COMMENTARY

Evidence-based Screening, Early Diagnosis and Treatment Strategy of Cervical Cancer for National Policy in Low-resource countries: Example of India

Upma Saxena[1], Catherine Sauvaget[2]*, Rengaswamy Sankaranarayanan[2]

Abstract

Cervical cancer remains the most frequent cancer in women from the developing world. More than 88% of deaths occur in low-income countries, and it is predicted to climb to 91.5% by 2030. Although Pap-based screening programmes have shown to be effective in reducing the disease burden in high-resource countries, implementation and sustention of cytology-based programmes is quite challenging in low-resource settings. The present paper reviews evidence-based alternatives of screening methods, triaging algorithm, treatment of cervical precancerous lesions, and age-group at screening appropriate for low-income countries. Evidence shows that visual inspection methods using diluted acid acetic or Lugol's iodine, and HPV-DNA testing are more sensitive tests than the Pap-smear screening test. Visual inspection allows an immediate result and, when appropriate, may be immediately followed by cryotherapy, the so called "screen-and-treat" approach, achieved in a single visit, by trained nurses and midwives. Examples of cervical cancer prevention programmes in India and selected low-income countries are given.

Keywords: Cervical neoplasm – screening methods – early detection – screen-and-treat approach – low-income countries

Asian Pacific J Cancer Prev, **13**, 1699-1703

Introduction

Cervical cancer is still one of the most common cancers among women worldwide (World Health Organization 2009). The estimated annual incidence cases and deaths in the low- and middle-income countries (LMIC) is more than 450,000 and 240,000, respectively. More than 88% of deaths are estimated to occur in these LMIC countries and this percentage is predicted to climb to at least 91.5% by 2030 (Ferlay et al., 2010).

In 2008 in India, the annual incidence and mortality from cervical cancer was 134,420 cases (age-standardized rate (ASR): 27/100,000) and 72,825 deaths (ASR: 15.2/100,000), respectively. Cervical cancer was the most common cancer in Indian women, accounting for nearly 25.9 % of new cancer cases and 23.3% of all cancer-related deaths in the country (Ferlay et al., 2010).

All the urban population-based cancer registries (PBCR) at Bangalore, Bhopal, Chennai, Delhi and Mumbai have shown a decrease in the age-standardized incidence rates, despite the absence of any organized screening programme. The decline in the ASR varied from 46.1 (in 1978-82) to 28.0 (in 1998-2002) per 100,000 women-years in Chennai to a minimal 15.7 (in 1988-92) to 10.6 (in 1998-2002) in Karunagappally (Figure 1). Cervical cancer accounted for 16% of all cancers in women in the urban registries in 2005, while in Barshi (rural PBCR), it represented 37% (National Cancer Registry Programme 2009).

In hospital-based cancer registries (HBCRs), cervical cancer was the leading cancer in Bangalore and Chennai, the second in Mumbai and Thiruvananthapuram and the third in Dibrugarh. Cervical cancer represented between 11.4 % (Thiruvananthapuram) and 30.7 % (Chennai) of all cancers in women in these five HBCRs (National Cancer Registry Programme 2007). In 99.7% of cases, cervical cancer results from a persistent infection by a high-risk subset of human papillomavirus (HPV) (Walboomers et al., 1999).

Most women's immune systems will eliminate HPV infection spontaneously, however, for a very small proportion of women, the infection will persist and can cause pre-cancerous changes in cells. In a multi-centric study in India, genotypes 16 and 18 alone or in co-infection with each other were detected in 76.3% cases and genotype 33 was the third most common type. Overall, genotypes 16, 18, 31, 33, and 45 were the five most common types, detected in 87.1% of the total cases (Basu et al., 2009). In a similar study, carried out in Delhi, twelve different HPV types were found, with HPV16 being the most common seen in 73.6% cases followed by HPV 18 (14.2%) and 45 (11.3%) (Bhatla et al., 2006).

