Chapter 8: Screening for cervical cancer in developing countries

Lynette Denny\textsuperscript{a,}\* , Michael Quinn\textsuperscript{b} , R. Sankaranarayanan\textsuperscript{c}

\textsuperscript{a} Groote Schuur Hospital, University of Cape Town, H45 Old Main Building, Observatory 7925, Cape Town, South Africa
\textsuperscript{b} University Department of Obstetrics and Gynaecology and Oncology/Dysplasia Unit, Royal Women's Hospital, Melbourne, Australia
\textsuperscript{c} Screening Group, International Agency for Research on Cancer, Lyon, France

Received 14 March 2006; accepted 31 May 2006

Abstract

Organised and quality assured cytology-based screening programmes have substantially reduced cervical cancer incidence in many developed countries. However, there are considerable barriers to setting up cytology-based screening programs, particularly in developing countries. This has stimulated the search for novel and alternative approaches to cytology for cervical cancer prevention. These approaches generally perform as well as cytology, and sometimes better, although many of them have a lower specificity, resulting in higher false-positive rates. The possibility of linking screening to treatment in a one- or two-visit strategy appears to be safe, feasible and effective. Barriers to establishing screening programs and the pitfalls encountered differ from one country to the next. Country-specific solutions need to be found, while being cognisant of the criteria that have enabled successful screening programmes.

© 2006 Elsevier Ltd. All rights reserved.

Keywords: Cervical cancer; Screening; Developing countries

1. Introduction

Successfully organised, population-based cervical cancer screening programmes have not yet been implemented in most developing countries, despite the greatest burden of cervical cancer in these countries\cite{[1]}, which is largely related to poverty, lack of resources and infrastructure and disenfranchisement of women.

2. Barriers to screening in developing countries

2.1. Competing health needs

Competing healthcare priorities posed by the impressive burden of diseases other than cancers, coupled with a trend of shrinking public health budgets, is overwhelming in many developing countries. In sub-Saharan Africa in 1995, for example, communicable diseases and maternal or perinatal complications caused approximately 70\% of all deaths in women; the equivalent figure in developed countries was 4.9\%. In 2000, the maternal mortality ratio in the least developed countries was estimated to be 830 per 100,000 with 251,000 of the 529,000 recorded maternal deaths (Maternal Mortality in 2000: Estimates by WHO, UNICER, WNFPA (http://www.who.int/reproductive-health/publications/maternal_mortality_2000/mme.pdf)). An additional significant health burden is the epidemic of human immunodeficiency virus (HIV) infection in many developing countries, particularly in Africa. In 2005, it was estimated that 40.3 million people were living with HIV worldwide, of whom nearly 50\% were women. While sub-Saharan Africa has just over 10\% of the world’s population, 60\% of all people living with HIV live in the region (UNAIDS/WHO AIDS Epidemic Update: 2005 (www.unaids.org/epi2005/doc/report_pdf.asp)).

2.2. Limited human and financial resources

Most countries in Eastern and Southern Africa have high incidences of cervical cancer coupled with extremely limited
facilities for screening or treatment [2]. Malawi, for instance, which has a cervical cancer incidence rate of 47 per 10,000 women, has one pathologist, one colposcope, no cytotechnicians and no facilities for cervical cancer screening or treatment. A similar or worse situation exists in many other sub-Saharan African countries such as Congo, Mozambique, Kenya, Tanzania and many others.

2.3. Poorly developed healthcare services

Primary healthcare facilities, where preventative healthcare such as cervical screening should be located, are limited, under-resourced and over-burdened in most developing countries. Most low-resource countries have very limited cancer diagnostic, treatment and palliative care services. A contributing factor to limited access to healthcare in poor countries is the urban/rural bias, which is extreme in sub-Saharan Africa [3]. While 87% of the region’s urban population has access to health services, more than 50% of the people in most sub-Saharan Africa countries live more than 10 km from the nearest primary care centre [3].

