Cervical cancer screening: state of the art

Victor M. Valdespino[a,b] and Victor E. Valdespino[c]

Purpose of review

The objective of cervical cancer screening is to prevent the occurrence of and death from cervical cancer by detecting and treating high-grade squamous intraepithelial lesions. A significant decline in occurrence and mortality from cervical cancer in developed countries has been associated with the application of organized cervical screening programs. The use of the available local health methods in cervical cancer screening can be adjusted in different countries. This review discusses the recent results in traditional and alternative cervical cancer screening.

Recent findings

The current recommendations of both the American Cancer Society and the American College of Obstetricians and Gynecologists concerning clinical practice guidelines for cervical cancer screening are commented upon. New methods and new technology for cervical cancer screening are described. Attributable failure factors in the screening process, particularly in the coverage, are analyzed. A critical assessment of the suitability of local cervical cancer screening resources is discussed.

Summary

Screening is clearly a complex multifactorial process, not a test. Nowadays, with the human papillomavirus vaccine on the horizon, screening is the best strategy for cervical cancer control. Good screening programs, with high coverage, quality control and follow-up included, are the basis of obtaining better results. The Papanicolaou test and its variants are the best methods of cervical cancer screening in high-resource settings. Alternative visual inspection using cervical dyes could be the most useful method in low-resource settings. The challenge for the future may be less of a technical nature and more dependent on local finances and screening policies.

Keywords

alternative and traditional methods, cervical cancer screening

Curr Opin Obstet Gynecol 18:35–40. © 2006 Lippincott Williams & Wilkins.

[a]Gynecologic Department, UMAE de Oncología del CMN SXXI, Instituto Mexicano del Seguro Social, Mexico City, Mexico, [b]Universidad Autónoma Metropolitana, Mexico City, Mexico, and [c]Centro Médico '20 de Noviembre', Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado, Mexico City, Mexico

Correspondence to Victor M. Valdespino MD, Angel Urraza 517, Colonia del Valle, México 03100 D.F. Mexico
Tel: +55 5559 7768; e-mail: valdespinov@yahoo.com

Current Opinion in Obstetrics and Gynecology 2006, 18:35–40

Abbreviations

ACS	American Cancer Society
ASC-US	atypical squamous cells of undetermined significance
CIN	cervical intraepithelial neoplasia
HPV	human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
LBC	liquid-based cytology
NHS	National Health Service

1040-872X

Introduction

Cervical cancer continues to be an important world health problem for women. The global yearly incidence of cervical cancer is 493 000 cases, and the annual death rate is 274 000. It is the third most common cancer in women worldwide. Eighty-three percent of cases occur in developing countries, where cervical cancer is the first or second most frequent cause of cancer death in women [1]. Cervical cancer is one of the best-understood neoplasms, given its well known viral cause and slow progression after the underlying cause of persistent infection with high-risk human papillomavirus (HPV). The prevalence of HPV-DNA in cervical specimens from women aged 30 years and above in countries with a high incidence of cervical cancer is about 11–40%, whereas the prevalence in low-incidence countries is 5–10% [2].

A steady 70% annual decline in mortality from cervical cancer has been observed since the mid 20th century after the introduction of widespread Papanicolaou (Pap) cytological screening [3]. Pap test cervical cytology screening has helped to reduce cervical cancer rates significantly through the detection of premalignant lesions. Potential benefits of screening have improved prognosis for those with screen-detected cancers. The possibility of less radical treatment, reassurance for those with negative test results, and resource savings if treatment costs are reduced, improving the quality of life, have helped to reduce cancer mortality. Potential negative effects of screening include physical, economic, and psychological consequences of false-positives and false-negatives, and the potential of overdiagnosis.

Although the incidence of cervical cancer in developed countries has declined dramatically in the 50 years since the clinical application of the Pap test, continued surveillance is needed. The natural history of cervical can-

cer lends itself well to screening programs [4]. As a rule, it takes at least one decade from the introduction of HPV to the basal layer of the cervical epithelium via sexual intercourse until the development of invasive cancer. The long latent period of this disease allows many opportunities to look for cytological abnormalities of high-risk HPV and to intervene and prevent progression to cancer. The utilization of screening tests is further justified by their relatively low cost and widespread acceptance in women. The mean sensibility, specificity, and positive and negative predictive values of a single Pap test in detecting cervical intraepithelial neoplasia (CIN) 2–3, however, were 58, 68, 19, and 99% [5, 6], respectively. With a second test or in combination with a HPV-DNA test, visual inspection using dyes such as 3–5% acetic acid (VIA) or Lugol's iodine (VILI), the sensitivity increases to 94, 83, and 89%, respectively.

