Screening for Cervical Cancer in Low-Resource Countries

6

Laurie Elit

Abstract

The World Health Organization (WHO) has outlined prerequisites necessary to determine if a mass screening programme should be developed. This chapter reviews the evidence for each of these prerequisites as they pertain to cervical cancer, with particular attention to low-resource settings. The evidence for cervical screening to prevent cervical cancer is based on a review of literature published between 2000 and 2011. The level of evidence supporting the use of three types of screening tests (cervical cytology, visual inspection, HPV testing), diagnosis (with colposcopy and biopsy), and treatment (with cryotherapy, laser, LEEP, cold-knife cone biopsy, or hysterectomy) is examined as a means of preventing cervical cancer or downstaging the disease. The benefits of a population-based programme are described and supported by examples of such programmes of in low-resource countries. In those jurisdictions where cervical cancer is a major cause of cancer incidence and mortality, the optimal approach is an organized screening programme. For low-resource settings, a "see-and-treat" approach with either VIA or careHPV™ followed by cryotherapy is the most cost-effective strategy.

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Dedicated to John Sellors 1946–2011: John Sellors and I were to co-author this chapter. Unfortunately, Dr. Sellors died on December 31, 2011. He spent the later decades of his life introducing, assessing, and implementing many of the screening methods described in this chapter in low-resource settings.

It is for man to tame the chaos; on every side, whilst he lives, to scatter the seeds of science and of song, that climate, corn, animals, men, may be milder, and the germs of love and benefit may be multiplied.

Ralph Waldo Emerson, Uses of Great Men: http://www.bartleby.com/109/9.html. Accessed 28 Dec 2011.

M.K. Shetty (ed.), *Breast and Gynecological Cancers: An Integrated Approach for Screening and Early Diagnosis in Developing Countries*, DOI 10.1007/978-1-4614-1876-4_6,
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Introduction

The WHO has outlined prerequisites necessary to determine if a mass screening programme should be developed [1]. These prerequisites include:

1. The disease must be common enough to justify mass screening
2. It must be associated with significant mortality
3. Effective treatment is available for pre-invasive or early invasive disease
4. Detection and treatment of a presymptomatic state result in benefits beyond those obtained through treatment of symptomatic disease

In this chapter, we will review the evidence available for each of these prerequisites as they pertain to cervical cancer [2].

Magnitude of the Problem

Globally, cervical cancer accounts for 10 % of all female cancers, making it the third leading cause of cancer and the fourth leading cause of cancer death in women [3]. Annually, 530,232 women are affected with cervical cancer (ASR 15.2), and 275,008 women die of their disease (ASR 7.8). The mortality to incidence ratio is 52 %. Eighty-five percent of cervical cancer cases occur in low-resource countries, and 85 % of these women die of their disease [4–8]. In low-resource settings, cervical cancer is the second leading cause of cancer and death compared to high-resource settings, where it is the tenth leading cause of cancer [3]. Age-standardized incidence rates are highest in Africa (i.e. ASR 69 per 100,000 in Tanzania), Central America (i.e. ASR 55 per 100,000 in Bolivia), south central and eastern Asia (i.e. ASR 24.6 per 100,000) and South America (i.e. ASR 23.9 per 100,000) [9]. These rates are astronomical when compared to rates of less than 6 per 100,000 in Australia/New Zealand, Europe, and North America [10]. These disparities in part are based on whether there is access to an organized screening programme [11]. Thus, in low-resource settings where such programmes are non-existent, women with cervical cancer often present to hospital with symptoms such as bleeding and foul smelling discharge, which reflect advanced/metastatic disease [12]. Thus, globally, cervical cancer is a common and deadly disease fulfilling the first and second prerequisites put forward by the WHO to justify mass screening.

Process of Cervical Cancer Development

Cervical cancer arises in the transformation zone of the uterine cervix. This area undergoes dynamic change especially at puberty where squamous epithelium impinges upon the glandular epithelium in a process known as metaplasia. The human papilloma viral infection is a very common sexually acquired infection that is introduced with the onset of sexual activity. In most cases, the viral infection is resolved by the woman's own immune system. However, if there is a persistent infection, especially with the oncogenic types of HPV (i.e. 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 57, 58, 68, etc.), the viral oncoproteins produce loss of the cell cycle controls. The cells reflect this with a change in nuclear to cytoplasmic ration, loss of nuclear regularity, and chromatin clumping. These cytologic changes are known as dysplasia or, following a more contemporary nomenclature using the Bethesda terminology, squamous and/or adeno intraepithelial lesion (SIL) (see ref. [20]). The degree of cellular and architectural changes in the cervical biopsy is classified in terms of levels of cervical intraepithelial neoplasia (CIN). In the mildest form, CIN 1, the HPV infection causes changes in the lowest one-third of the epithelium. Often (80 %), a CIN 1 lesion will resolve over 12–24 months, especially in young women. However, in the most severe form, CIN 3, the cellular changes affect the whole epithelium above the basement membrane. The risk of a CIN 3 lesion progression to cancer is estimated to be 31.3 % (95 % CI 22.7–42.3) if the lesion is not detected and treated [13]. The peak incidence of an HPV infection occurs when a women is in her 20s. The peak incidence of CIN 3 is seen in her 30s [13, 14]. The peak incidence of cervical cancer is in the mid-40s [15]. This transition from infection to dysplasia (SIL or CIN) to cancer takes several years, thus

allowing the opportunity for detection by a screening test.

In the case of cervical cancer, there is a presymptomatic/precancerous disease state that spans a significant period of time during which, if identified, there is the potential to remove the disease. This meets prerequisite 4 of the WHO criteria justifying mass screening (Table 6.1).

Prevention as a Component of the Disease Continuum (Framework)

Cervical Screening should be part of a woman's regular health journey, where asymptomatic women are assessed with a test to determine if a precancerous lesion is present. Then, if found, *Cervical Diagnosis* becomes part of the cervical cancer journey, where women with a positive screening test are sent for further diagnostic test(s). Further along that path, *Cervical Treatment* involves removing the disease to prevent the occurrence of cancer or identifying and treating asymptomatic early stage cancer (Fig. 6.1).

Table 6.1 Comparing Classification Systems for Squamous Lesions.

Dysplasia (cytology)	CIN (histology)	Bethesda (cytology)
Normal	Normal	Normal
Atypia	Atypia	ASCUS
HPV effect	HPV effect	LSIL
Mild dysplasia	CIN 1	
Moderate dysplasia	CIN 2	HSIL
Severe dysplasia	CIN 3	
Carcinoma in Situ (CIS)		
Cancer	Cancer	Cancer

Definition of Low-, Medium-, and High-Resource Countries

There are many ways of defining "developing" or "low-resource countries." Some agencies use a definition based on rate of literacy or life expectancy [16]. For this chapter, we will use the classification put forward by the World Bank. The Gross National Income per capita is divided into three strata: low-resource countries (US$ 1,005 or less), middle-resource (low-middle is US$ 1,006–3,975; upper-middle US$ 3,976–12,275), and high-resource countries (US$ 12,276 or more) [17].

The remainder of this chapter will focus in more detail on the WHO prerequisites 3 and 4 as they pertain to cervical cancer prevention.

Methods

For this chapter, we reviewed the literature on the screening modalities for cervical cancer in low-resource settings, and we included MEDLINE,

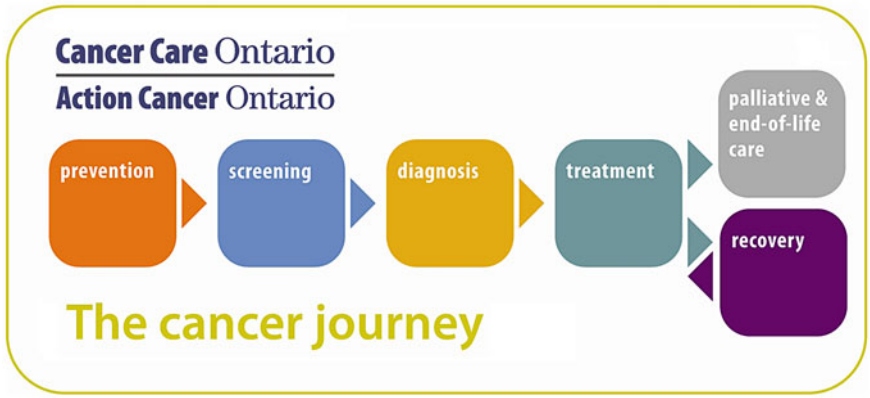

Fig. 6.1 Prevention as part of the disease continuum. (Courtesy of Cancer Care Ontario, Toronto, Ontario, Canada)

CINAHL, EMBASE, GOOGLE, and the Cochrane library from 2000 to December 2011. Bibliographies of relevant review articles and included studies were scanned for additional relevant publications. Included in the literature search strategy were terms such as "cervical cancer," "cervical neoplasm," "utero-cervical neoplasm," "screening," "developing country," "low-resource country," "cervical cytology," and "VIA testing" and "HPV testing." We excluded non-English publications.

Screening Tests

What Makes a Good Screening Test?

For a screening test to be clinically useful, it must be simple, inexpensive, accurate, and acceptable by the patient. In this section, we will review the available screening tests, their efficacy, advantages, and limitations. There are three screening tests which will be reviewed: cervical cytology, visual inspection, and oncogenic HPV assessment. The best way to think about screening is as a therapeutic intervention. In this chapter, randomized trials examine the effect of screening on patient important outcomes. The outcomes of interest are that cervical cancer screening will (1) reduce the *incidence* of cervical cancer through detection and removal of precancerous lesions and (2) reduce disease progression through detection of invasive cancers in the early stages, thereby improving the chance for cure and reducing *mortality* [18]. See Table 6.2.

