including the appearance of any previous smears (table V, box 7).

Results from smear tests can be difficult to interpret. There is a whole spectrum, from completely normal to definitely malignant. The exact risk consequent on each grade is not clear. When recommending further action, referral of all grades of abnormality would lead to considerable overinvestigation and overdiagnosis. A careful balance thus has to be reached, taking into account the benefits and costs both to women and to

Box 6—Reasons for failure of cervical smear test[9]

- Patient very tense owing to failure of reassurance
- Cervix not visualised adequately
- Cervix not scraped firmly enough
- Transformation zone not completely scraped
- Material incompletely transferred to the slide
- Sample poorly spread (too thick or too thin or distortion due to excessive pressure)
- Smear allowed to dry before fixation
- Insufficient fixative used
- Smear consisting mainly of blood or inflammatory cell exudate, possibly associated with menstruation
- Contamination of the smear with lubricant, vaginal cream, or spermicide
- Menstrual smears containing large numbers of endometrial cells

TABLE IV—*Interpretation of specific incidental observations on reports for negative results on cervical smear testing*[7,9]

Result	Explanation	Action
Specific infections	*Trichomonas, Candida*, and cell changes associated with herpes simplex can be identified	*Trichomonas*—treat *Candida*—treat if symptoms Herpes—no treatment—discuss with patient
Actinomyces	Organisms associated with intrauterine device	No consensus. Either do nothing unless other symptoms (pain or discharge) or change coil and the actinomyces organisms will disappear
Endocervical cells	Cells from the glandular epithelium of the cervical canal. During its formation the transformation zone will include similar epithelium	No action needed
Metaplastic cells (metaplasia/squamous metaplasia)	Normal cells from the transformation zone that are ideally contained in a smear	No action needed
Cytolysis	Normal process of cell disintegration	No action needed
Endometrial cells	Cells derived from the endometrial lining of the uterine cavity. Shed during menstruation and in some other circumstances	Probably normal finding if intrauterine device present or if days 1-12 of 28 day cycle Otherwise discuss with laboratory or local gynaecologist
Inflammatory changes	Cellular appearance present in some degree in many smears and not evidence of cervical intraepithelial neoplasia	No consensus. Either do nothing or take high vaginal swabs for culture and sensitivity and take chlamydial swabs. Then treat as necessary
Atrophic smear	Cell shrinkage or wastage. Common in postmenopausal smears—that is, oestrogen and progesterone levels are low. Similar changes are seen in postnatal smears	No action needed

TABLE V—*Interpretation of results of smear testing*[10]

Result	Action
Inadequate	Repeat smear
Negative	Routine recall*
Borderline changes, with or without changes due to human papillomavirus	Repeat smear at six months Consider for colposcopy if changes persist
Mild dyskaryosis with or without changes due to human papillomavirus	Repeat smear at six months Consider for colposcopy if changes persist
Moderate dyskaryosis with or without changes due to human papillomavirus	Refer for colposcopy
Severe dyskaryosis with or without changes due to human papillomavirus	Refer for colposcopy
Severe dyskaryosis/?invasive carcinoma	Urgent referral to a gynaecological oncologist
Glandular neoplasia or suspicion of glandular neoplasia	Urgent referral to a gynaecological oncologist

*Recall for negative results will also depend on any history of previous abnormal smears or cervical intraepithelial neoplasia (see boxes 7, 9, and 11).

the health service. Inevitably opinions will differ on how such a balance is arrived at.

The management of mild dyskaryosis presents precisely such a dilemma. Although the consensus is that a single mildly dyskaryotic smear should be managed by a repeat smear test at six months, with referral for colposcopy only if the abnormality persists, there are those who believe that women with such smears should be referred immediately for colposcopy. This is because, although the majority of such smears will revert to normal or persist as mildly dyskaryotic, a small proportion may progress to severe dyskaryosis. A balance obviously has to be achieved between ensuring appropriate management and not subjecting too many women to unnecessary medical procedures. A recent study from Aberdeen concluded that cytological surveillance, although safe, is not an efficient strategy for managing women with mildly abnormal smears. Three quarters of the women in the study subsequently required colposcopy and there was a high default rate among those put on surveillance. However, others have argued that referring all women with one mildly dyskaryotic smear for colposcopy would result in overinvestigation of very many more women than would ever go on to develop invasive disease. Ultimately, it may prove possible to differentiate high risk women within the broader group that has mild dyskaryosis by testing for high risk human papillomavirus types. Such testing could possibly be used as an adjunct to current screening methods. Further research is clearly needed to assess the role of cytological surveillance in mild dyskaryosis and to determine its optimal management. It will also be important to assess the psychological implications for women put on cytological surveillance as opposed to those who proceed to immediate colposcopy.