Colposcopy, along with colposcopically directed biopsies, has become the primary method for evaluating women with an abnormal Pap test. If the entire squamocolumnar junction of the cervix is visualized, the examination is considered satisfactory. Reid's colposcopic index differentiates low-grade from high-grade cervical disease [7]. If the cervical biopsy reveals CIN 2 or 3, further therapy, consisting of a cold-knife conization, loop electrosurgical excision procedure, cryotherapy, or laser ablation, is indicated.

Of the health-care costs that are associated with cervical HPV-related disease, 66% apply to routine cervical cancer screening, 10% to invasive cancer treatment, 17% to cervical precancer treatment, and 9% to dispensing with false-positive Pap test results [8•]. In this study, it was estimated that 40 million US women underwent a Pap test in 1998, with a total health-care cost of $3.4 billion [8•]. Individual countries may have a different willingness to pay for a year of life saved; in the United States, a threshold of $50 000 per year of life saved is often cited.

Several countries have adopted nationally organized cervical screening programs, but many continue with opportunistic screening. High coverage is associated with effectiveness and efficiency of cervical cancer control [9]. Poor coverage and overscreening of a minority of women contributes to its inefficiency [10].

Ideally, all cervical cancers should be detected as premalignant lesions and treated before they progress to invasive cervical cancer. Therefore, the occurrence of an invasive cervical cancer represents a failure in the cancer screening process.

Clinical practice guidelines for cervical cancer screening

The current recommendations of both the American Cancer Society (ACS) and American College of Obstetricians and Gynecologists (ACOG) are in agreement regarding key aspects of cervical cytological screening [11,12,13••]. They recommend that screening begin approximately 3 years after the onset of vaginal intercourse or age 21, whichever comes first. Both recommend that after the age of 30 a woman whose last three Pap tests were negative may prolong her screening interval to every 2 to 3 years. Both agree that there may be a role for triennial screening with cytologic examination plus high-risk HPV-DNA testing in women more than 30 years of age. Both ACS and ACOG discourage vaginal cytological screening in women who have had a hysterectomy that included removal of the cervix for benign indications, and recognize the same high-risk categories for women for whom continued annual screening is appropriate; that is immunocompromised women, those exposed *in utero* to diethylstilbestrol, and women with a history of cervical cancer. The ACS suggests that well screened women aged 70 and older may elect to discontinue cytological screening after consultation with their provider. The ACS recommends annual cervical cytology from the onset of screening until age 30 if conventional Pap tests are used, but screening every 2 years if liquid-based cytology (LBC) analysis is used. Adding high-risk HPV-DNA testing to the Pap test in women older than 30 years increases the negative predictive value of testing if both tests are negative.

The Pap test would be suitably reported by the Bethesda System 2001, using atypical squamous cells (ASC), -of undetermined significance (ASC-US), -cannot exclude HSIL (ASC-H), low-grade squamous intraepithelial lesion (LSIL) and high-grade squamous intraepithelial lesion (HSIL). A College of American Pathologists study in 1998 found median rates for ASC-US and ASC-H of 4.5%, atypical glandular cells (AGC) of 0.3%, LSIL of 1.6% and HSIL of 0.5%, with a rate of invasive cervical cancer of 9.9 per 100 000 [8•]. A biopsy should be performed on any grossly visible lesions on the cervix because a Pap test can be reported as negative. A Pap test reported as unsatisfactory should be repeated as soon as practical. Underlying infection, if indicated, should be treated prior to obtaining the subsequent Pap test. Pap tests reported as 'satisfactory, but limited by' or with 'benign cellular changes', but otherwise negative for epithelial abnormalities, should be repeated at 1 year, or sooner if high-risk factors are present. In ASC-US, three options are consistent with the Consensus Conference sponsored by the American Society for Colposcopy and Cervical Cytology (ASCCP): repeat cervical cytology with referral for col-

poscopy in six months; direct referral for colposcopy; or HPV-DNA testing for high-risk virus with referral for colposcopy if there is a positive identification. In LSIL or ASC-H, the approach to the management depends on the age of the patient. For adolescent patients, the recommendation is to repeat the cervical cytology in six months; for adult patients, it is to proceed directly to colposcopy [11,12,14].