The possible consequences of screening are that some women will have a true-positive result (a) (i.e. HSIL) with clinically significant disease (CIN 3), and they will benefit from treatment. However there are some patients with inconsequential disease (ASCUS), and they may experience the consequences of labelling, investigation, and treatment for disease (HPV infection) which may never affect their lives. Women with a false-positive result (b) may be adversely affected by the risks associated with investigation (i.e. colposcopically directed biopsy). False Negative (c) involves women who, for example, have a normal Pap test when they actually have disease; this result delays investigations. Patients with a true negative (d) experience the benefit associated with accurate reassurance of being disease free, but they may have experienced inconvenience, cost, and anxiety associated with screening [19].

Cervical Cytology (Otherwise Known as the Pap Test or Pap Smear)

In 1940, George Papanicolaou discovered that cells retrieved from the apex of the vagina could reflect changes in the cervix that over time led to cervical cancer. Today, cervical cytology is obtained usually by a physician. After the woman is counselled about the purpose of the test and gives permission to have the test, she is examined

Table 6.2 Test parameters

		Disease		
		Present	Negative	
Screening Test	Positive	a-True positive	b-False positive	a+b
	Negative	c-False negative	d-True negative	c+d
		a+c	b+d	a+b+c+d

True positive (a)—The screening test is positive in a patient with the disease
False positive (b)—The screening test is positive in a patient without disease
True negative (d)—The screening test is negative in a patient without disease
False negative (c)—The screening test is negative but the patient has disease
Sensitivity: a/a+c—The rate of test positivity in patients with the disease
Specificity: d/b+d—The rate of test negativity in patients without the disease
Positive predictive value: a/a+b—Rate of disease in patients with a positive test
Negative predictive value: d/c+d—Rate of no disease in patients with a negative test

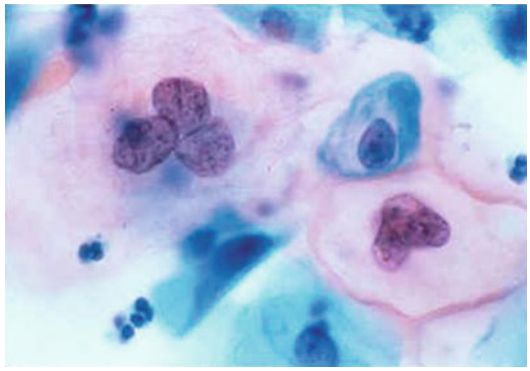

Fig. 6.2 Example of a cervical cytology specimen

in the lithotomy position. With a speculum in the vagina and either using either a spatula and/or a brush, cells are scraped from the cervix and either spread across a glass slide and fixed with cytospray (or hairspray in some jurisdictions) (Fig. 6.2). Alternatively the cells are placed in a liquid-based media (such as Hologic's Thin Prep®, Bedford, MA), or BD SurePath™ (Franklin Lakes, NJ). This specimen is processed in a lab with various stains and read by a cytotechnologist and/or cytologist. The results are reported using the Bethesda 2001 classification system [20]. A few weeks after the test is obtained, the woman must return or call her physician's office for her results and disposition planning.

Efficacy

There has only been one randomized trial comparing a once-in-a-lifetime cervical cytology to no screening. Fifty-two villages in India, with a total of 131,746 healthy women aged 30–59 years, were randomly assigned to one of four groups [21]. These groups received screening by a single lifetime cervical cytology (n=32,058), HPV test (n=34,126), visual inspection by acetic acid (n=34,074), or standard care which involved giving women information on how to seek screening at local hospitals (n=31,488). The single lifetime cytology test had no significant impact on 8 years mortality (age-adjusted HR 0.89, 95 % CI 0.62–1.28, p=0.53). The single lifetime cytology test had no statistical impact on 8 years incidence of cervical cancer (age-adjusted HR 1.34, 95 % CI 0.99–1.81, p=0.06). The higher incidence of cervical cancer in the screened group is explained by the active detection of disease in the screened group and the fact that this was the first screen almost any woman had received. A single lifetime cytology test had no statistical impact on 8-year incidence of Stage 2 or higher cervical cancer (age-adjusted HR 0.75, 95 % CI 0.51–1.10, p=0.14).

Although there is no direct evidence from randomized trials for the efficacy of a single cervical cytology test in decreasing rates of cervical cancer, there is overwhelming epidemiologic data to infer the impact of cytology screening on reducing cervical cancer rates. These data come from two types of work. First, case–control studies have been reported from many jurisdictions around the world comparing the history of cervical cytology of women with cervical cancer and age-matched controls of those without cervical cancer (i.e. Canada, Columbia, Costa Rica, Finland, Japan, Italy, South Africa, Panama, Sweden, USA). These studies show consistently that the odds of developing cervical cancer are lower in those women who received at least one Pap test (in the order of OR 0.036) compared to those not screened [18, 22–34]. The second body of epidemiologic evidence is the correlation of incidence and mortality trends of cervical cancer in screened populations such as reported from Canada, the Nordic countries, and the UK [35–38].

The test parameters for conventional cervical cytology to define lesions of CIN 2 or worse are sensitivity 44–78 % and specificity 91–96 % [39, 40]. The low sensitivity means that, in those women with a normal test, it must be repeated frequently (i.e. at least every 3 years) to ensure that a lesion has not been missed or that a new lesion has not developed [15]. The high specificity means that those women without disease will have a normal test result.

Advantages

The advantages of cervical cytology are that the test is easy to learn to perform and the consumables (i.e. spatula) are low cost.

Limitations

Since cervical cytology has been available for at least 50 years, its limitations are well documented:

1. As discussed earlier, a single Pap test has low sensitivity, and this sensitivity can be improved with repeated cytological assessments over time. The low sensitivity can be related to process issues: for example, the physician may fail to sample the squamocolumnar junction (more common in perimenopausal or postmenopausal women). This high false-negative rate is a serious weakness [41].
2. A high rate of unsatisfactory smears can occur: for example, if the sample is not fixed appropriately, if cotton tips applicators are used to retrieve the specimen (as the cotton fibres create artefact on the slide), or if the woman has an infection. If the woman has an unsatisfactory smear, she should return for a repeat test. Liquid-based cytology has been developed to decrease the amount of time necessary to assess each specimen, to decrease the number of unsatisfactory cervical cytology reports, and to allow the residual fluid to be available for HPV assessment; it can be automated. However, a systematic review and meta-analysis of liquid-based cytology show that sensitivity and specificity are the same as for conventional cytology [40].
3. Another limitation is that evaluation of the cytology test is highly subjective. The cytologists and cytotechnologists must be trained to recognize various cellular patterns. Thus, at the laboratory level, there must be an ongoing system of quality assurance both in optimally staining the slides and pattern recognition.
4. The cost of infrastructure, including laboratory space, personnel, and information networks, can be daunting. Conventional cytology screening is resilient and the reagents are low in cost, compared to those jurisdictions that use liquid-based cytology, which requires expensive equipment, a reliable electrical source, and daily maintenance, which may not be available in all settings [42, 43].
5. The attitudes and beliefs of a woman influence her willingness to have a screening test. For example, a pelvic exam may not be acceptable to all women, and this may be related, in part, to the gender of the provider.
6. Access to the test may be a limitation. In some settings, the test is accessible only through reproductive health clinics. Thus, peri- and menopausal women, who are at the highest risk for dysplasia, may not attend and so be disadvantaged.
7. A cytology-based system requires that a woman return to see the physician repeatedly (for the test, for test results, and subsequent tests, resulting in reduced patient compliance as discussed later in this chapter). Out-of-pocket costs for health care and indirect costs of lost hours of productive work, child care expenses, or long distance travel can put a great burden on poor women. Thus, a cytology-based system may fail due to low compliance [42, 44–48].

Other Considerations from Experiences in Low-Resource Settings

In Central and South America, there was a high coverage in screening appropriate women, but the quality of cytology assessment was poor, and so rates of cervical cancer remain high [49]. Strategies to improve this problem included implementing telemedicine systems to help bring high-quality cytology assessment to remote settings. For example, the Italian NGO Associazione Patologi Oltre Frontiera (APOF) has worked since 2000 to help countries in Sub-Saharan Africa [50]. A pilot project in Chirundu, Southern Zambia, showed that it was feasible to train histology lab workers to screen Pap smears, take digital photographs of suspicious or positive cases, and then by digital scanner and satellite connection confirm a diagnosis within four days. Original slides are reviewed in Italy every 6 months for quality-control purposes.

Conclusion

Cervical cytology, especially if repeated periodically during a woman's lifetime, has resulted in a fall in cervical cancer rates; however, there are limitations not just with the test but the context in which it is applied. We will discuss these in more detail later in this chapter.

Visual Inspection (Otherwise Known as Direct Visual Inspection)

Visual inspection involves inspecting the cervix with the naked eye using a bright light source and is followed by the application of either a 3–5 % dilute acetic acid for one minute (known as visual inspection with acetic acid, VIA) or acetic acid test (AAT). If Lugol's iodine is used, this is called visual inspection with Lugol's iodine (VILI) or the Schiller's test.

Visual Inspection with Acetic Acid

With the application of acetic acid to the cervix, there is a reversible coagulation of intracellular proteins. If dysplasia is present, a pronounced white lesion is seen. A VIA test can be reported as "negative" if no lesion is seen, "positive" if there is detection of a well-defined aceto-white area close to the squamocolumnar junction (Fig. 6.3), and "suspicious for cancer" if an irregularly exophytic or ulcerative lesion is identified (Fig. 6.4) [51, 52]. VIA can only reliably be used in women where the squamocolumnar junction is visible on the ectocervix; thus, it should mainly be used in women 30–45 years old.