Cervical intraepithelial neoplasia (CIN) occurs along a spectrum of grades from low (CIN1), moderate (CIN2) to severe (CIN3). Of the three precancerous grades, CIN2 and CIN3 are of greatest concern and require immediate treatment and follow-up. If left untreated, CIN 3 generally progresses to invasive cancer. The process from low-grade

*[1]Department of Obstetrics & Gynaecology, Dr Ram Manohar Lohia Hospital, New Delhi, India, [2]Screening Group, Early Detection and Prevention Section, International Agency for Research on Cancer, Lyon, France *For correspondence: sauvagetc@iarc.fr*

CIN to cervical cancer takes from 10 to 20 years, during which time screening for pre-cancerous lesions and early treatment is highly effective in preventing the onset of the disease. This is the rationale for cervical cancer screening (Cole and Morrison 1980).

There are several screening tests to identify pre-cancerous lesions, including the Pap test (cytology), visual inspection with acetic acid (VIA), with Lugol's iodine (VILI), and the HPV-DNA test.

Pap-based screening programs are effective in high-income countries (HIC), but health systems in developing countries are ill-equipped to effectively provide Pap screening to all women insofar as they are hindered by the challenges of reaching target populations, carrying out appropriate testing, following up and treating women. Today, highly effective alternative low-cost screening approaches and early treatment technologies are available and appropriate for LMIC (Sherris et al., 2009). These breakthrough tools and approaches resolve many obstacles that prevented Pap-based screening programmes from being effective in these countries. VIA, VILI and HPV-DNA testing offer new options for screening. These can be immediately followed by cryotherapy, a highly effective and low-cost approach for early treatment. These new tools allow for combined screening and treatment, known as the screen-and-treat approach, that can be performed at the same sitting (Denny et al., 2005). Hence, there is a need to design an effective screening and treatment strategy that targets high-risk women once or twice in their lifetime, using a highly sensitive test, with an emphasis on high coverage (>80%) of the targeted population (Sankaranarayanan et al., 2001).

Based on recent studies and analyses we have tried to find the most evidence-based, safe, effective, operationally feasible and culturally appropriate strategies for secondary prevention of cervical cancer in the Indian scenario.

Cervical Cancer Screening Approaches

1. Cytology

Cytology-based screening programmes using Pap smears have resulted in dramatic declines in cervical cancer deaths in HIC, over the last four decades. The process requires a doctor or a nurse to collect the sample, a cytotechnician to process and analyze the smears, and a pathologist to confirm the positive findings on the biopsy. Once a positive Pap smear result is available, the women must be notified, counselled and referred for additional diagnostics or treatment modality. The screening process, along with the delays between screening, test results and ultimate treatment are major obstacles to the success of cytology-based programs in low-resource settings. Although cytology screening has been introduced in LMIC over the past 30 years, it has not resulted in the expected decreases in cervical cancer incidence and mortality similar to those observed in the HIC, primarily because of the above mentioned hurdles associated with low coverage of the target population (Dzuba et al., 2005; International Agency for Research on Cancer 2005; Moodley et al., 2006).

As cytology has only moderate sensitivity to detect the CIN2 and CIN 3 (53% in HIC, and 26-65% in LMIC) (Almonte et al., 2007; Cuzick et al., 2006; Sankaranarayanan et al., 2004b; Sarian et al., 2005), repeated screening at regular intervals is necessary for the programmes to be effective. This low sensitivity in developed countries is overcome by organized periodic screening, which is not feasible with the opportunistic screening carried in low-resource setting. This, combined with the documented challenges of implementing and sustaining cytology-based programs, has led researchers to look for effective, accessible, acceptable and feasible alternatives for LMIC.

2. Alternatives to cytology: visual inspection methods and HPV-DNA testing

The evidence in support of alternative screening strategies has been obtained from large-scale field studies in India, Latin America, South-Africa, Peru, Thailand and China over the last few years. These studies have focused on assessing VIA, VILI, HPV-DNA testing (International Agency for Research on Cancer 2005).

VIA: This involves inspection of the cervix with the naked eye, one to two minutes after the application of 3–5% acetic acid under adequate light and white areas in or near transformation zone (TZ) are considered positive.

VILI: This similar technique, is performed with Lugol's iodine and mustard-yellow unstained lesion(s) in or near TZ are reported as positive.

Evidence shows that the sensitivity for VIA and VILI screening are comparable to or greater than that of cytology. When physicians and mid-level workers were properly trained and supervised, VIA showed a sensitivity from 41% to 79% (Almonte et al., 2007; Belinson et al., 1999; Megevand et al., 1996; Sankaranarayanan et al., 2004a; Sankaranarayanan et al., 2005b; Sankaranarayanan et al., 2007a; Sauvaget et al., 2011; University of Zimbabwe/JHPIEGO Cervical Cancer Project 1999), and VILI presented a sensitivity from 57% to 98% (Muwonge et al., 2010; Ngoma et al., 2010; Sankaranarayanan et al., 2005a).