Sexually active adolescents and women more than 30 years of age may benefit from an annual reproductive health examination. The annual gynecologic examination need not be discarded with the annual Pap test.

Colposcopy is an integral part of the management of women presenting abnormal cervical cytology. The ASCCP guidelines show detailed flowchart protocols [15].

New methods and new technology for cervical cancer screening

The improvements in technology, particularly the advent of liquid-based monolayer cytology and computer-assisted reading of Pap slides, has offered the opportunity to address both the inadequate smear rate and the false-negative result rate in current cervical screening. Thin-layer technology has reduced the clumping of cells and removed mucus, blood, and debris, reducing the rate of inadequate smears; the residual fluid from the test also provides a sufficient aliquot for any further adjunct test, such as HPV or Chlamydia screening. In the ThinPrep Imaging System, a computer-based system [16•], the machine-aided screening appears to be a viable alternative to manual screening. This shift towards a more automated method of screening brings with it a change in expectations; considering cytology to be both an art and a science, machine-aided screening techniques are expected to be more science than art [17•]. The cost of LBC tests may be more than three times that of the conventional Pap test. There is a growing body of evidence that LBC addresses the limitations of the smear method and improves detection of cervical lesions. Recent government sponsored reviews by the National Health Service (NHS) in the United Kingdom and in the United States concluded that LBC is a cost-effective alternative to conventional smear-based cytology, and should be adopted [18].

High-risk HPV testing combined with cytology has higher sensitivity and higher negative predictive value for CIN 3 and cancer than cytology alone. The classic and real-time polymerase chain reaction, Digene Hybrid Capture 2 (HC2), and new technologies such as the Roche Amplicor/Linear array and NorChip Pre Tect investigate their prevalence. Specificity was, however, slightly lower for HPV testing and cytology (93%) than cytology alone (95%) [19]. HPV testing may be cost-effective if it allows for a longer screening interval, or for screening to be discontinued at an earlier age than currently recommended [20]. Protocols that add HPV-DNA testing to the traditional Pap test in ASC-US have demonstrated increased sensitivity over repeated Pap smear testing [21,22].

The constraints of cytology-based screening in low-resource settings have led recently to the Alliance for Cervical Cancer Prevention, supported by the Bill & Melinda Gates Foundation, evaluating the role of alternative tests in cervical cancer screening programs in low-resource settings, and their usefulness was proven. VIA, VILI, and magnified visual inspection with acetic acid (VIAM) have also been evaluated. In comparison with the sensitivity and specificity of conventional cytology, VIA varied from 67 to 79% and from 49 to 86% [23,24••], VIAM resulted in 50 and 87% [24••,25], and VILI resulted in 92 and 85%, respectively [24••]. This shows that the visual screening tests, VIA, VIAM and VILI, are promising approaches, particularly in low-resource settings.

At the present time, however, traditional cytological screening with Pap smears remains the primary method of screening.

Attributable failure factors in the screening process

Nowadays, all screening tests are imperfect, and the Pap is no exception. It is important for both providers and users of screening to understand the limited accuracy of a test [26••,27].

A lack of Pap screening, which often results from a lack of health-care access, has been identified universally as the most common attributable factor in the development of invasive cervical cancer. Other factors involved were Pap test detection failure and inadequate follow-up of abnormalities detected by the Pap test. In the series of a multicenter Detection of Early Tumors Enables Cancer Therapy (DETECT) study [26••], the factors associated with invasive cervical cancer among women enrolled in prepaid comprehensive health plans were examined. The results showed that the majority of cases (56%) occurred in women who had no Pap tests during the period 4–36 months prior to diagnosis. Of the remaining cases, 32% were attributed to Pap test detection failure and 13% to follow-up failure. Almost half of the women with invasive cervical cancer in this series were excluded because they had not been mem-

bers of a health plan or had no contact with a primary-care provider for at least 33 months prior to diagnosis. Advanced age, living in an area of higher poverty or having a lower education level were associated with low use of cervical cancer screening [28,29].

In the 2000 National Health Interview Survey (USA) study [30••], nearly half of the women who had not had a recent Pap test (48%) specified no main reason for it, and the most common specific main reason given was that a doctor did not order a test or say that they needed a test.

High coverage is necessary to obtain better results. One of the definite successes for the NHS has been the NHS Cervical Screening Programme. Screening has been defined as 'actively seeking to identify a disease or predisease condition in people who are presumed and presume themselves to be healthy' [30••,31••]. In countries that have introduced population-based screening with good coverage, there was a clear reduction in the incidence of and mortality from cervical cancer.