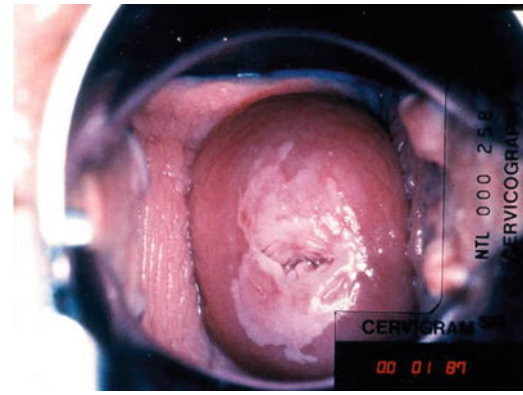

Fig. 6.3 Cervix after the application of 3-5 % vinegar showing a white lesion. This is an example of VIA positive

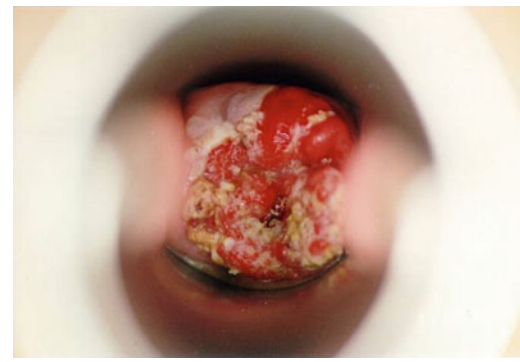

Fig. 6.4 Cervical cancer. This is an example of VIA suspicious for cancer

Efficacy

A cluster-randomized trial in the Dindigul district of India involved 49,311 women aged 30–59 years. They were randomized to health education or VIA. At 7 years, the VIA group had a lower incidence of cancer (HR 0.75 95 % CI 0.55–0.95) and lower mortality (HR 0.65, 95 % CI 0.47–0.89) [53].

A cluster-randomized trial in India involved 142,701 women aged 30–59 years. One group was given education alone. The three other groups involved a once-in-a-life time cervical cytology or VIA or oncogenic HPV test. Detection of CIN 2/3 was the same for all three screening tests at 0.7 % for VIA, 1 % for cytology, and 0.9 % for oncogenic HPV DNA [21].

The test parameters for VIA have been critically assessed, and the sensitivity ranges from 49–96 % and the specificity ranges from 49–98 % [54, 55].

Advantages

VIA has several advantages. It is inexpensive [9, 56, 57] . When used in already existing health centres, the instruments required for VIA are already present, and there are few disposables [9, 56–59]. VIA is easy to learn [57] and can be performed by a wide range of health-care workers (i.e. physician, nurse, midwife, local health-care worker) [52, 56, 57, 60–63]. The accuracy of VIA is the same as cervical cytology. Sensitivity is the same or higher than cervical cytology. VIA provides immediate results, which can be given to the woman during the same physician visit [9, 56–59, 63, 64]. VIA can be used in a screen-and-treat algorithm which decreases issues related to compliance (to be discussed later in this chapter). VIA does not require a lab infrastructure [59]. VIA can be associated with increasing screening coverage, which in part means laying down the framework to integrate novel, more sensitive technologies in the future [65].

Limitations

In VIA the acetic acid can cause a temporary stinging sensation for the woman.VIA is not suitable for older women because the squamocolumnar junction is not visible on the exocervix [57, 58]. VIA is a subjective test with high inter-rater variability, so substantial provider-training and ongoing quality assurance assessments are needed [55, 66–70]. Some fear that the quality assurance of VIA may be more difficult to control than the quality of cervical cytology [71]. VIA has a lower specificity and higher false-positive rate, which means that women need to be referred for a second test like colposcopy to determine if the disease is truly present. This might mean the colposcopy and pathology departments could be overwhelmed [58]. If a second test is performed, the cost is increased [70]. In a see-and-treat scenario, if a second test is not performed, many women would be treated who do not have disease [72]. One of the problems with many of the studies is the lack of verification bias (i.e. the disease status of those who were test negative was not assessed) [21, 43, 54, 73–78]. Similarly, there is a correlation between visual screening tests and colposcopy, so it is possible that the sensitivity and specificity of VIA and VILI are overestimated [55].

Some barriers to VIA uptake include the resistance of medical professionals to using a screening test other than cervical cytology. Some national policies restrict screening and treatment to physician providers, and they do not recognize or support use of VIA, especially when done by midwives or nurses.

Other Considerations

VIA lends itself to mobile telemedicine technology. In Gaborone, Botswana, four nurse midwives collected VIA images by mobile phone, and these were transferred to a website by MMS without need for an Internet connection. Unfortunately, in this study in a third of cases the images were insufficient [56, 79]. The concept of VIA image capture was assessed in El Salvador. Here, a digital camera gave the opportunity for a second assessment which resulted in a higher sensitivity than using the naked eye alone [80]. Capturing the images can be useful for getting further input from colleagues or physician staff, medical record storage, or quality assurance.

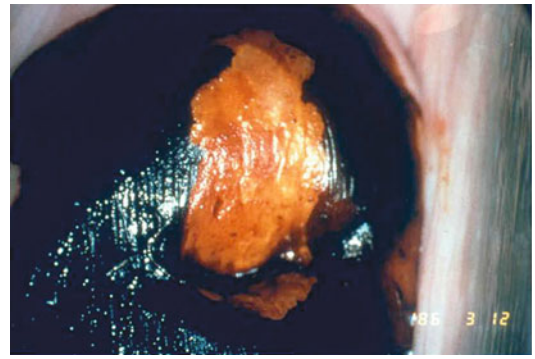

Fig. 6.5 Cervix after the application of Lugol's iodine. This is an example of VILLI positive

Visual Inspection with Lugol's Iodine

In visual inspection with Lugol's iodine (VILI), the cervix is washed with Lugol's iodine and the glycogenated cells of the vagina and cervix stain a deep mahogany brown. The non-glycogenated cells such as the glandular epithelium and areas of dysplasia do not stain. Findings are reported in terms of "VILI negative" (no lesion or abnormality), "VILI positive" (a lesion is identified) (Fig. 6.5), and "suspicious for cancer."

Efficacy

There are several studies assessing the use of VILI. A multi-centre study involving 49,000 women in India and Africa compared evaluations with VIA and VILI. The sensitivity of VILI was 92 % and the specificity was 85 % [64]. Another study involving 3,000 Latin-American women showed less optimistic findings, with sensitivity of 53 % and specificity of 78 % [81].

Advantages

VILI can be conducted by nurses or midwives after being trained. It requires minimal supplies (i.e. Lugol's iodine). Results are available at the time of test.

Limitations

Lugol's iodine is quite messy and can stain a person's clothes. Providers require training and ongoing quality reviews as the assessment is subjective. There are no studies on the efficacy of VILI in decreasing the incidence or mortality from cervical cancer.

VIA with Magnification

The AviScope™ is one example of VIA with Magnification. Here, the cervix is inspected with LED illumination with four-fold magnification of the cervix [82].There are no reports on efficacy. The advantage is better identification of lesions. The limitations in low-resource settings are the occurrences of power outages, power fluctuations, and difficulty in repairing equipment or getting parts [83].

Oncogenic HPV Test

A persistent oncogenic HPV infection is the known cause of cervical dysplasia and, ultimately, cancer. The genital tract can be swabbed for oncogenic HPV. There are a number of commercially available tests available for assessing for the presence or absence of oncogenic HPV types (i.e. HC2, HPV, DNA test produced by Qiagen (Hilden, Germany), also called the Digene® HPV test) or specific oncogenic HPV types (i.e. cobas® HPV test by Roche Molecular Diagnositics (Pleasanton, CA)). The number of HPV types varies slightly across tests.

The global estimates are that the overall age-adjusted prevalence of HPV is 10.5 %. Geographic variation of oncogenic HPV prevalence exists with the higher rates being noted in resource-poor regions (i.e. 35 % in Mongolia) [84]. Prevalence is known to decline as a woman ages. Using an HPV test in women over 30 years of age is more likely to pick up persistent HPV infection associated with dysplasia compared to the transient infection seen in younger women.

Efficacy

The efficacy of a once-in-a-lifetime oncogenic HPV test was evaluated in fifty-two clusters of villages in India, with a total of 131,746 healthy women between the ages of 30 and 59 years [21]. The villages were randomly assigned to four groups: one group underwent screening by a once-in-a-lifetime HPV test (34,126 women), and one group received the standard of care which involved giving women information on how to seek screening at local hospitals (31,488). The once-in-a-lifetime screen made an impact on mortality. Screening using a single lifetime HPV test made a significant impact on 8-year mortality when compared to no screening (age-adjusted HR 0.52, 95 %CI 0.33–0.83, $p=0.005$). There was no impact on overall incidence of cervical cancer (age-adjusted HR 1.05, 95 % CI 0.77–1.43, $p=0.76$). However, a randomized study from Finland using cancer registry data showed in 58,076 women that HPV testing with cytology triage was superior to cytology alone in identifying CIN 3 or worse (HR 1.77, 95 %CI 1.16–2.74) [85]. The study from India showed that only HPV testing had an impact on *the incidence of advanced cancer* (*Stage 2 or higher cancer*), by significantly decreased advanced cervical cancer (age-adjusted HR 0.47, 95 %CI 0.32–0.69, $p=0.0001$) [35].

There have been six randomized controlled trials in Europe and one in Canada evaluating HPV test, either alone or in combination with cytology. HPV DNA is more sensitive than cytology in women over 30 years (96 % compared to 53 %) but less specific (91 % compared to 96 %) [86–88]. The very high negative predictive value of HPV testing allows prolongation of the interval between tests (i.e. the test need only be repeated every 5 or more years) [22, 49, 88].

Twenty-five cross-sectional studies where women were concomitantly tested with Pap test and HC 2 HPV test also showed that the sensitivity for CIN 2/3 was 89.7 % (95 %CI 86.4–93.0) [22, 38]. Specificity was 85–90 % [22]. Unfortunately, the HC2 HPV test has consistently

high sensitivity in Europe and North America [89, 90] but not in all low- and middle-resource countries. For example, sensitivity of HC2 HPV test in three cross-sectional studies in India were 50, 70, and 80 %; Peru was 77 %; Zimbabwe was 81 %; Brazil was 83 %; and South Africa was 88 % [15]. A cross-sectional comparison of screening performance of five screening methods (VIA, VILI, VIA with magnification (VIAM), cytology, and HPV) in 11 study sites in low-resource settings showed the following results for the detection of CIN 2 or worse: cytology (sensitivity was 57 %, specificity 93 %), VIA (sensitivity 79 % and specificity 85 %), and HPV (sensitivity 62 % and specificity 94 %) [40, 90].