In practice, mild and moderately dyskaryotic smear test results do not correlate well with the histological diagnosis of mild or moderate dyskaryosis—that is, grade I or II cervical intraepithelial neoplasia. The difference is more in the quantity of cervical intraepithelial neoplasia rather than the quality. Grade III cervical intraepithelial neoplasia in the presence of mild or moderate dyskaryosis generally speaking occupies a smaller proportion of the transformation zone than when it exists in the presence of severe dyskaryosis on the smear. Women with one moderately dyskaryotic or two mildly dyskaryotic smears should be referred for colposcopy (box 7). A fairly large proportion of grade III cervical intraepithelial neoplasia could be expected in such women.

Figure 4 shows a protocol for managing patients with abnormal smear test results.

How should human papillomavirus infection be managed?

Increasing evidence implicates certain strains of human papillomavirus or wart virus as causing cervical cancer. Different strains of human papillomavirus have been identified, and they vary in their oncogenic potential. Correlation of virus type with the morphology of the cervical lesion shows that human papillomaviruses 16 and 18 are present in over 80% of invasive squamous cancers of the cervix and grade III cervical intraepithelial neoplasia.

Reporting changes due to human papillomavirus in

Box 7—Interpretation of smears: summary of recommendations[7,10]

- A smear showing borderline nuclear or mildly dyskaryotic change should be repeated six months later and consideration should be given to colposcopic referral only if it is not then normal
- A minimum of two consecutive negative smears at least six months apart are needed after a borderline or mildly dyskaryotic result before surveillance is reduced to the normal screening frequency (preferably three yearly)
- Moderate and severe dyskaryosis should be referred for colposcopy straight away
- Management of women with human papillomavirus must be according to the grade of cervical intraepithelial neoplasia and not simply because of the presence of human papillomavirus

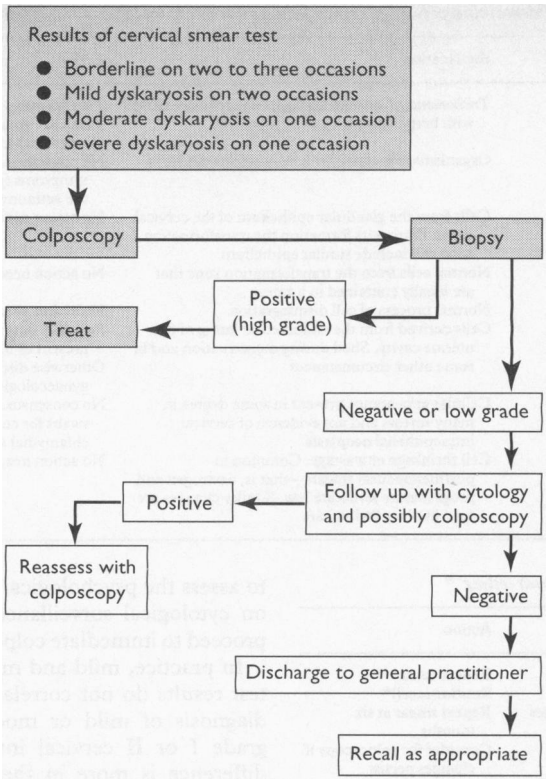

FIG 4—*Protocol for managing patients with abnormal smear results. Whether to take biopsy specimen or treat immediately depends on balance between cytological and colposcopic findings and local protocols*

cervical smears poses particular problems, both for women and for those who take smears who have to explain findings (boxes 7 and 8). No cell with evidence of human papillomavirus infection is normal, and no smear in which there is evidence of human papillomavirus infection should be reported as negative whether or not there is a substantial nuclear abnormality. Cells in which there is dyskaryosis in addition to cytoplasmic features of human papillomavirus infection should be reported according to the grade of dyskaryosis, regardless of the cytoplasmic changes.