2.4. Women are uninformed and disempowered

The World Development Report has cited education as an essential component to human health, stating that “Households with more education enjoy better health, both for adults and for children (a result that) is strikingly consistent in a great number of studies, despite differences in research methods, time periods and population samples” [4]. Women in developing countries tend to be poorly educated, which has profound ramifications for the total quality of their lives, ranging from healthcare access, to health-seeking behaviour, to the ability to generate income. In most societies they have a status subservient to men, with less control over family resources, minimal access to money and, in general, inferior social power [3].

2.5. War and civil strife

In many developing countries, civil upheaval and general violence have been the status quo for decades. Some of the important consequences of war include displacement of people, the creation of refugees, disruption of healthcare services, with subsequent loss of infrastructure and personnel and the diversion of state money to defence, all of which make the establishment of successful screening programmes particularly difficult.

2.6. Widespread poverty

Widespread poverty characterises many developing countries. In sub-Saharan African countries, for instance, only 41% of the total population of the region has access to safe water and 26% to sanitation; these are the lowest percentages of all the developing country regions [3].

2.7. The nature of the screening test

While the factors described above are probably the most important reasons that cervical screening programmes have not been established in developing countries, the nature of the current screening process is also a contributing factor. For many developing countries, establishing quality, national, cytology-based screening programmes is beyond their capacity and resources.

The first barrier to cytology-based screening programmes is to develop the necessary infrastructure to obtain and transport the Pap smears to laboratories for processing and interpretation. Thereafter, the results need to be communicated to the referring clinic and to the women who have been screened. This delay in itself is known to be a significant barrier to screening, with large numbers of women not returning for results.

Secondly, high-quality cytology laboratories need to be established for cytology-based screening programmes to be effective. Interpreting cervical smears is one of the most difficult tasks and obtaining a high level of proficiency requires several years of training. Maintaining skills requires ongoing education, close supervision and a built-in quality control program.

Once a woman with an abnormal smear has been identified, she requires a referral for colposcopic assessment. Colposcopy, where available, tends to be located in tertiary, urban-based institutions and provided by specialists. This requirement creates problems of access for poor women, both urban and rural.

The modern management of pre-invasive lesions has been considerably simplified by the introduction of loop excision electrosurgical procedure (LEEP), also known as large loop excision of the transformation zone (LLETZ). This procedure can be performed in an outpatient setting, using local anaesthetic and relatively unsophisticated equipment. The complication rate of LEEP is low and the reported cure rate ranges from 80 to 95% [5]. For most countries with limited or no screening, there is a concomitant lack of colposcopic services and outpatient methods of treating pre-invasive disease. Hence, in those countries with limited screening, most women with abnormal smears are subjected to cone biopsy or hysterectomy, both of which are radical and expensive treatments that would be unsustainable for a population-screening programme.

3. Screening in low-resource settings

The challenges and failure of cytology screening programmes to be developed and sustained in low-resource countries has stimulated the search for alternative methods of screening that would overcome the many barriers identified.
To screen successfully in low-resource settings, the following requirements are essential:

- screening, diagnosis and treatment provided on-site, or in clinics accessible to the majority of at-risk women;
- low-cost, low-technology screening test that can lead to immediate treatment of abnormalities;
- wide coverage of at-risk women;
- appropriate educational programmes directed towards health workers and women to ensure correct implementation and high participation;
- built-in mechanism for evaluation of the screening programme.

A number of different tests have been developed and investigated over the years as alternative screening tests to cytology (Table 1). Physical methods such as the Polar Probe and the optical detection method require fairly sophisticated equipment, have only been tested in specialised clinics and have not to date shown greater test performances than cytology. Molecular tests, particularly tests that could detect integrated HPV-DNA or its products offer the possibility of identifying those precursors that are most likely to progress to cervical cancer [6–10]. These tests are still being researched and developed.