Through funds from the Bill and Melinda Gates Foundation (Washington State), an HPV test (careHPV™, Qiagen, Hilden, Germany) was specifically developed with the issues unique to low-resource countries in mind. careHPV™ assesses for 14 oncogenic HPV types [16, 18, 31, 33, 35, 38, 44, 50, 51, 55, 57, 58, 65, 67]. It is affordable (<US$ 5 per test). The results are available in 3 h compared to 7 h for HC2. It requires very basic laboratory supplies—for example, no running water is required—making it simpler to perform. This test was evaluated in 2,400 women in Shanxi province, China. Sensitivity was 90 % and specificity was 84 % compared to cytology at 41 and 95 %, respectively [91].

Advantages

An oncogenic HPV test is objective, reproducible, and less demanding in terms of training, and it can be performed by a technician, and quality assurance is easier to demonstrate compared to cytology [11]. Because of the excellent negative predictive value of the test, it provides 5–10 years of reassurance against high-grade disease, thus allowing for an increase screening interval [92].

One of the unique attributes of the oncogenic HPV test is that it provides an opportunity for a woman to complete the test by herself without a pelvic exam. This self-sampling of the vagina, although less sensitive (74 %) and less specific (84 %) than a physician-acquired sampling test from the cervix, is a potential option for hard-to-reach populations (i.e. due to geographic isolation or populations where there is a cultural hesitancy to pelvic examinations). Self-sampling should increase population coverage among women who are uncomfortable with provider-conducted screening (i.e. fear of speculum exam, loss of privacy, resistance from spouse) [11, 93–102]. Self-sampling is cost-effective and reduces time to do screening [103]. It is highly accepted by women [103, 104].

Limitations

An oncogenic HPV test involves doing an endocervical swab and this should not be done in pregnancy [57]. Laboratory equipment and reagents are required even for the careHPV™ test [57]. Laboratory technicians do require some basic training [57]. There is a cost for the equipment to take and perform the test [57, 105]. Currently, the algorithms for using the test are not clearly defined. This is important as the lower specificity of the HPV test means that a "see-and-treat" policy would result in a high number of women with infection, but not dysplasia, being treated. Using a second test after a positive HPV test (prior to referral to colposcopy) could involve cytology or VIA triage, which increases the number of appointments, with the associated compliance problems, and increases cost [57].

In conclusion, screening does identify precancerous lesions and results in a stage shift to earlier stages of disease and therefore benefits women. This meets prerequisite four of the WHO guidelines for screening.

Diagnosis

In high-resource countries, women with an abnormal result on a screening test often go for further diagnostic assessment. This usually involves a colposcopic assessment with cervical biopsies. The colposcope was first introduced by Hans Hinselmann from Germany in 1925. It allows for magnification (5- to 15-fold) and illuminates the

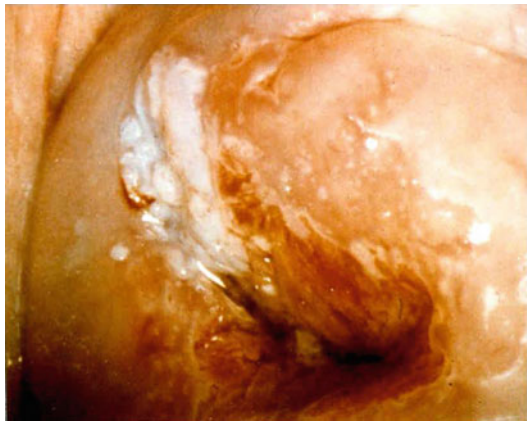

Fig. 6.6 Colpophotograph of a white lesion

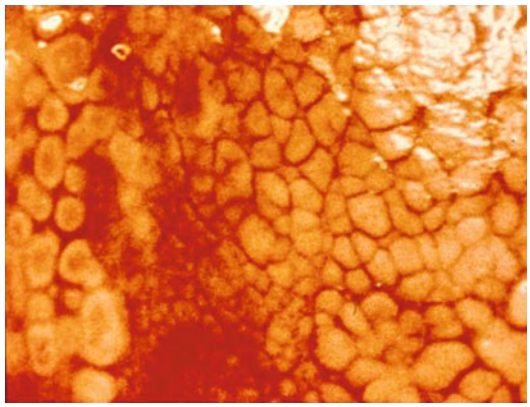

Fig. 6.7 Colpophotograph of mosaicism

cervix. The cervix is examined once the speculum is placed and then again after the application of acetic acid. Features indicative of high-grade dysplasia include a well-demarcated white lesion (Fig. 6.6) near the squamocolumnar junction, especially if there is an abnormal vessel pattern with punctuation or mosaicism (Fig. 6.7). The more severe the dysplasia, the more it is characterized by an opaque colour of the lesion, well-demarcated boarders, and a coarser vascular pattern. Visualizing the lesion with a green filter can often enhance the vascular pattern (Fig. 6.8). The adequacy of the colposcopic examination involves assessing whether the extent of the lesion can be seen, especially into the endocervical canal. Colposcopy is a subjective assessment and thus requires training and ongoing quality assurance. Many jurisdictions (i.e. British Columbia, Canada, and the UK) have an accreditation system for certifying and ongoing assessment of medical staff that perform colposcopy.

Efficacy

Although colposcopically directed biopsies have been the gold standard against which screening tests have been evaluated, when colposcopically directed biopsies are assessed against larger excisional biopsies or hysterectomy, the sensitivity of colposcopy is only 44–77 %, the specificity is 85–90 %, and the positive predictive value is low [106, 107]. More recently, the use of colposcopically directed biopsies was evaluated in China against routinely completing four quadrant biopsies and an endocervical sample. The latter procedure identified more disease ($p=0.03$ to $p<0.001$) [108–112].

Advantages

A colposcopic exam with biopsies means that only women with histologically proven high-grade dysplasia are offered treatment. Women with a cytology assessment that shows high-grade disease but a non-confirming biopsy are usually offered further assessment with a cone biopsy (to be discussed later in this chapter).

Limitations

A colposcopic examination requires at least two visits: one visit for assessment and one for the provision of results and counselling around next steps. Colposcopy is usually available only at specialized centres, and this increases the direct payment (for the assessment and the evaluation of the biopsies) and indirect costs (travel to attend the examination, childcare costs, lost time from work) that a woman assumes. For these reasons, women may not comply with this strategy. Colposcopy requires pattern recognition training for both colposcopists and pathologists.

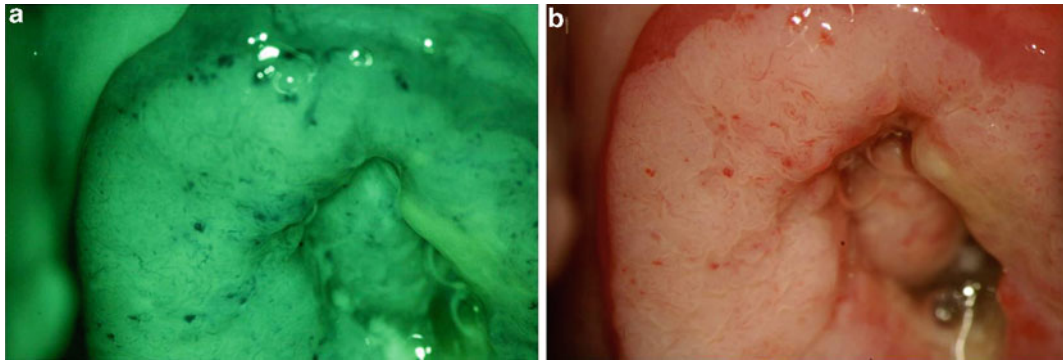

Fig. 6.8 Colpophotograph with the *green* filter (**a**) and without the *green* filter (**b**)

Colposcopy requires expensive colposcopy and pathology equipment that requires maintenance and replacement parts. Colposcopy requires a reliable electrical supply.

Treatment of Precancerous Lesions

Once high-grade disease is identified, there are several treatment options available for removing the lesion (i.e. cryotherapy, loop electrosurgical excisional procedure (LEEP), laser, cold-knife cone biopsy, and hysterectomy) for removing the lesion. Each option has its own attributes and limitations.

Cryotherapy

Cryotherapy has been in use for more than 40 years. Cryotherapy means the cells are exposed to temperatures of −20˚C for more than one minute and so undergo cryonecrosis. Cryotherapy is mainly used to treat small lesions on the ectocervix. Cryotherapy leaves no histological sample for assessment. The procedure involves visualizing the cervix, the cryotherapy probe with its circular metal tip is applied to the ectocervix, and a refrigerant gas (either nitrous oxide or carbon dioxide) is allowed to flow through the instrument cooling the metal tip. With cervical tissue, the recommendation is to freeze for 3 min, allow a thaw for 5 min, and then refreeze for three minutes [113, 114].

Efficacy

With cryotherapy, 90 % of women with dysplasia are disease free at one year after treatment. Efficacy decreases as the severity of the disease increases; for example 83–100 % of CIN 1 cases are disease free at one year compared to 65–95 % of CIN 2 cases and 55–92 % of CIN 3 [115]. Eighty-five percent of women found the procedure acceptable [60].

Side Effects

Immediate side effects from cryotherapy include mild to moderate cramping and/or fainting during the procedure [60, 114]. During the first couple of weeks after the treatment, there is a profuse, watery, vaginal discharge [60, 114]. Cervicitis and/or PID can occur in 1 % of women [53, 57, 114], vaginal wall injury in 0.1–0.8 % [114], and hospitalization in 0.5–1 % [114]. Long-term complications can include cervical stenosis or infertility, but these are rare [114]. Following cryotherapy, it is difficult to assess the squamocolumnar junction in future colposcopic evaluations.