Besides VIA being feasible and efficient, the other advantage is that results are available immediately and, when indicated, treatment can be provided during the same visit. A single-visit approach markedly increases programme effectiveness as it overcomes the obstacle of high rates of loss to follow-up that are common in LMIC. However, visual tests have the drawback that they are not reliable in post-menopausal women due to the inward recession of TZ and this has led to emergence of HPV-DNA testing as a new option for cervical cancer screening.

HPV-DNA testing: This uses cervical or vaginal samples, obtained with a brush instead of a swab. The samples are collected either by a trained provider or, in the case of vaginal sampling, by the woman herself. Self-sampling does not require a speculum examination making it more acceptable, leading to better feasibility and population coverage in some settings. In both HIC and LMIC, the accuracy of testing on self-collected specimens is nearly as high as that for clinician-collected specimens and continues to improve, with sensitivities in the range

of 80 to 86% (Belinson and Belinson 2010; Qiao et al., 2008). Once collected, the samples can be stored in a preservative solution until testing. HPV-testing samples are processed with the use of the Hybrid Capture 2 assay for 13 high-risk HPV types (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, and 68).

A recent large study in India reported about a 50% reduction in cervical cancer incidence and mortality following a programme strategy based on a single round of HPV testing. However, no similar benefit was seen with strategies based on a single round of VIA or Pap screening (Sankaranarayanan et al., 2009).

The sensitivity of HPV-DNA for detecting CIN 2-3 ranges from 66-95% with most studies reporting values greater than 85% among women 30 years or older (Almonte et al., 2007; Qiao et al., 2008; Sankaranarayanan et al., 2005a) because they are at the highest risk for precancerous lesions due to persistent HPV infection.
New evidence also advocates the use of HPV-DNA testing as the primary technology for cervical cancer screening, both in developed and in developing countries (Franceschi et al., 2011; Franco 2010; Schiffman and Wentzensen 2010).

Although HPV-DNA testing performs well when compared with other screening tests, commercially available HPV-DNA tests such as Hybrid Capture 2 (QIAGEN Inc.) is relatively expensive, complex and interpretation needs seven hours. These factors—combined with potential challenges in collecting specimens—limit the applicability of the currently marketed test in LMIC. It can be fully utilized for reducing cervical cancer in these countries only if a test with similar performance, but simpler to use, less expensive and equally effective is made available.

The Screen-and-Treat Approach

The use of HPV-DNA testing followed by cryotherapy resulted in a greater reduction in the incidence of cervical cancer precursors than the use of other screen-and-treat approaches. Two key studies have followed up screened women using various approaches and treated with cryotherapy to determine their long-term risk of high-grade cervical lesions, cervical cancer or both.

The first study conducted in South Africa, in which 7,000 women were screened with VIA and HPV-DNA testing (Denny et al., 2005). Women with positive results were randomized to one of three arms and were followed up for 36 months: HPV-DNA positive followed by immediate treatment with cryotherapy; VIA-positive followed by immediate cryotherapy; or delayed treatment. HPV-DNA testing plus treatment with cryotherapy reduced the occurrence of CIN3+ by more than 77%, and VIA screening followed by cryotherapy reduced it by 38%, as compared to the control group with delayed treatment. Sensitivity for HPV-DNA and VIA was 90% and 53%, respectively, and specificity was 83% and 78% (Denny et al., 2010). Because HPV-DNA testing correctly identified both positive and negative women more often than VIA, using this test for screening was associated with less under-treatment as well as less over-treatment. Cryotherapy was highly successful in this trial, eliminating 75 to 77% of CIN2+ lesions.