Giving results to women with abnormal smears

Considerable evidence suggests that women with abnormal results on smear testing are extremely anxious because of concern about investigative procedures such as colposcopy and about the outcome, in particular fears about cancer. In one study 65% of women were worried or alarmed on receipt of a positive smear test result; 27% were shocked, stunned, or devastated.

The way in which a woman is told about an abnormal smear test result will often affect how she will cope with any treatment or future follow up. The most effective and efficient way of conveying this is to ensure that each woman receives her result in writing. A randomised study in the context of an abnormal smear test result concluded that inclusion of an information leaflet with the postal notification of the results led to significantly lower levels of anxiety. The information should be understandable and not alarming. Two studies found that the readability of the written information relating to abnormal results was a key issue in the acceptability of the information provided to women.

Women who receive an abnormal smear test result should be offered an opportunity to speak with their general practitioner to discuss the implications of the results. Waiting and uncertainty are often the most difficult part of the follow up process. If the result is not normal women often assume that it means cancer. It is therefore important to explain terms such as dyskaryosis and preinvasive cancer, and what further steps in investigation, follow up, and treatment may be needed.

Research has shown that anxiety and distress are considerably less in women who have had colposcopy explained to them before their appointment. A randomised study has shown that the high levels of anxiety experienced by women referred for colposcopy were reduced by providing a brief simple booklet about colposcopy with the appointment letter. More detailed information added to knowledge but did not reduce anxiety.

Who needs colposcopy?

Cervical intraepithelial neoplasia may be suspected in patients with abnormal cervical cytology, but diagnosis and treatment will depend on referral of such women for colposcopic assessment. The two main indications for colposcopy are to investigate an abnormal smear test result (table V, box 7) and to assess a clinically suspicious cervix more thoroughly even when smear test results are normal.

When should the cervix be treated?

In order to know when to treat the cervix it is important to have some idea of the rate of progression of abnormalities. Those at high risk of progression must be treated. There is currently inadequate information about the natural history of the lower grades of abnormality. The majority may not progress, but some would lead eventually to invasive disease if not treated at any stage. A balance must thus be reached between potential overdiagnosis and overtreatment and the need to ensure that progression to invasive cancer does not occur. It is therefore not possible to define a treatment policy with any degree of certainty. Although grade I cervical intraepithelial neoplasia carries low risk and grade III carries high risk, grade II cervical intraepithelial neoplasia is more difficult to categorise. On balance, it is currently believed that grades II and III cervical intraepithelial neoplasia should be treated once diagnosed. Grade I cervical intraepithelial neoplasia may be treated or kept under close surveillance (box 9).

Treatment aims at destroying cells in the transformation zone of the cervix. Extremes of heat or cold are equally effective. Some methods of treatment require two visits, while others deal with diagnosis and treatment in one visit, which has obvious advantages

Box 8—What women need to know if human papillomavirus is reported*

- The wart virus in its subclinical state requires no specific treatment such as antibiotics. Referral to specialised clinic is not necessary
- The changes are evidence of contact with the virus at some stage in the woman's life and may not indicate an active infection
- There are parallels with skin warts and many other viral conditions in which only very few contacts develop the clinical infection
- The virus is usually transmitted sexually, but this is not the only way as it has been isolated from other sites in the body and has also been found in children
- The natural history of wart virus changes is to regress over a period of several years. One particular strain of the virus, human papillomavirus 16, may be an important prognostic marker for identifying patients who are at risk of developing severe cervical disease. Other factors such as smoking or lowered immunity may also come into play
- In a steady relationship there is no need to change contraception, but if a woman is likely to have any sexual contact outside an established relationship barrier methods might be used
- Subclinical warts are not known to affect pregnancy, fertility, or a baby. Clinical warts should be treated before delivery
- Visible cervical warts are thought to be more easily transmitted than subclinical human papillomavirus infection
- Colposcopic treatment does not eradicate wart virus

*Adapted from Oxfordshire District Health Authority[11]

Box 9—When should the cervix be treated?