Advantages

Cryotherapy requires no anaesthesia or electricity. The equipment is portable, and the consumables are low in cost. With adequate training and supervision, primary health-care professionals (i.e. nurses) can provide cryotherapy [116].

Limitations

Cryotherapy is not recommended in the following situations: pregnancy; women who have large

lesions involving more than three quadrants; a lesion which extends beyond the cryoprobe by 2 mm; endocervical lesions; a lesion that extends onto the vagina; situations where there are polyps, ulcers, a distorted or atrophic cervix; situations where cervicitis or PID is present; a bleeding diathesis; vaginal wall prolapsed causing inadequate visualization of the cervix; or any lesion suspicious for cancer. If a lesion has not resolved after two cryotherapy sessions, the patient should have a cone biopsy. The equipment must be properly decontaminated before reuse to prevent spread of infection (usually in 10 % bleach solution or 70 % ethyl alcohol). The costs of cryotherapy involve the cryotherapy unit ($400/unit), the carbon dioxide or nitrous oxygen gas, the tank, and the refrigerant. There has been an issue with clogging or blockage of the gas flow within the cryo unit, and various techniques exist to deal with these problems [117].

Loop Electrosurgical Excisional Procedure or Large Loop Excision of Transformation Zone

LEEP involves the use of a fine wire to excise a lesion from the cervix. The loops come in various sizes and shapes. The loops attach to a handheld apparatus that allows for cutting or coagulation settings. The handheld piece is attached to an electrosurgical power generator. A smoke evacuator is used to minimize the plume. When doing a LEEP, a specially coated speculum should be used. The cervix is usually washed with Lugol's iodine to ensure that the physician sees the extent of the lesion. Some physicians would use local anaesthetic to minimize the woman's discomfort during the procedure. Some physicians add epinephrine or vasopressin to minimize bleeding.

Efficacy

LEEP, laser, and cold-knife cone all have the same efficacy (reduction of invasive cancer by 95 % for at least 8 years) [106, 118–120].

Side Effects

Immediate side effects from a LEEP include cramping or pain. This pain is no different in severity or duration compared to cryotherapy [114]. During the first days after a treatment, all patients have some vaginal discharge [114] or bleeding. Significant bleeding can occur in 2 % of women and is usually related to the extent of the procedure and/or a superimposed infection [114]. Vaginal wall injuries occur in 0.4–4.4 % of women. Cervical stenosis is a long-term complication that occurs in 4–6 % of women [114]. Of all of the treatment options, LEEP is the maneuver that most likely allows preservation of the squamocolumnar junction for future assessments. Long-term complications can include premature rupture of membranes (OR 2.69, 95 % CI 1.62–4.46) [120, 121], preterm delivery (OR 1.81, 95 % 1.18–2.76), low-birth weight infants (<2,500 g) (OR 1.60, 95 % CI 1.01–2.52), and cervical stenosis [120, 122].

Advantages

LEEP can be used for small or large lesions of the cervix [123]. LEEP provides a histological specimen for confirmation of the extent and severity of disease. The LEEP specimen may involve one pass or multiple passes. Adequacy of excision is more difficult to assess when there have been multiple passes. Access to the coagulation setting on the handheld device allows an immediate resource to stop bleeding in the event that this is an issue.

Limitations

Compared to cryotherapy, LEEP requires more training and is usually only performed by physicians in specialized centres; these requirements have implications for patient access to care. It requires more equipment (i.e. electrocautery generator, one-time use loops, handheld disposable devise, smoke evacuator with tubing and filters, specialized speculums to minimize transduction of heat) and so the cost is higher. It requires a reliable electrical supply. Although LEEP provides a histological specimen, the cautery artefact at the edges of the sample may make it difficult to assess the adequacy of excision (i.e. margins) in some cases.

Laser

Laser involves using a very high energy light beam to either evaporate the cells of the high-grade lesions or excise them. The laser works by being attached to a colposcope. A smoke evacuator is necessary. Everyone in the room must wear eye protection and masks to filter evaporated particles/plume. Any flammable material (sheets, paper drapes) must either be moved away from the area of work or made wet to decrease the risk of fire.

Efficacy

As listed for LEEP.

Advantages

The advantages are the same as those listed for LEEP. The laser energy beam can be defocused to deal with immediate bleeding. The laser is very useful for dealing with lesions that extend onto the vagina/vulva.

Limitations

Laser requires very expensive equipment (i.e. laser power source, micromanipulator, colposcope, galvanized speculum, smoke evacuator with tubing and filter, eye protection for everyone in the room, CO_2 gas). It requires a reliable power supply. The laser requires access to replace parts. There is a need for both extensive training and experience for the physician operator, the nurse staffing the laser control panel, and a biomedical engineer for dealing with equipment issues. Although laser excision provides a histological specimen, due to cautery artefact, it may be difficult to assess the margins.

Cold-Knife Cone

A cold-knife cone is usually recommended for those lesions where (1) the endocervical extent of the disease is not visible; (2) the work-up suggests adenocarcinoma in situ or possible malignancy; or (3) there is a significant discrepancy between the cytology result with a negative colposcopically directed biopsy.

A cold-knife cone biopsy is performed in the operating room with the woman either under general anaesthesia or under epidural or spinal block. The physician washes the cervix with Lugol's iodine solution to outline the extent of the lesion. The cervix is infiltrated with Xylocaine® with epinephrine/vasopressin. Stay sutures are placed at 3 and 9 o'clock. A knife (i.e. "beaver blade") is used to remove the lesion, and the ultimate defect is in the shape of an inverted cone. Pathology can assess the severity of the lesion and if the lesion has been completely excised or if any of the margins (deep endocervical, lateral, or ectocervical) are involved. A post-cone endocervical curettage (ECC) helps define if disease is still present above the level of the excised specimen. Any bleeding from the defect in the cervix can be cauterized, sutured, covered in thickened ferrous sulphate, or packed with an agent like Surgicel R or Fibrillar TM (Ethicon, Somerville, NJ).

Side Effects

The immediate risks of a cold-knife cone biopsy are related to the anaesthesia risk from spinal, epidural, or general anaesthetic and bleeding. There is a 9 % post-cone bleeding risk, which usually occurs 7–10 days post-procedure and is usually related to a superimposed infection. Long-term sequelae include PTROM, preterm delivery (RR 2.19, 95 % CI 1.93–2.49), low-birth weight (2.53, 1.19–5.36), caesarean section (3.17, 1.07–9.40), and cervical stenosis [22, 124]. The future ability to assess the squamocolumnar junction is compromised by a cone biopsy.

Advantages

Cold-knife cone biopsy provides a histological specimen where margins can be easily assessed.

Limitations

Cold-knife cone biopsy requires access to an operating room, an anaesthetist, and surgeon. The cost is very high.

Hysterectomy

A hysterectomy may be recommended when screening and diagnostic tests show that disease persists after attempted conservative treatment.

Hysterectomy is the definitive way to remove cervical disease, especially in a woman who has completed her childbearing. A hysterectomy involves removing the cervix and uterus with or without the tube and ovaries. A hysterectomy can be completed by the vaginal route, by the abdominal route with a Pfannenstiel or vertical incision, or by laparoscopic approach.

Side Effects

The immediate risks are bleeding, infection, thromboembolic disease, and injury to surrounding structures (i.e. bladder, bowel, or ureters). Hysterectomy has the highest rate of complications. Recovery from surgery takes 4–6 weeks.

Advantages

Hysterectomy provides the best histological specimen for evaluation. It is definitive treatment for the cervical disease.

Limitations

Hysterectomy can only be performed in specialized centres. It is the most costly treatment strategy. It results in loss of fertility.

Assessment of Treatment Options

All five treatment options demonstrate that effective treatment is available for pre-invasive or early invasive disease, meeting the third WHO (i.e. prerequisite of effective treatment being available) [1]. Clearly, the first four treatment options for managing presymptomatic disease allow preservation of fertility with minimal side effects meeting the fourth WHO prerequisite (i.e. treatment of presymptomatic disease results in benefits beyond those obtained through treatment of symptomatic disease) [1].

Approaches to Screening, Diagnosis, and Treatment for Cervical Disease

There are several approaches to screening, diagnosis, and treatment of cervical disease. Three approaches are described here. The "traditional approach" is to screen using cervical cytology, diagnose disease using the colposcope, confirm disease with a biopsy, and then treat the disease using LEEP. An "intermediate approach" is to screen using an oncogenic HPV test, diagnose using either VIA or cervical cytology, and then treat with cryotherapy. The "screen-and-treat" approach is to screen with VIA and treat using cryotherapy at the same visit.

The "traditional approach" that has evolved in high-resource settings includes cervical cytology, colposcopic examination for those with an abnormal screen, biopsy confirmation, and LEEP. It involves multiple visits: a visit for the Pap test, a visit to get the results, a visit to another consultant for the colposcopy exam and biopsies, another visit for the results, a visit for the LEEP procedure, and one or more follow-up visits to ensure that the disease has been removed. To minimize loss to follow-up, various programmes have developed "call recall" systems to remind especially non-compliant women. This traditional approach is costly to the health-care system and to the woman (i.e. travel, childcare, lost time at work). This multiple visit approach has not been successful in low-resource settings for two reasons: low compliance and lack of access to treatment at the point of care. Thus, in low-resource settings, this strategy has resulted in poor outcomes.

The "screen-and-treat" approach, otherwise known as the "same visit treatment" or "see-and-treat" approach, is a single visit for screening and treatment. This approach minimizes the chance that an abnormal finding goes unmanaged. To be successful the screening test must provide results rapidly and accurately. The treatment must also be safe, appropriate to the training of the staff, and effective. For screen and treat to be successful, both components need to happen at the same visit. The infrastructure must be simple without the need for specialized care. The screening test could be a rapidly read cervical cytology, careHPV™ test, or VIA. Although attempted with cervical cytology, the problem is the time to complete the cytological assessment [51, 125]. The treatment can be cryotherapy or LEEP [59]; however, cryotherapy has many advantages in the low-resource setting.