In a second study, where women screened by VIA were provided cryotherapy by nurses in field clinics in Dindigul district in India, a high cure rate of 81% was reported in women with CIN1 lesions and 71% in those with CIN 2–3 lesions, (Sankaranarayanan et al., 2007b)

Cryotherapy is accomplished by freezing the entire area on the TZ, where lesions occur. Women who are screened positive ideally must be further evaluated by colposcopy and then treated. However, this confirmatory diagnostic step may be difficult to implement in low-resource settings where appropriately trained specialists or necessary equipment may not be available. In such settings, VIA or VILI should be performed following a positive HPV test before treatment to determine whether the cervix has precancerous changes, whether it has any affected areas too large or too inaccessible for cryotherapy, and whether cancer is suspected. In the absence of contraindications, women who are HPV-positive can undergo cryotherapy even if they do not have any visible cervical lesions (especially if the chances are poor that they will return to the clinic for follow-up care), given that such women are at relatively high risk for developing CIN (Denny et al., 2005).

When conducted by competent providers, cryotherapy is a safe way of treating precancerous cervical lesions and results in cure rates of at least 85% (Sherris et al., 2009). Cryotherapy is widely considered to be an effective and appropriate means of treating precancerous cervical lesions. In 2003, the Alliance for Cervical Cancer Prevention (ACCP) published a systematic literature review of 38 studies on the safety, effectiveness and acceptability of this therapy (Castro et al., 2003). The results showed an overall cure rate of about 90% and complications, such as severe bleeding and pelvic inflammatory disease, were rare. The review also concluded that cryotherapy was as effective as other outpatient treatment methods, particularly for treating mild and moderate lesions (CIN 1–2). Other ACCP studies have similarly shown extremely low rates of serious adverse events requiring hospitalization, with the most common side effects being fever, pain, watery discharge, bleeding and cramping (Denny et al., 2005; Gaffikin et al., 2003; Sankaranarayanan et al., 2007b).

Optimal Age for Cervical Cancer Screening

Screening is considered optimal when the greatest benefit is achieved from the least resources. To determine the optimal age for cervical cancer screening, a cost-effectiveness modelling comparing screening strategies in five developing countries predicted that for 35-year-old women screened only once in their life, a single-visit or two-visit approach with the VIA and HPV-DNA testing could reduce the lifetime risk of cervical cancer by 25% and 36%, respectively. Screening women twice, at ages 35 and 40, was predicted to reduce lifetime cancer risk by 65% (with VIA) or 76% (with HPV-DNA testing) (Goldie et al., 2005). The model estimated that the cost per life-year saved with these approaches would be less

than each country's per capita gross domestic product making them highly cost-effective according to standards set by the World Health Organization's Commission on Macroeconomics and Health (World Health Organization 2001).

Similarly in India, 49,000 women aged 30 to 59 years in a field study were followed for more than seven years after a single round of VIA screening with immediate treatment with cryotherapy. Authors observed an overall reduction in cervical cancer incidence and mortality of 25% and 35%, respectively but they were 38% and 66% in the 30–39 age-group. Hence, they concluded that the intervention had the greatest impact among women in their 30s (Sankaranarayanan et al., 2007a).

These two results suggest that targeting women between 30-40 years can achieve the greatest public health benefit.

Conclusions and the Future

Every woman has the right to cervical screening at least once in her lifetime and the most optimal age for screening to achieve the greatest public health impact is between 30 and 40 years. Cytology-based screening programmes using Pap-smears have been shown to be effective in HIC, but it is difficult to sustain high quality cytology programmes in LMIC. Therefore, in situations where health care resources are scarce, resources should be directed towards alternative cost-effective strategies that are more affordable and for which quality can be assured. Studies have shown that the most efficient and effective strategy for secondary prevention of cervical cancer in low-resource settings is to screen using either HPV-DNA testing or VIA, then treat pre-cancerous lesions using cryotherapy. This is optimally achieved in a single visit (currently possible with VIA plus cryotherapy) and can be carried out both by physicians and mid-level workers such as trained nurses and midwives. While the sensitivity of visual inspection methods is not as high as that of HPV-DNA testing, most investigations have found that the sensitivity is as high as or higher than that of cytology. Besides that, VIA is feasible in many low-resource areas, where cytology, with its requirements for significant infrastructure, is not possible.

HPV-DNA testing followed by cryotherapy has resulted in greater reduction of cervical cancer precursors than the use of other screening and treatment approaches. However, triage using VIA is necessary following an HPV-DNA screening test in order to identify those patients for whom cryotherapy is not appropriate.