- Grades II and III cervical intraepithelial neoplasia should be treated once diagnosed
- Grade I cervical intraepithelial neoplasia may be treated or kept under close surveillance
- Grade I cervical intraepithelial neoplasia not treated requires two negative smear test results six to 12 months apart before returning to the normal screening frequency (preferably every three years)
- Many women are unlikely to accept even a low risk of malignancy and would prefer treatment
- If a surveillance policy is adopted for grade I cervical intraepithelial neoplasia, local circumstances must be taken into account, including the patient default rate

Box 10—Treatment of cervical intraepithelial neoplasia

- Local destructive therapy

Carbon dioxide laser ablation
"Cold" coagulation
Cryosurgery
Electrocoagulation

- Local excision

Knife cone biopsy
Laser cone biopsy
Large loop excision of the transformation zone

- Hysterectomy (rare)

for the woman. Box 10 shows current methods of treatment. None of these methods has been evaluated in a randomised study and there is not strong evidence supporting one method over another. General practitioners and practice nurses should be familiar with the type of treatment offered locally.

Follow up of treated patients

There are four reasons for follow up.

- To identify residual disease
- To identify new cervical intraepithelial neoplasia
- To identify new invasive disease
- To reassure both the patient and the clinician.

The risks of the first three occurring are probably no different whether the patient has undergone an ablative or excisional technique.

Box 11 shows the recommendations for the follow up of treated patients.

Running an effective fail safe system

General practitioners have a key role in the fail safe mechanism, contributing to it in several ways (box 12).

When smears are taken by general practice trainees or practice nurses, responsibility lies with the general practitioner principal recorded on the request form. When smears are taken outside primary care and the result is sent to the general practitioner it is important to determine who is looking after follow up and referral as necessary.

Conclusion

Cervical screening is safe, reasonably specific, and has been proved in several countries. It does have disadvantages—a major problem being overdiagnosis, whereby many more women are found with intraepithelial disease than would be expected to develop invasive cancer in their lifetime. It does, however, have the potential to make a significant impact on incidence of and mortality from the disease.

Primary care teams have a vital role in ensuring the success of the cervical screening programme. Numerous studies have looked at the involvement of general practice in cervical screening, identifying many ways in which the service offered by practices can be improved. The setting of targets has provided a stimulus to most practices, a large percentage of which have now obtained the higher target of 80%. Many practices are now running well organised and effective schemes.

Box 11—Follow up of treated patients[7,10]

- Cytological follow up is essential after treatment for cervical intraepithelial neoplasia. Colposcopy is not essential, but may enhance detection of persistent disease at six months
- After treatment the first smear should be taken at six months and, if results are normal, repeated at 12 months and then annually up to five years
- More frequent surveillance need not be continued beyond five years of normal findings after conservative treatment for grade III cervical intraepithelial neoplasia. At five years women should be returned to the normal screening frequency (preferably every three years)
- Women undergoing hysterectomy with previous or current grade III cervical intraepithelial neoplasia need have no further smears taken if the cytology is normal six and 12 months after surgery. If there is any suspicion that the premalignant condition has not been completely removed, screening every three years should continue

Box 12—Role of general practitioners in running an effective fail safe system[12]

- Checking that all smear reports have been received
- Informing the women of the result
- Initiating further investigation
- Contacting women who do not attend for further investigation
- Informing family health services authority if a woman requiring investigation has moved away
- Monitoring the "suspend" and "repeat advised" lists sent by the authority

A well organised programme depends on screening a sufficiently wide age range, at an interval between three and five years. It requires adequate population registers, an effective call-recall system, a reliable fail safe procedure, and good quality control. If uniform acceptance rates of 80% can be achieved a reduction in mortality of 65% to 70% can then be expected in the long term.

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A complete list of references is available from the author.