Efficacy

As described previously, a "see-and-treat" approach was used in 80,000 women in India aged 30–59 years. There was a 25 % reduction in cervical cancer incidence and a 35 % reduction in cervical cancer deaths compared to a non-screened group [51, 73, 126].

A safety study of the "see-and-treat" approach in Thailand using VIA as the screening test and cryotherapy as the treatment showed that, among women who were VIA positive and were treated, 94.3 % were disease free at one year (i.e. VIA negative). These results have been replicated in other settings like Ghana [42]. However, such excellent results are not universal. For example, in Osmanabad, India, the success rate was only 50 % [21], and in Dindigul, in Southern India, there was no benefit [127].

A different "see-and-treat" approach was used in South Africa. Here 6,555 nonpregnant women aged 35–65 years received either HPV test (HC2), VIA, or no screening test. They were randomized to immediate or delayed treatment with cryotherapy. Treatment was given if the woman was HPV positive or if they were VIA positive. The rates of dysplasia were lower in both groups at 6 and 12 months. Safety and feasibility were confirmed [76]. In the subgroup of women followed to 36 months, those with a positive HPV test (HC2) and treatment had the greatest benefit [76].

A cost-effectiveness study assessed several screening strategies involving India, Kenya, Peru, South Africa, and Thailand. Screening women once in their lifetime at age 35 years with a one or two visit screening strategy involving VIA and cryotherapy at the same visit was the most cost-effective strategy [94, 128]. This strategy reduced lifetime risk of cancer by 25–36 % and cost less than $500 (international dollars) per year of life saved [93]. This strategy had a cost-effectiveness ratio less than the country's per capita GDP. According to the Commission on Macroeconomics and Health, this is considered very cost-effective [129]. To put this in the context of other well-known public health interventions, this strategy was as cost-effective as Hepatitis B vaccination in India, second treatment for TB in Peru, and malaria prevention with nets in Kenya.

Limitations

The limitations of this approach are the limitations listed for each of the components. In addition, some national decision makers will not accept the "see-and-treat" approach if cervical cytology and colposcopy are currently available within the country [130].

Cervical Cancer Prevention Programme

There are several of ways to implement a cervical screening programme. *Opportunistic cervical screening* means that the woman initiates the interaction to be screened, or a woman who sees a physician for another reason is offered the opportunity to be screened at that visit. In contrast, an *organized screening programme* involves a clear system of education, age-appropriate invitation to screening, access to screen and treatment, quality assurance, and programme evaluation.

According to the International Agency for Research on Cancer (IARC), there are eight essential features an organized screening programme:

1. A clearly defined target population
2. Eligible screening participants are identifiable (e.g. a list with names and addresses)
3. Processes are in place to maximize reach and encourage participation (e.g. personalized invitation letters)
4. Suitable field and lab facilities exist for collecting and analysing specimens
5. Systematic quality-control procedures are in place to assess how tests are performed and interpreted
6. Appropriate facilities exist for diagnosis, treatment, and follow-up of patients with confirmed abnormalities
7. An organized referral system is in place to manage any identified abnormalities and provide information about normal results
8. An organized performance measurement/monitoring system is in place to enable collection of relevant and timely epidemiological data [131]

Studies from the Nordic countries and the Netherlands have shown that when such programmes are in place there is a significant drop in cervical cancer incidence and mortality [132–135]. Next, we present examples from low-resource setting that highlight problems and successes in cervical cancer prevention.

Problems

Organization

It is important that an organized programme encompasses training of health-care providers involved in screening (family doctors, nurses, colposcopists, cytologist, cytotechnician). The literature focuses especially on training in cytology [136]. An example of why this is so important is that, in some countries such as Argentina, up until recently gynaecologists read the Pap test [137].

The programme needs to ensure equipment and supply chain, and high-quality lab services. Honduras is an example where 80 % of the population is screened, but there is an extremely high false-negative rate of Pap smears. In part, this is due to poor Pap smear quality as a result of lack of supplies such as fixatives, spatulas, and cytobrushes [90, 138].

An organized programme also needs to establish a referral pathway for assessment and treatment of women with abnormal results. Capacity needs to be developed to ensure treatment for pre-invasive (i.e. colposcopy, LEEP) and invasive disease (radical surgery and radiation therapy). In Central and South America, coverage is high but a woman's access to treatment is poor; thus, rates of cervical cancer remain high [49, 139, 140].

The population needs to be educated concerning cervical cancer and prevention opportunities. Studies show that participation in screening programmes is proportional to awareness and knowledge [141–143]. There are numerous studies from low-resource settings showing that women are unfamiliar with cervical cancer and HPV infection as the cause of cancer [142, 144–147].

Screening tests and the way they are implemented also need to be culturally relevant to ensure patient participation [148–150].

Extent of Use

It is clear that screening benefits older women (30 and above) and that overscreening harms women in their teens. Thus, the emphasis of screening should address participation rates in a target population. A review of cancer screening in 57 countries using data from 2002 found that only 18 % of 25- to 64-year-old women in developing countries had a pelvic exam and Pap test in the last 3 years [151]. Screening occurs at even lower rates of <1 % in Bangladesh, Ethiopia, and Myanmar; <10 % in Ethiopia, Bangladesh, and Malawi.

Data Registration

A centralized database for detailed information on the date and result of a screen and follow-up tests for abnormal results allows tracking for compliance with follow-up. When a review was conducted in Peru, it was identified that 56 % of women with high-grade Pap tests were lost to follow-up and 3 % died of cervical cancer [152].

Successes

Organization

Prior to undertaking a cervical screening programme, each country needs to define whether cervical cancer is a problem in their jurisdiction by assessing incidence and mortality from the disease. Next, they need to determine whether there is the political will to designate resources toward developing an effective plan, implementation, and monitoring [153]. A cervical cancer prevention programme involves more than just the screening test. A cervical screening programme encompasses all of the services, from provision of the test to diagnosis and treatment [81]. An organized programme involves national policies that define, among other things, the ages during which screening is to occur, the screening interval, and the method of screening. These guidelines are to be implemented on a population basis with effective recruitment strategies to achieve high coverage. This could involve access to a population-based cancer registry and a computerized call and recall system.

In Vietnam several agencies came together to launch a population-based Pap smear screening system in Ho Chi Minh City (150 women per day). They developed community outreach methods, quality control, and quality assurance programmes with a centralized cytology lab and access to curative treatment [129].

In Chile, prior to 1987, only 10 % of women were screened annually. In 1987, the Chilean Ministry of Health and WHO collaborated to train health professionals, establish a system of patient follow-up, improve cytology accuracy, and improve patient education. In 1990, screening coverage increased to 66 % for women aged 25–64 years. Mortality from cervical cancer fell by 39 % by 2001. This is a success story showing that reallocating resources and infrastructure led to a fall in cervical cancer rates [49, 90, 154].

Another aspect of organization involves incorporating screening into the existing health-care system. The system of HIV care in Africa has taught us that cervical cancer screening is feasible and acceptable within the setting of an HIV care and treatment clinic. An example of this is in Nyanza province on the shores of Lake Victoria in Kenya. Collaboration was built between the Family AIDS Care and Education Services Program (FACES) and the University of California, University of San Francisco, and Kenya Medical Research Institute, Nairobi, Kenya, to provide cervical cancer screening for HIV-positive women [155, 156].

A similar successful collaboration has been described in Zambia between the University Teaching Hospital in Lusaka and the University of Alabama at Birmingham, and the Center for Infectious Disease Research in Zambia and the Zambian Ministry of Health [105, 123, 157, 158].

A programme should encompass training of health-care providers like cytologists. The Argentine Society of Cytology [137] mandated certification of professionals by scientific organizations according to national and international standards to ensure professional standards. Certification of professionals was felt to be a prerequisite to lab certification.

A programme needs to identify mechanisms to ensure attendance for screening or follow-up. Transportation incentives increase adherence to follow-up [159, 160].

HIV care has taught health planners in Africa that if you want people to adhere to treatment you have to work with community health workers. They live in the villages with their neighbours. They are a source of education and reinforcement [161]. Personalized follow-up letters increase adherence to follow-up [159, 160]. Counselling and telephone calls increase adherence to treatment appointments and follow-up [159, 162].

Method of Quality Assurance

The Argentine Society of Cytology [137] currently mandates that first screen must be carried out by cytotechnicians under supervision of a pathologist who re-reads 100 % of abnormal smears and a percent of normals. Labs should read 10,000 smears annually [137].

Peru uses lab certification by the Peruvian Scientific Society of Cytology after they verify certain conditions, including that a certain number of Pap smears are read annually [137].

The United States implemented the Clinical Laboratory Improvement Amendment, which involves an evaluation of eight steps within the lab system as a means of evaluating and maintaining cytology quality [163].

Monitoring Systems are built for the purpose of evaluation through performance indicators and quality assurance (i.e. cytology assessment). Performance indicators can include documenting the coverage, interval from the test to reporting the results, proportion of unsatisfactory Pap tests, treatment compliance, timeliness of follow-up of abnormal results, sensitivity, specificity, and interval cancers. Use of these indicators has pointed to areas where improvement is needed.

When follow-up was assessed in three rural areas of Honduras that offered cytology screening, it was identified that when VIA was followed by immediate colposcopy, compliance was 83 %. When Pap test was followed up by an appointment to give results and then colposcopy, compliance was only 38 % [164].

The programme needs to have a designated management team responsible for planning, implementation, and evaluation [163, 165].