In evaluating evidence for screening methods, many of the studies reviewed here concluded that HPV-DNA testing alone should eventually become the primary test in women aged 30 years or older because the high-risk HPV-DNA negative women are at an extremely low risk of developing cervical cancer in the next 5 to 10 years. Hence, HPV-DNA testing has the additional advantage of cost-effectiveness, gained from lengthening the screening interval for HPV-negative women as the test detects a very high percentage of cervical abnormalities, leaving very few that need to be found at subsequent screenings.

Recent meta-analyses show that the most common cervical HPV genotypes in women with normal cytology, as well those associated with cervical cancer, are similar worldwide. These findings are important for evaluating the impact of the current prophylactic vaccines, as well as for developing new vaccines.

A new, rapid HPV-DNA test called CareHPVTM is being developed for use in LMIC markets (Gravitt et al., 2008; Qiao et al., 2008). It will have a low cost and will be simple to perform. Moreover, it will be portable, field interpretation of results possible within 2.5 hours and with an accuracy substantially better than that of VIA and approaches that of Hybrid Capture 2. Though recent information supports the use of HPV-DNA technologies however, until low-cost HPV-DNA testing becomes more widely available for LMIC, visual inspection methods, especially VIA will continue to provide a reliable and effective means for reducing the burden of cervical cancer.

Besides these innovative approaches for cervical cancer screening and treatment, it is also important to focus on service delivery systems, incorporate community perspectives and needs, and to increase awareness for cervical cancer and prevention strategies.

References

Almonte M, Ferreccio C, Winkler JL, et al (2007). Cervical screening by visual inspection, HPV testing, liquid-based and conventional cytology in Amazonian Peru. *Int J Cancer*, **121**, 796-802.

Basu P, Roychowdhury S, Bafna UD, et al (2009). Human papillomavirus genotype distribution in cervical cancer in India: results from a multi-center study. *Asian Pac J Cancer Prev*, **10**, 27-34.

Belinson J, Qiao Y, Pretorius R, et al (1999). Prevalence of cervical cancer and feasibility of screening in rural China: a pilot study for the Shanxi Province Cervical Cancer Screening Study. *Int J Gynecol Cancer*, **9**, 411-7.

Belinson SE, Belinson JL (2010). Human papillomavirus DNA testing for cervical cancer screening: practical aspects in developing countries. *Mol Diagn Ther*, **14**, 215-22.

Bhatla N, Dar L, Patro AR, et al (2006). Human papillomavirus type distribution in cervical cancer in Delhi, India. *Int J Gynecol Pathol*, **25**, 398-402.

Castro W, Gage J, Gaffikin L, et al (2003) 'Effectiveness, safety, and acceptability of cryotherapy: a systematic literature review: Cervical Cancer Prevention Issues in Depth # 1.' Alliance for Cervical Cancer Prevention (ACCP): Seattle

Cole P, Morrison AS (1980). Basic issues in population screening for cancer. *J Natl Cancer Inst*, **64**, 1263-72.

Cuzick J, Clavel C, Petry KU, et al (2006). Overview of the European and North American studies on HPV testing in primary cervical cancer screening. *Int J Cancer*, **119**, 1095-101.

Denny L, Kuhn L, De SM, et al (2005). Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA*, **294**, 2173-2181.

Denny L, Kuhn L, Hu CC, et al (2010). Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. *J Natl Cancer Inst*, **102**, 1557-67.

Dzuba IG, Calderon R, Bliesner S, et al (2005). A participatory assessment to identify strategies for improved cervical cancer prevention and treatment in Bolivia. *Rev Panam Salud Publica*, **18**, 53-63.

Ferlay J, Shin HR, Bray F, et al(2010) 'GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet].' International Agency for Research on Cancer: Lyon.

Franceschi S, Denny L, Irwin KL, et al (2011). Eurogin 2010 roadmap on cervical cancer prevention. *Int J Cancer*, 128, 2765-2774.

Franco EL (2010). Persistent HPV infection and cervical cancer risk: is the scientific rationale for changing the screening paradigm enough? *J Natl Cancer Inst*, **102**, 1451-3.

Gaffikin L, Blumenthal PD, Emerson M, et al (2003). Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project. *Lancet*, **361**, 814-20.

Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, et al (2005). Cost-effectiveness of cervical-cancer screening in five developing countries. *N Engl J Med*, **353**, 2158-68.