The two most widely studied alternative approaches to cervical cancer prevention are visual inspection (with acetic acid or Lugol’s iodine) and HPV-DNA testing. HPV-DNA testing is being considered as an additional test to the conventional Pap screening test and as a primary screening test in older women. It is briefly reviewed in this chapter as it is covered in Chapter 10.

3.1. Visual inspection with acetic acid (VIA)

VIA, also known as direct visual inspection (DVI), the acetic acid test (AAT) or cervicoscopy, involves examination of the cervix with the naked eye, using a bright light source, after one min of 3–5% dilute acetic acid application using a cotton swab or a spray. Detection of well-defined aceto-white areas close to the squamocolumnar junction (SCJ) indicates a positive test. Although aceto-whitening can occur in immature squamous metaplasia and in inflamed and regenerating cervical epithelium, aceto-whitening associated with cervical intraepithelial neoplasia (CIN) is well demarcated, intensely opaque and localised to the transformation zone. Early microinvasive cancers also turn white after application of acetic acid. Aceto-whitening is thought to be due to a reversible coagulation of intracellular proteins following acetic acid application. The higher concentrations of intracellular proteins in neoplasia lead to the dense aceto-whitening following acetic acid application.

One of the main advantages of VIA is that it yields an immediate result, thus making it theoretically possible for treatment of abnormal lesions to be performed at the same visit—the so-called “screen-and-treat” approach, without colposcopy or histological sampling. This method is inexpensive and can be carried out using modest equipment and widely available consumables without the need for a laboratory infrastructure. A range of personnel including doctors, nurses, midwives and paramedical health workers can be rapidly trained to perform VIA in short courses of 5–10 days duration [11]. A wide range of teaching materials is now available for VIA training courses, making VIA particularly attractive as a screening test in low-resource settings.

The test characteristics of VIA have been evaluated in several cross-sectional studies in less-developed countries [12]. These studies together have involved more than 150,000 women and have reported promising results that support its use as an alternative to cervical cytology. The sensitivity of VIA to detect high-grade precursor lesions and invasive cervical cancer has varied from 49 to 96% and the specificity from 49 to 98% [12]. However, many of these studies suffered from verification bias, which occurs when only a subset of all screened women, commonly women who are screen-positive, is subject to definitive assessment of final disease status using the reference diagnostic investigations (“gold standard”), which conventionally is colposcopically directed biopsy, and thus the true disease status is not known for a large fraction of the individuals in the study. However, colposcopy has a relatively low sensitivity (see Table 1) and is

<table>
<thead>
<tr>
<th>Screening test</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional cytology</td>
<td>Moderate (44–78%)</td>
<td>High (91–96%)</td>
<td>Requires adequate healthcare infrastructure; laboratory based; stringent training and quality control</td>
</tr>
<tr>
<td>HPV-DNA testing</td>
<td>High (66–100%)</td>
<td>Moderate (61–96%)</td>
<td>Laboratory based; high throughput; objective, reproducible and robust; currently expensive</td>
</tr>
<tr>
<td>Visual inspection methods</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VIA</td>
<td>Moderate (67–79%)</td>
<td>Low (49–86%)</td>
<td>Low technology; low cost</td>
</tr>
<tr>
<td>VIAM</td>
<td>Moderate (62–73%)</td>
<td>Low (86–87%)</td>
<td>Linkage to immediate treatment possible; suitable for low-resource settings</td>
</tr>
<tr>
<td>VILI</td>
<td>Moderate to high (78–98%)</td>
<td>Low (73–93%)</td>
<td></td>
</tr>
<tr>
<td>Colposcopy</td>
<td>Low (44–77%)</td>
<td>Low (85–90%)</td>
<td>Expensive; inappropriate for low-resource settings</td>
</tr>
<tr>
<td>Polar Probe</td>
<td>Moderate (67–74%)</td>
<td>Low (65–72%)</td>
<td>High technology but gives immediate result and could be linked to immediate treatment</td>
</tr>
</tbody>
</table>

\( ^{a} \) Ranges of sensitivity and specificity adapted from reference [12].
currently being challenged as new prevention strategies are emerging [13]. Under such circumstances, the estimates for sensitivity and specificity must be corrected to account for those with unknown final disease status. Pooled estimates of sensitivity vary from 62 to 80% and specificity from 77 to 84% for VIA to detect high-grade CIN, after adjusting for the effects of verification bias.