One main piece in this success was the NHS Cervical Screening Call and Recall program [31••]. The Call and Recall arranged for women 20–64 years of age to be invited for cervical screening either every 3 years or using the provider's guidelines. At the most conservative estimate, 83% in the USA [30••] and 83.7% in the UK [31••] of women at risk had undergone screening with cervical cytology in the last 5 years. CIN 2 and CIN 3 were treated by large loop excision of the transformation zone. These interventions achieved an 80% reduction in incidence and mortality, with a mortality rate of 2.5 per 100 000 women in Finland, Iceland, England and the USA.

High coverage in developing countries could be solved with a similar Cervical Screening Call and Recall program to obtain coverage of most women at risk.

In these countries, the application of new low-technology methods of visual inspection screening is inexpensive, and would require minimal infrastructure and a short training period for health professionals. As the results are available immediately, further diagnostic investigations, eventuality planning and treatment are possible during the same visit. This avoids recall of women for procedures, resulting in logistic advantages, better compliance and cost savings [18]. The use of a 'see and treat' protocol for patients with HSIL Pap smear, with satisfactory colposcopy, and with Reid colposcopic average index of 3.5 was an acceptable treatment option [32]. In low-resource settings, especially in non-urban or rural populations of women, this alternative cervical cancer screening test could solve resource limitations for the screening with the Pap test.

Cervical cancer screening: state of the art

Screening is clearly a complex multifactorial process of detection, not a test.

The objective of cervical cancer screening is to reduce cervical cancer incidence and mortality by detecting and treating precancerous lesions, and the ultimate proof of success is to do this in a cost-effective manner. The screening should have adequate sensitivity and specificity for detection of precancerous lesions, yield reproducible results, be cheap, simple and easy to apply, be without side effects or complications, be as painless as possible and be socioculturally acceptable.

Although organized and frequently repeated cytology screening has resulted in a large reduction in the cervical cancer burden in developed countries, with this apparent screening program the incidence rates in developing countries continue to be unchanged.

Conventional cervical cytology is the most widely used cervical screening test. An adequate specimen describes endocervical/transformation zone components. Smears without endocervical or metaplastic cells are inadequate. The automated and manual prescreening/rescreening methods in a Pap test reduce the false-negative rate [33,34]. All screening test results need a reference standard. The most widely used reference standards are histological study and negative colposcopy.

The success of cervical cytology in organized screening programs in developed countries is based on a repeated testing at frequent intervals (1–5 years), a high population coverage and medical supervision on the women with abnormalities detected by the Pap test in a follow-up examination.

To reduce further the incidence of invasive cervical cancer among women with access to screening and treatment, Pap screening adherence should be increased, particularly among older women.

The liquid-based monolayer cytology and computer-assisted reading of Pap slides is a high-technology methodology that increases the quality of cervical cancer detection. High-risk HPV testing is a valuable adjunct to the Pap test in primary cervical screening for women aged 30 and above.

Medical doctors need to keep their knowledge on screening up-to-date, and offer counseling that helps women to make an informed decision to participate in screening [35•,36]. People have begun to be more critical concerning the basis for recommending medical interventions such as screening in the new 'evidence-based' medicine era [37].

Sociodemographic conditions and health-care access are related to cancer screening. Cytology is not a viable option in the non-urban or rural populations of women of many low-resource countries. In these conditions, the visual inspection screening test, using acetic acid or Lugol's iodine, is the alternative approach to use. The immediate availability of results after visual testing provides a major logistic advantage in providing follow-up care for screening-positive women. Controlled trials have demonstrated the efficacy and cost-effectiveness of screening programs in reducing cervical cancer burden.

Low-cost, low-technology screening methods should become a valid option for developing countries over the next few years, depending on the availability of HPV vaccines on an industrial scale. Because visual tests, like cytology, are essentially subjective, quality control is an important issue.

According to the NHS (USA), the next goal is to achieve the cervical cancer screening of 85% of women at risk.

Many interdisciplinary scientific groups worldwide work on HPV-related diseases. More than 500 works are presented annually in the International Papillomavirus Conference (the last was the 22nd Conference in Vancouver, May 2005) [38]. Detailed information about beating HPV can be obtained at www.hpvtoday.com.

Enthusiasm for new technology should not distract from the well known requirements for good screening programs, namely high coverage, quality control and follow-up.