Gravitt PE, Coutlee F, Iftner T, et al (2008). New technologies in cervical cancer screening. *Vaccine*, **26 Suppl 10**, K42-K52.

International Agency for Research on Cancer (2005) 'IARC Handbooks of Cancer Prevention Volume 10: Cervix Cancer Screening.' IARCPress: Lyon.

Megevand E, Denny L, Dehaeck K, et al (1996). Acetic acid visualization of the cervix: an alternative to cytologic screening. *Obstet Gynecol*, **88**, 383-6.

Moodley J, Kawonga M, Bradley J, et al (2006). Challenges in implementing a cervical screening program in South Africa. *Cancer Detect Prev*, **30**, 361-8.

Muwonge R, Manuel MG, Filipe AP, et al (2010). Visual screening for early detection of cervical neoplasia in Angola. *Int J Gynaecol Obstet*, **111**, 68-72.

National Cancer Registry Programme (2007) 'Consolidated report of hospital based cancer registries 2001-2003.' NCPR, ICMR: Bangalore.

National Cancer Registry Programme (2009) 'Time trends in cancer incidence rates: 1982-2005.' NCRP, ICMR: Bangalore.

Ngoma T, Muwonge R, Mwaiselage J, et al (2010). Evaluation of cervical visual inspection screening in Dar es Salaam, Tanzania. *Int J Gynaecol Obstet*, **109**, 100-4.

Qiao YL, Sellors JW, Eder PS, et al (2008). A new HPV-DNA test for cervical-cancer screening in developing regions: a cross-sectional study of clinical accuracy in rural China. *Lancet Oncol*, **9**, 929-36.

Sankaranarayanan R, Basu P, Wesley RS, et al (2004a). Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. *Int J Cancer*, **110**, 907-13.

Sankaranarayanan R, Budukh AM, Rajkumar R (2001). Effective screening programmes for cervical cancer in low- and middle-income developing countries. *Bull WHO*, **79**, 954-62.

Sankaranarayanan R, Esmy PO, Rajkumar R, et al (2007a). Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet*, **370**, 398-406.

Sankaranarayanan R, Gaffikin L, Jacob M, et al (2005a). A critical assessment of screening methods for cervical neoplasia. *Int J Gynaecol Obstet*, **89 Suppl 2**, S4-S12.

Sankaranarayanan R, Nene BM, Dinshaw KA, et al (2005b). A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer*, 116, 617-623.

Sankaranarayanan R, Nene BM, Shastri SS, et al (2009). HPV screening for cervical cancer in rural India. *N Engl J Med*, **360**, 1385-94.

Sankaranarayanan R, Rajkumar R, Esmy PO, et al (2007b). Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer*, **96**, 738-43.

Sankaranarayanan R, Thara S, Sharma A, et al (2004b). Accuracy of conventional cytology: results from a multicentre screening study in India. *J Med Screen*, **11**, 77-84.

Sarian LO, Derchain SF, Naud P, et al (2005). Evaluation of visual inspection with acetic acid (VIA), Lugol's iodine (VILI), cervical cytology and HPV testing as cervical screening tools in Latin America. This report refers to partial results from the LAMS (Latin AMerican Screening) study. *J Med Screen*, **12**, 142-9.

Sauvaget C, Fayette JM, Muwonge R, et al (2011). Accuracy of visual inspection with acetic acid for cervical cancer screening. *Int J Gynaecol Obstet*, **113**, 14-24.

Schiffman M, Wentzensen N (2010). From human papillomavirus to cervical cancer. *Obstet Gynecol*, **116**, 177-85.

Sherris J, Wittet S, Kleine A, et al (2009). Evidence-based, alternative cervical cancer screening approaches in low-resource settings. *Int Perspect Sex Reprod Health*, **35**, 147-54.

University of Zimbabwe/JHPIEGO Cervical Cancer Project (1999). Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. *Lancet*, **353**, 869-73.

Walboomers JM, Jacobs MV, Manos MM, et al (1999). Human papillomavirus is a necessary cause of invasive cervical cancer worldwide. *J Pathol*, **189**, 12-19.

World Health Organization (2001) 'Macroeconomics and health: investing in health for economic development. Report of the commission on Macroeconomics and health.' WHO: Geneva.

World Health Organization (2009) 'The global burden of disease: Death and DALY estimates for 2004 by cause for WHO member States, 2004 Update.' WHO: Geneva.