3.2. Visual inspection with Lugol’s iodine (VILI)

VILI involves examination of the cervix with the naked eye to identify mustard-yellow areas on the cervix after application of Lugol’s iodine. A multi-centre study in India and Africa involving around 49,000 women concurrently evaluated VIA and VILI by independent providers, using a common protocol [14]. The pooled sensitivity and specificity to detect high-grade CIN were 92 and 85%, respectively, as opposed to 77 and 86% for VIA, thus indicating a higher sensitivity than VIA in this study but similar specificity was observed. In a Latin American study involving about 3000 women, VILI had a significantly lower sensitivity of 53% and a specificity of 78% to detect high-grade CIN [15].

Denny et al. investigated the influence of concurrent sexually transmitted infections on the test characteristics of VIA in a South African study and found that there were no significant differences in the sensitivity and specificity of VIA relating to the presence or absence of N. gonorrhoea, C. trachomatis, or T. vaginalis. The specificity of VIA was, however, significantly lower among HIV-positive women [16] in relation to HIV-status.

A study that assessed the cost-effectiveness of a variety of cervical-cancer screening strategies in India, Kenya, Peru, South Africa and Thailand reported that screening women once in their lifetime, at the age of 35 years, with a one-visit or two-visit screening strategy involving VIA, reduced the lifetime risk of cancer by approximately 25–36%, and cost less than 500 international dollars per year of life saved [17]. Relative cancer risk declined by an additional 40% with two screenings at 35 and 40 years of age, resulting in a cost per year of life saved that was less than each country’s per capita GDP, which is a very cost-effective result according to the Commission on Macroeconomics and Health. The study concluded that VIA in one clinical visit (with immediate treatment of positive cases) or two clinical visits (followed by treatment without colposcopic evaluation of positive cases) is one of the most cost-effective alternatives to conventional three-visit (with colposcopy and biopsy in positive cases and treatment of cervical intraepithelial neoplasia) cytology-based screening programs in resource-poor settings.

4. Screen-and-treat approach to cervical cancer prevention

In an attempt to overcome the obstacles posed by traditional cytology-based screening programmes, a number of studies have investigated an approach where screening is linked to either immediate treatment in a single-visit strategy or shortly after the screening test is performed.

Denny et al. performed a randomised controlled trial of 6555 non-pregnant, unscreened women aged 35–65 years [18]. All women were screened using HPV-DNA testing (Hybrid Capture 2, which tests for 13 high-risk types of HPV) and with VIA. Women were randomised thereafter to one of three groups: cryotherapy if the HPV test was positive, cryotherapy if VIA was positive or delayed treatment regardless of the result of the screening test. The prevalence of high-grade CIN (defined histologically) was significantly lower in the two screen-and-treat groups at 6 and 12 months post-randomisation compared to the delayed evaluation group. This was the first study of alternative screening approaches to the secondary prevention of cervical cancer that evaluated effectiveness. The safety and feasibility of the screen-and-treat approach were also confirmed in a study conducted in Thailand [19].

5. Colposcopy in cervical cancer screening

In most countries colposcopy is used to evaluate women who have abnormal cytology. In some countries, specifically countries in Central and Eastern Europe and parts of Latin America, colposcopy is incorporated into the routine gynecological examination of women. There are no data to support the use of colposcopy as a primary screening test and this is not generally recommended.