Good cervical cancer screening requires controls and effort in each stage of the process: (i) women with adequate test adherence, a representative sample, cytology spread and dying technique, reliable microscopic interpretation and appropriate reporting; (ii) collective programs require high coverage, adequate treatment of HSILs and follow-up; and (iii) collective national politics requires adequate scientific and financial resources, administration resources, the use of mass specific screening methods, sufficient numbers of health professionals and controlled quality feedback levels for the screening process.

Conclusion

In conclusion, well organized cervical cytological screening programs have reduced by 60–80% the incidence of and mortality from cervical cancer in developed countries. These organized screening programs include repeated testing at frequent intervals (1–5 years) with a high population coverage and, moreover, treatment of HSILs and further medical supervision.

Replication of this process is necessary in developing countries, and/or the use of alternative screening programmes in low-resource settings with high efficacy and cost-effectiveness for reducing cervical cancer burden is required.

The challenge for the future may be less of a technical nature and rather more dependent on local finances and screening policies.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
- • of special interest
- •• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 77).

1 Parkin DM, Bray F, Ferlay J, *et al*. Global cancer statistics, 2002. CA Cancer J Clin 2005; 55:74–108.

2 Bosch FX, de Sanjose S. Human papillomavirus and cervical cancer-burden and assessment of causality. J Natl Cancer Inst Mon 2003; 32:3–13.

3 American Cancer Society. Cancer facts and figures, 2003. Atlanta: American Cancer Society; 2003.

4 Holowaty P, Miller AB, Rohan T, *et al*. Natural history of dysplasia of the uterine cervix. J Natl Cancer Inst 1999; 91:252–258.

5 Fahey MT, Irwing L, Macaskill P. Meta-analysis of Pap test accuracy. Am J Epidemiol 1995; 141:680–689.

6 Nanda K, McCrory DC, Myers ER, *et al*. Accuracy of the Papanicolaou test in screening for a follow-up of cervical cytological abnormalities: a systematic review. Ann Intern Med 2000; 132:810–819.

7 Reid R, Campion MJ. HPV-associated lesions of the cervix: biology and colposcopic features. Clin Obstet Gynecol 1989; 32:157–179.

8 • Insinga RP, Glass AG, Rush BB. The health care cost of cervical human papillomavirus-related disease. Obstet Gynecol 2004; 191:114–120.
An interesting analysis on health-care cost of cervical cancer attention.

9 Kim JJ, Leung GM, Woo PP, Goldie SJ. Cost-effectiveness of organized versus opportunistic cervical cytology screening in Hong Kong. J Public Health (Oxf) 2004; 16:130–137.

10 Adab P, McGhee SM, Yanova J, *et al*. Effectiveness and efficiency of opportunistic cervical cancer screening. Med Care 2004; 42:600–609.

11 Saslow D, Runowicz CD, Solomon D, *et al*. American Cancer Society Guideline for the early detection of cervical neoplasia and cancer. CA Cancer J Clin 2002; 52:342–362.

12 American College of Obstetricians and Gynecologists. Cervical cytology screening. ACOG Practice Bulletin No. 45. Int J Gynaecol Obstet 2003; 83:237–247.

13 •• Waxman AG. Guidelines for cervical cancer screening: history and scientific rationale. Clin Obstet Gynecol 2005; 48:77–97.
This article provides information about the three classic guidelines (USA) for cervical cancer screening, and for successful implementation.

14 National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology. Cervical Screening – v.1. 2005 (From Saslow D, Runowicz C, Solomon D, et al. Cancer Journal for Clinicians 2002;52(6): 342-376).

15 Wright TC, Cox JT, Massad LS, *et al*. 2001 Consensus guidelines for the management of women with cervical cytological abnormalities. JAMA 2002; 287:2120–2129.

16 • Dawson AE. Can we change the way we screen?: the ThinPrep Imaging System: clinical trial data and early experience. Cancer (Cytopathol) 2004; 102:340–344.
This article discusses widely the ThinPrep Imaging System.

17 • Renshaw AA. Quality assessment in the age of machine-aided cervical cytology screening: changing art into science with prescreening. Cancer (Cytopathol) 2004; 102:345–347.
This paper provides interesting reflections on the use of third-generation screening devices.

18 Monsonego J, Bosch FX, Coursaget P, *et al*. Mini review. Cervical cancer control, priorities and new directions. Int J Cancer 2004; 108:329–333.