Statistics Notes

One and two sided tests of significance

J Martin Bland, Douglas G Altman

This is the eighth in a series of occasional notes on medical statistics.

In some comparisons—for example, between two means or two proportions—there is a choice between two sided or one sided tests of significance (all comparisons of three or more groups are two sided).

When we use a test of significance to compare two groups we usually start with the null hypothesis that there is no difference between the populations from which the data come. If this hypothesis is not true the alternative hypothesis must be true—that there is a difference. Since the null hypothesis specifies no direction for the difference nor does the alternative hypothesis, and so we have a two sided test. In a one sided test the alternative hypothesis does specify a direction—for example, that an active treatment is better than a placebo. This is sometimes justified by saying that we are not interested in the possibility that the active treatment is worse than no treatment. This possibility is still part of the test; it is part of the null hypothesis, which now states that the difference in the population is zero or in favour of the placebo.

Paired t test analyses of difference in forced vital capacity (ml) between first and subsequent visits (n=25)

	Change in forced vital capacity from baseline		
	1 week	3 months	1 year
Mean	48	−63	−49
Standard error	42	33	55
P (one-sided)	0·13	0·032	0·19

A one sided test is sometimes appropriate. Luthra *et al* investigated the effects of laparoscopy and hydrotubation on the fertility of women presenting at an infertility clinic.[1] After some months laparoscopy was carried out on those who had still not conceived. These women were then observed for several further months and some of these women also conceived. The conception rate in the period before laparoscopy was compared with that afterwards. The less fertile a woman is the longer it is likely to take her to conceive. Hence, the women who had the laparoscopy should have a lower conception rate (by an unknown amount) than the larger group who entered the study, because the more fertile women had conceived before their turn for laparoscopy came. To see whether laparoscopy increased fertility, Luthra *et al* tested the null hypothesis that the conception rate after laparoscopy was less than or equal to that before. The alternative hypothesis was that the conception rate after laparoscopy was higher than that before. A two sided test was inappropriate because if the laparoscopy had no effect on fertility the conception rate after laparoscopy was expected to be lower.

One sided tests are not often used, and sometimes they are not justified. Consider the following example. Twenty five patients with breast cancer were given radiotherapy treatment of 50 Gy in fractions of 2 Gy over 5 weeks.[2] Lung function was measured initially, at one week, at three months, and at one year. The aim of the study was to see whether lung function was lowered following radiotherapy. Some of the results are shown in the table, the forced vital capacity being compared between the initial and each subsequent visit using one sided tests. The direction of the one sided tests was not specified, but it may appear reasonable to test the alternative hypothesis that forced vital capacity decreases after radiotherapy, as there is no reason to suppose that damage to the lungs would increase it. The null hypothesis is that forced vital capacity does not change or increases. If the forced vital capacity increases, this is consistent with the null hypothesis, and the more it increases the more consistent the data are with the null hypothesis. Because the differences are not all in the same direction, at least one P value should be greater than 0·5. What has been done here is to test the null hypothesis that forced vital capacity does not change or decreases from visit 1 to visit 2 (nine week), and to test the null hypothesis that it does not change or increases from visit 1 to visit 3 (three months) or visit 4 (one year). These authors seem to have carried out one sided tests in both directions for each visit and then taken the smaller probability. If there is no difference in the population the probability of getting a significant difference by this approach is 10%, not 5% as it should be. The chance of a spurious significant difference is doubled. Two sided tests should be used, which would give probabilities of 0·26, 0·064, and 0·38, and no significant differences.

In general a one sided test is appropriate when a large difference in one direction would lead to the same action as no difference at all. Expectation of a difference in a particular direction is not adequate justification. In medicine, things do not always work out as expected, and researchers may be surprised by their results. For example, Galløe *et al* found that oral magnesium significantly increased the risk of cardiac events, rather than decreasing it as they had hoped.[3] If a new treatment kills a lot of patients we should not simply abandon it; we should ask why this happened.

Two sided tests should be used unless there is a very good reason for doing otherwise. If one sided tests are to be used the direction of the test must be specified in advance. One sided tests should never be used simply as a device to make a conventionally non-significant difference significant.

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