6. Case studies of cervical cancer and cervical cancer prevention in different regions of the world

The striking differences in incidence rates of cervical cancer in different regions of the world are a reflection of the impact of screening programmes on the incidence of invasive disease. It is estimated that at any given point in time, more than 75% of women in the developed world have had some sort of screening undertaken in the previous 5 years compared to less than 5% of women in the developing world. The following sections describe a selection of screening programmes and experiences in resource-restricted areas of the world.

6.1. Mexico

The mortality rate from cancer of the cervix has been falling since the mid-1980s, with current rates being slightly under 12 per 100,000. This is most likely due to an increase in screening. The National Survey of Health in Mexico has demonstrated a rise in the annual cytology uptake from 31 to 38% between 2000 and 2003, with almost 70% of the population having had a Pap smear in the preceding 3 years. Uptake in rural areas has tripled in the last 5 years. However,
there is a lack of standardisation of cytology reporting, with poor quality assurance. Further, colposcopy is overused as a diagnostic tool, with very little quality assurance, which results in false-negative rates for Pap smears ranging from 12 to 45%, with false-positive rates of almost 10% in some centres.

Mexico, like other Latin American countries, needs to reorganize its cervical screening program in order to reach marginalized rural and urban women, ensure reliable cytology with good quality control and provide ongoing training. Colposcopy should be used to triage abnormal smears and not used as a diagnostic tool. Education of both the community and health professionals is essential if any gains made in cervical cancer prevention are to be maintained.

6.2. India

Control of cervical cancer in India would have a major global impact as it accounts for a fifth of the world burden of cervical cancer. Although data from population-based cancer registries indicate a slow but steady decline in cervical cancer incidence rates over the last two decades, the risk of disease is still high, particularly in rural areas. Despite the high burden of disease and the increasing absolute number of cases due to population growth, there are no organized screening programmes for cervical cancer prevention anywhere in India, although some level of opportunistic cytology screening is practiced in urban areas. It is estimated that around a million cervical smears are taken in India annually, 80% of which are through private-sector providers.

However, there have been several research studies addressing feasible and cost-effective alternative screening options for possible wide-scale implementation in the future [12,17,20–22]. The Indian studies showed that visual screening tests for cervical abnormalities are affordable, simple, acceptable, feasible and reasonably accurate clinical tools for early detection that can be readily used in a variety of healthcare settings in both developing and developed countries.

A recent task force constituted by the Government of India has recommended the introduction of VIA-based screening in primary health centres in about 50 districts in the next 5 years and the development of a central treatment centre in each of the districts where VIA-positive women will be referred, investigated and treated. Nationwide coverage is eventually planned. For the first time, there seems to be a real opportunity to integrate early detection of CIN-3 into the primary healthcare settings in India.

6.3. Eastern Europe—Serbia and Montenegro

The incidence of cervical cancer has risen steadily in Serbia since 1982, when the age-standardised incidence rate (ASIR) was 18.6 per 100,000. In 2005, the incidence rate was 27.4 per 100,000, and in some regions of Central Serbia, the estimate was as high as 40 per 100,000. As in most countries in Eastern Europe, cervical cancer prevention in Serbia and Montenegro has relied on opportunistic screening, with some additional efforts to provide annual screening to women employed in large companies. This has had little effect on the burden of cervical cancer and has led to the Ministry of Health to set up a special taskforce to develop a national screening program. Several studies have been undertaken to plan future programs, including a study conducted by the Institute of International Social Affairs, which showed that an educational campaign will increase participation rates of women by more than 60%.

6.4. The Philippines

The incidence of cervical cancer in the Philippines has remained stable since the 1980s at approximately 22 per 100,000. Pap smears are not particularly available as a screening test in the Philippines, as only 42% of the 389 nationwide hospitals offer screening, with only 8% having dedicated screening clinics. Only one in five hospitals have a cytology technician, and less than half of these hospitals have a pathologist. Colposcopy is not available in local community hospitals, with only one in four tertiary hospitals having this facility available.