19 Franceschi S, Mahé C. Human papillomavirus testing in cervical cancer screening. Br J Cancer 2005; 92:1591–1592.

20 Bulkmans NWJ, Rozendaal L, Voorhorst FJ, *et al*. Long term protective effect of high-risk human papillomavirus testing in population-based cervical screening. Br J Cancer 2005; 92:1800–1802.

21 Bais AG, Rebolj M, Snijders PJF, *et al*. Triage using HPV-testing in persistent borderline and mildly dyskaryotic smears: proposal for new guidelines. Int J Cancer 2005; 116:122–129.

22 Brink AATP, Zielinski GD, Steenbergen RDM, *et al*. Clinical relevance of human papillomavirus testing in cytopathology. Cytopathology 2005; 16:7–12.

23 Jeronimo J, Morales O, Horna J, *et al*. Visual inspection with acetic acid for cervical cancer screening outside of low-resource settings. Rev Pan Salud Publica 2005; 17:1–5.

24 •• Sankaranarayanan R, Gaffikin L, Jacob M, *et al*. A critical assessment of screening methods for cervical neoplasia. Int J Gynecol Obstet 2005; 89: S4–S12.
This interesting paper discusses the applications and limitations of screening in the scope of the Alliance for Cervical Cancer Prevention.

25 Perez-Cruz E, Winkler JL, Velasco-Mondragon E, *et al*. Visual detection and monitoring of the cervix for the prevention of cervical cancer in rural Mexico [in Spanish]. Salud Publica Mex 2005; 47:39–48.

26 •• Leyden WA, Manos MM, Gelger AM, *et al*. Cervical cancer in women with comprehensive health care access: attributable factors in the screening process. J Natl Cancer Inst 2005; 97:675–683.
This article provides interesting data on the characteristics of patients according to screening failure category (USA).

27 Sung HY, Kearney KA, Miller M, *et al*. Papanicolaou smear history and diagnosis of invasive cervical carcinoma among members of a large prepaid health plan. Cancer 2000; 88:2283–2289.

28 Sawaya GF, Sung HY, Kearney KA, *et al*. Advancing age and cervical cancer screening and prognosis. J Am Geriatr Soc 2001; 49:1499–1504.

29 Grainge MJ, Seth R, Coupland C, *et al*. Human papillomavirus infection in women who develop high-grade cervical intraepithelial neoplasia or cervical cancer: a case-control study in UK. Br J Cancer 2005; 92:1794–1799.

30 •• Hewitt M, Devesa SS, Breen N. Cervical cancer screening among U.S. women: analyses of the 2000 National Health Interview Survey. Prev Med 2004; 39:270–278.
This paper identifies the sociodemographic conditions and health-care access related to cancer screening.

31 •• Walker P. The English National Health Service Cervical Screening Programme-approach to new technologies and quality assurance. J Low Genit Tract Dis 2005; 9:118–123.
This paper underlines the importance of the NHS Cervical Screening Call and Recall program to obtain a high population coverage.

32 Numnum TM, Kirby TO, Leath CA III. A prospective evaluation of "see and treat" in women with HSIL Pap smear results: is this an appropriate strategy? J Low Genit Tract Dis 2005; 9:2–5.

33 O'Leary TJ. State of the art symposium. Prescreening Rescreening Cancer (Cytopathol) 2004; 102:331–333.

34 Arbyn M, Schenck U, Ellison E, *et al*. Metaanalysis of the accuracy of rapid prescreening relative to full screening of pap smears. Cancer (Cytopathol) 2003; 99:9–16.

35 • Chingang IC, Bischof U, Anall-Brereton G, *et al*. "Have a pap smear" – doctors, their clients, and opportunistic cervical cancer screening. Int J STD AIDS 2005; 16:233–236.
This article emphasizes the need of medical doctors to keep their knowledge on screening up-to-date, and to offer counseling on screening.

36 Grimes DA, Schultz KF. Uses and abuses of screening tests. Lancet 2002; 359:881–884.

37 Meissner HI, Vernon SW, Rimer BK, *et al*. The future of research that promotes cancer screening. Cancer 2004; 101 (5 Suppl):1251–1259.

38 22nd International Papillomavirus Conference and Clinical Workshop 2005. Vancouver B.C. Canada. Book of Abstracts (Screening methods C-01-C-08, P-399-P-418, P-478, P-482, P-484, P-486, P-497, P-503; Screening in developing countries P-303, P-318, P-379, P-378, P-502) (www.hpv2005.org).