6.5. Thailand

Cervical cancer is the most common cancer in women in Thailand, with 6000 new cases diagnosed annually. Pap smear screening has been available opportunistically for over 40 years but used for mainly diagnostic purposes. A National Cancer Control Programme and a mass campaign to raise awareness have been instituted, mainly by government health providers. A Mobile Unit Programme was established in 1993 targeting women between 25 and 60 years of age, and supported by provincial health offices. Three education campaigns have been evaluated in the Mae Sot District and Tak Province, with a substantial improvement in women’s awareness of cervical cancer and screening.

6.6. South Africa

South Africa launched a cancer registry in 1986 that relies on pathology-based information reported by 80 private and public laboratories. In 1986, the total number of cancers reported in women was 16,559, of which 2897 (17.4%) were new cases of histologically confirmed cervical cancer (Cancer Registry of South Africa, 1986). In 1992, the total number of reported cancers in women had increased to 25,143 and the percentage of new cases of cervical cancer (4467) over the total number of cases remained at the same proportion as was reported in 1986 (17.8%). It is acknowledged, however, that a significant number of women with cervical cancer die without a diagnosis of cervical cancer being made, no histological sampling is performed nor was the disease registered, which suggests that the reported number of cases of cervical
cancer is an underestimate of the true number of cases. South Africa now has a prioritised policy to screen all women aged 30 years and older at 10-year intervals; this is yet to be widely implemented.

7. An experience in South Africa: the Project Screen Soweto (PSS)

Project Screen Soweto [23] illustrates well the difficulties of establishing a cytology-based screening programme. In 1980, at Baragwanath Hospital, which is a large tertiary institution serving the inhabitants of Soweto (an African township outside Johannesburg, South Africa), an approximate 50% increase in admissions for cervical cancer was documented, from 150 cases in 1970 to 236 cases in 1980. In addition, an excess of 70% of women with abnormal cervical smears had not been followed up. In recognition of the poor quality of the existing opportunistic screening programme and the apparently rising incidence of cervical cancer, PSS was initiated in 1986 [23]. Prior to the establishment of the project, laboratory capacity for screening had been 3000 and increased to 90,000 smears per annum. Pilot studies identified the prime screening target as an existing pool of women ages through the network of primary healthcare clinics. The unresolved problem at the time was the development of an accessible public education programme. This problem arose because of the lack of resources but also due to fears that too vigorous and too early a public education program would flood an untested screening network and swamp primary healthcare clinics, laboratories, colposcopy clinics and hospital wards. A decision was thus made to launch Project Screen Soweto prior to instituting any public health educational programme.

During the planning phase of the project in 1982, 32,365 smears were taken. After the launch of the project, however, the number of smears taken decreased to 24,251 in 1983 and 26,216 in 1984. In addition, there was a rapid decline in the diagnosis of both pre-invasive and invasive cervical cancer, the opposite of what should occur in a screening program in a previously unscreened population. The failure of the PSS was acknowledged 5 years after the commencement of the project. The reasons for the failure of PSS are complex. An important cause of the failure of the programme appeared to be the very low priority given for Pap smears at the level of the primary healthcare services and the competing health needs of the largely poor community. In addition, the failure to establish an effective public health educational programme resulted in women remaining ignorant about cervical cancer prevention and no consumer demand for screening was created.

It was calculated, however, that had available laboratory facilities been utilised to full capacity during that 5-year period, an excess of 300,000 women in Soweto would have received at least one smear, which should have detected 6000 pre-invasive or invasive cancers.

Disclosed Potential Conflict of Interest

MQ: Advisory Board (GlaxoSmithKline)

Acknowledgements

Mauricio Hernandez-Avila (Mexico), Eduardo Lazcano (Mexico), Peter Bosze (Hungary), John Sellers (PATH, USA), Vesna Kevic (Serbia), Cecilia Lave (The Phillipines), respectively.

References