Conclusion

In this chapter, we identified four prerequisites necessary for defining whether a mass screening programme should be developed. We have shown that cervical cancer is one of the leading cancers in women, especially in low-resource settings, and it is a major cause of mortality. Cervical cancer is preceded by a long asymptomatic phase of disease. Several screening strategies can be used to identify precancer, and, if treated, the screening programme can decrease the occurrence of cancer or shift the presentation of cancer to earlier stage, which, when treated, results in low mortality. Organized screening programmes provide the best population prevention of disease with the lowest rate of harm. Various models of screening, diagnosis, and treatment exist and have been assessed within the low-, medium-, and high-resource settings. Given that the four WHO prerequisites have been met, each jurisdiction must decide on the model that meets the needs of that population. For low-resource settings with limited health infrastructure, a national "see-and-treat" programme with a once or twice in a lifetime assessment with VIA or HPV testing and cryotherapy for those with positive tests will lead to a quick reduction in cervical cancer rates at low cost with low technology. The emphasis should be on screening women aged 30–49. It is important that a screening programme address the populations' knowledge and awareness of cervical cancer and HPV, facilitate compliance with screening, followup on abnormal test result, and ensure quality control.

References

1. Wilson JMG, Jungner G. Principles and practice of screening for disease, Public health papers, vol. 34. Geneva: World Health Organization; 1968.
2. Cole P, Morrison AS. Basic issues in cancer screening. In: Miller AB, editor. Screening in Cancer. Geneva: UICC; 1978.
3. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global Cancer Statistics. CA Cancer J Clin. 2011;61:69–90.
4. GLOBOCAN: country fact stat. 2008. http://globocan.iarc.fr/factsheets/populations/factsheet.asp?uno=900. Accessed 29 Dec 2011.
5. Maree JE, Wright SCD. Cervical cancer: does our message promote screening? A pilot study in a South African context. Eur J Oncol Nurs. 2011;15(2):118–23.
6. Shanta V, Krishnamurthi S, Gajalakshmi CK, Swaminathan R, Ravichandran K. Epidemiology of cancer of the cervix: global and national perspective. J Indian Med Assoc. 2000;98:49–52.
7. Ferlay J. Cancer incidence in five continents. Processing of data. IARC Sci Publ. 1992;120:39–44.
8. Ferlay J, Bray F, Pisani P, Parkin DM. GLOBOCAN 2002: cancer incidence, mortality and prevalence worldwide. Lyon: IARC; 2004.
9. Reeler A, Qiao Y, Dare L, Li J, Zhang AL, Saba J. Women's cancers in developing countries: from research to an integrated health systems approach. Asian Pac J Cancer Prev. 2009;10:519–26.
10. Kitchener HC, Castle PE, Cox JT. Achievements and limitations of cervical cytology screening. Vaccine. 2006;24:S63–70.
11. Arbyn M, Raifu AO, Bray F, Weiderpass E, Anttila A. Treads of cervical cancer mortality in the member states of the European Union. Eur J Cancer. 2009;45(15):2640–8.
12. Anorlu RI, Orakwue CO, Oyeneyin L, Abudu OO. Late presentation of patients with cervical cancer to a tertiary hospital in Lagos: what is responsible? Eur J Gynaecol Oncol. 2004;25:729–32.
13. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley F, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. Lancet Oncol. 2008;9:425–34.
14. McIndoe WA, McLean MR, Jones RW, Mullins PR. The invasive potential of carcinoma in situ of the cervix. Obstet Gynecol. 1984;64:451–8.
15. Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrand MH, et al. Overview of Human Papillomavirus-based and other novel options for cervical cancer screening in developed and developing countries. Vaccine. 2008;26S:K29–41.
16. Wikipedia the Free Encyclopaedia. Developing countries<>, last modified 30 Mar 2012. Available from: http://en.wikipedia.org/wiki/Developing_country.
17. The World Bank. How we classify countries. http://data.worldbank.org/about/country-classifications. 2011.
18. Andrae B, Kemetli L, Sparén P, Silfverdal L, Strander B, Ryd W, et al. Screening-preventable cervical cancer risks: evidence from a nationwide audit in Sweden. J Natl Cancer Inst. 2008;100(9):622–9.
19. DiCenso A, Guyatt G. Recommendations about screening. In: DiCenso A, Guyatt G, Ciliska D, editors. Evidence-based nursing. A guide to clinical practice. St. Louis, MO: Mosby; 2005. p. 526–41.

20. Solomon D, Davey D, Kuman R, Moriarty A, O'Connor D, Prey M. The 2001 Bethesda System: terminology for reporting results of cervical cytology. JAMA. 2002;287:2114–9.
21. Sankaranarayanan R, Nene BM, Shastri SS, Jayant K, Muwonge R, Budukh A. HPV screening for cervical cancer in rural India. N Engl J Med. 2009;360(14):1385–94.
22. IARC Working Group on evaluation of cervical cancer screening programmes. Screening for squamous cervical cancer: duration of low risk after negative results of cervical cytology and its implication for screening policies. Br Med J (Clin Res Ed). 1986;293(6548):659–64.
23. Sasieni PD, Cuzick J, Lynch-Farmery E. Estimating the efficacy of screening by auditing smear histories of women with and without cervical cancer. The National Co-ordinating Network for cervical screening Working Group. Br J Cancer. 1996;73(8): 1001–5.
24. Nieminen P, Kallio M, Anttila A, Akama M. Organised versus spontaneous Pap smear screening for cervical cancer: a case–control study. Int J Cancer. 1999;83(1):55–8.
25. Decker K, Demers A, Chateau D, Musto G, Nugent Z, Lotocki R, et al. Papanicolaou test utilization and frequency of screening opportunities among women diagnosed with cervical cancer. Open Med. 2009; 3(3):e140–7.
26. Hernandez-Avila M. Lacano[Ponce ED, de Ruiz PA, Romieu I. Evaluation of the cervical cancer screening programme in Mexico: a population-based case–control study. Int J Epidemiol. 1998;27:370–6.
27. Hoffman M, Cooper D, Carara H, Rosenberg I. Limited pap screening associated with reduced risk of Cervical Cancer in South Africa. Int J Epidemiol. 2003;32:573–7.
28. Jiménez PM, Thomas DB. Has the use of pap smears reduced the risk of invasive cervical cancer in Guadalajara, Mexico? Int J Cancer. 1999;82(6): 804–9.
29. Makino H, Sato S, Yajima A, Komatsu S, Fukao A. Evaluation of the effectiveness of cervical cancer screening: a case–control study in Miyagi, Japan. Tohoku J Exp Med. 1995;175(3):171–8.
30. Talbott EO, Norman SA, Kuller LH, Ishii EK, Baffone KM, Dunn MS, et al. Refining preventive strategies for invasive cervical cancer: a population-based case–control study. J Womens Health (Larchmt). 1995;4(4):387–95.
31. Aristizabal N, Cuello C, Correa P, Collazos T, Haenszel W. The impact of vaginal cytology on cervical cancer risks in Cali, Colombia. Int J Cancer. 1984;34(1):5–9.
32. Berrino F, Gatta G, d'Alto M, Crosignani P, Riboli E. Efficacy of screening in preventing invasive cervical cancer: a case–control study in Milan, Italy. IARC Sci Publ 1986;(76):111–23.
33. Clarke EA, Anderson TW. Does screening by "Pap" smears help prevent cervical cancer? A case–control study. Lancet. 1979;2(8132):1–4.
34. Herrero R, Brinton LA, Reeves WC, Brenes MM, de Britton RC, Gaitan E, et al. Screening for cervical cancer in Latin America: a case–control study. Int J Epidemiol. 1992;21(6):1050–6.
35. Parkin DM. Screening for cervix cancer in developing countries. In: Miller AB, Chamberlain J, Day NE, Hakama M, Proroc PC, editors. Cancer screening. Cambridge: Cambridge University Press; 1991. p. 184–98.
36. Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age period cohort model. BMJ. 1999;318(7193):1244–5.
37. Van der Aa MA, Pukkala E, Coebergh JW, Anttila A, Siesling S. Mass screening programmes and trends in cervical cancer in Finland and the Netherlands. Int J Cancer. 2008;122(8):1854–8.
38. Bulkmans NW, Rozendall L, Voorhoorhorst FJ, Snijders PJ, Meijer CJ. Long-term protective effect of high-risk human papillomavirus testing in population-based cervical screening. Br J Cancer. 2005;92(9):1800–2.
39. Fahey MT, Irwig L, Macaskill P. Meta-analysis of Pap test accuracy. Am J Epidemiol. 1995;141(7): 680–9.
40. Arbyn M, Bergeron C, Klinkhamer P. Liquid compared with conventional cervical cytology. Obstet Gynecol. 2008;111(1):167–77.
41. Spence AR, Goggin P, Franco EL. Process of care failures in invasive cervical cancers: a systemic review and metaanalysis. Prev Med. 2007;45: 93–106.
42. Blumenthal PD, Gaffikin L, Deganus S, Lewis R, Emerson M. Cervical cancer prevention: safety, acceptability, and feasibility of a single-visit approach in Accra, Ghana. Am J Obstet Gynecol. 2007;196(4):e1–407.e9.
43. Denny L, Quinn M, Sankaranarayanan R. Screening for cervical cancer in developing countries. Vaccine. 2006;24 Suppl 3:S71–7.
44. Huong DB, Phuong NK, Bales S. Rural health care in Vietnam and China: conflict between market reforms and social need. Int J Health Serv. 2007;37(3):555–72.
45. McIntyre D, Thiede M, Dahlgren G. What are the economic consequences for households of illness and of paying for health care in low- and middle-income country contexts? Soc Sci Med. 2006;62(4):858–65.
46. Houts PS, Lipton A, Harvey HA. Nonmedical costs to patients and their families associated with outpatient chemotherapy. Cancer. 1984;53(11):2388–92.
47. Stommel M, Given CW, Given BA. The cost of cancer home care to families. Cancer. 1993;71(5): 1867–74.
48. Ohaeri JU, Campbell OB, Ilesanmi AO. The psychosocial burden of caring for some Nigerian women with breast cancer and cervical cancer. Soc Sci Med. 1999;49(11):1541–9.
49. Sepulveda C, Prado R. Effective cervical cytology screening programmes in middle-income countries:

the Chilean experience. Cancer Detect Prev. 2005; 29(5):405–11.
50. Micheli A, Sanz N, Mwangi-Powell F, Coleman MP, Neal C, Ullrich A, et al. International collaborations in cancer control and the Third International Cancer Control Congress. Tumori. 2009;95:579–96.
51. Megevand E, Van Wyk W, Knight B, Bloch B. Can cervical cancer be prevented by a see, screen, and treat program? A pilot study. Am J Obstet Gynecol. 1996;174(3):923–8.
52. University of Zimbabwe/JHPIEGO Cervical Cancer Project. Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. Lancet. 1999;353(9156):869–73.
53. Sankaranarayanan R, Esmy PO, Rajkumar R, Muwonge R, Swaminathan R, Shanthakumari S. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster randomised trial. Lancet. 2007;370(9585):398–406.
54. Sangwa-Lugoma G, Mahmud S, Nasr SH, Liaras J, Kayembe PK, Tozin RR, et al. Visual inspection as a cervical cancer screening method in a primary health care setting in Africa. Int J Cancer. 2006;119(6): 1389–95.
55. Arbyn M, Sankaranarayanan R, Muwonge R. Pooled analysis of the accuracy of 5 cervical cancer screening tests assessed in eleven studies in Africa and India. Int J Cancer. 2008;123:153–60.
56. Quinley KE, Gormley RH, Ratcliffe SJ, Shih T, Szep Z, Steiner A, et al. Use of mobile telemedicine for cervical cancer screening. J Telemed Telecare. 2011;17(4):203–9.
57. Ngan HYS, Garland SM, Bhatla N, Pagliusi SR, Chan KKL, Cheung ANY, et al. Asia Oceania Guidelines for the implementation of programs for cervical cancer prevention and control. J Cancer Epidemiol. 2011;2011:794861. doi:10.1155/2011/794861.
58. Safaeian M, Solomon D. Cervical cancer prevention—cervical screening: science in evolution. Obstet Gynecol Clin North Am. 2007;34(4):739–60, ix.
59. Gaffikin L, Blumenthal PD, Emerson M, Limpaphayom K. Safety, acceptability and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project. Lancet. 2003;361(9360):814–20.
60. FIGO Global Guidance for Cervical Cancer Prevention and Control. http://www.figo.org/files/figo-corp/English_version.pdf. 2009.
61. Mergevand E, Denny L, Dehaeck K, Soeters R, Bloch B. Acetic acid visualization of the cervix: an alternative to cytologic screening. Obstet Gynecol. 1996;88(3):383–6.
62. Sankaranarayanan R, Black RJ, Swaminathan R, Parkin DM. An overview of cancer survival in developing countires. IARC Sci Publ. 1998;(145):135–73.
63. Denny L. The prevention of cervical cancer in developing countries. Br J Obstet Gynaecol. 2005;112: 1204–12.
64. Sankanranarayanan R, Basu P, Wesley RS, Mahe C, Keita N, Mbalawa CC. Accuracy of visual screening for cervical neoplasia: results from an IARC multicentre study in India and Africa. Int J Cancer. 2004;110(6):907–13.
65. WHO. New options for cervical cancer screening and treatment in low-resource settings. Geneva: World Health Organization; 2010.
66. Jeronim J, Sciffman M. Colposcopy at a crossroads. Am J Obstet Gynecol. 2006;195:349–53.
67. WHO Department of Reproductive Health and Research and Department of Chronic Diseases and Health Promotion. Comprehensive cervical cancer control. Geneva: WHO; 2006.
68. Almonte M, Ferreccio C, Winkler JL. Cervical screening by visual inspection, HPV testing, liquid based and conventional cytology in Amazonian Peru. Int J Cancer. 2007;121:796–802.
69. Sellors J, Jeronimo J, Sanakaranarayanan R. Assessment of the cervix after acetic acid wash: interrater agreement using photographs. Obstet Gynecol. 2002;99:635–40.
70. Sherigar B, Dalal A, Durdi G. Cervical cancer screening by visual inspection with acetic acid-interobserver variability between nurse and physician. Asian Pac J Cancer Prev. 2010;11:619–22.
71. Wright TC, Denny L, Kuhn L, Pollack A, Lorincz A. HPV DNA testing of self-collected vaginal samples compared with cytologic screening to detect cervical cancer. JAMA. 2000;283:81–6.
72. Park IU, Diaz ML, Bowey C, Magaril R, Ferris DG, on behalf of the INCCA Foundation. Cervical cancer prevention in the developing world. JLGTD. 2007;11(4):273.
73. Sankaranarayanan R, Gaffikin L, Jacob M, Sellors J, Robles S. A critical assessment of screening methods for cervical neoplasia. Int J Gynecol Obstet. 2005;89(Supp 2):S2–14.
74. Mittra I, Mishra GA, Singh S, Aranke S, Notani P, Badwe R, et al. A cluster randomized controlled trial of breast and cervix cancer screening in Mumbai India: methodology and interim results after three rounds of screening. Int J Cancer. 2010;126(4): 976–84.
75. Velázquez-Hernández N, Sánchez-Anguiano LF, Lares-Bayona EF, Cisneros-Pérez V, Milla-Villeda RH, Arreola-Herrera Fde A, et al. Comparison of the diagnostic utility for visual inspection with acetic acid and cervical cytology. Ginecol Obstet Mex. 2010;78(5):261–7.
76. Denny L, Kuhn L, Hu CC, Tsa WY, Wright TC. Human papillomavirus-based cervical cancer prevention: long-term results of a randomized screening trial. J Natl Cancer Inst. 2010;102(20):1557–67.
77. Dinshaw K, Mishra G, Shastri S, Badwe R, Kerkar R, Ramani S, et al. Determinants of compliance in a cluster randomised controlled trial on screening of breast and cervix cancer in Mumbai, India. 1. Compliance to screening. Oncology. 2007;73(3–4): 143–53.
78. Doh AS, Nkele NN, Achu P, Essimbi F, Essame O, Nkegoum B. Visual inspection with acetic acid and

cytology as screening methods for cervical lesions in Cameroon. Int J Gynaecol Obstet. 2005;89(2): 167–73.
79. Jamshida R, Blumenthal P. Digital assessment of the reproductive tract (DART). J Acquir Immune Defic Syndr. 2004;37:S171–3.
80. Cremer M, Jamshidi RM, Muderspach L, Tsao-Wei D, Felix JC, Blumenthal PD. Digital camera assessment for detection of cervical intraepithelial neoplasia in rural El Salvador. Int J Gynecol Obstet. 2005;91(1):42–6.
81. Sarian LO, Derchain SF, Naud P. Roteli-MartensC, Longatto-Filho A, Tatti S. 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. 2005;12(3):142–9.
82. Sellors JW, Winkler JL, Kreysar DF. Illumination optics and clinical performance of a hand-held magnified visual inspection device (Avi Scope) a comparison with colposcopy. J Acquir Immune Defic Syndr. 2004;37 Suppl 3:S160–6.
83. Robyler D, Park SY, Adewole I, Follen M. Objective screening for cervical cancer in developing nations: lessons from Nigeria. Gynecol Oncol. 2007;107(1 Suppl 1):S94–7.
84. Dondog B, Clifford GM, Vaccarella S, Waterboer T, Unurjargal D, Avirmed D. Human papillomavirus infection in Ulaanbaatar, Mongolia: a population-based study. Cancer Epidemiol Biomarkers Prev. 2008;17(7):1731–8.
85. Anttila A, Kotaniemi-Talonen L, Leinonen M, Hakama M, Laurila P, Tarkkanen J, et al. Rate of cervical cancer, severe intraepithelial neoplasia, and adenocarcinoma in situ in primary HPV DNA screening with cytology triage: randomized study within organized screening programme. BMJ. 2010;340:c1804.
86. Cuzick J, Clavel C, Petry KU. Overview of the European and North American Studies on HPV testing in primary cervical cancer screening. Int J Cancer. 2006;119(5):1095–101.
87. Grce M. Primary and secondary prevention of cervical cancer. Expert Rev Mol Diagn. 2009;9(8): 851–64.
88. Bulkmans NW, Berkhof J, Rozendaal L. Human papillomavirus DNA testing for the detection of cervical intraepithelial neoplasia grade 3 and cancer. 5 year follow-up of a randomised controlled implementation trial. Lancet. 2007;370(9601):1764–72.
89. Longatto-Filho A, Erzen M, Branca M, et al. Human Papillomavirus testing as an optional screening tool in low-resource settings of Latin America: experience from the Latin America Screening Study. Int J Gynecol Cancer. 2006;16:955–62.
90. Ditzian LR, David-West G, Maza M, Hartmann B, Shirazian T, Cremer M. Cervical cancer screening in low- and middle-income countries. Mt Sinai J Med. 2011;78:319–26.
91. Qiao YL, Sellors JW, Eder PS. A new HPV-DNA test for cervical-cancer screening in developing regions: a cross sectional study of clinical accuracy in rural China. Lancet Oncol. 2008;9(10):929–36.
92. Sherman ME, Lorincz AT. Scott Dr. Baseline cytology, human papillomavirus testing and risk for cervical neoplasia: a 10-year cohort analysis. J Natl Cancer Inst. 2003;95:46–52.
93. Olgilvie GS, Patrick DM, Schulzer M, Sellors JW, Petric M, Chambers K, et al. Diagnostic accuracy of self collected vaginal specimens for human papillomavirus compared to clinician collected human papillomavirus specimens: a meta-analysis. Sex Transm Infect. 2005;81(3):207–12.
94. Goldie SJ, Gaffikin L, Goldhaber-Fiebert JD, Gordillo-Tobar A, Levin C, Mahe C. Cost effectiveness of cervical-cancer screening in five developing countries. N Engl J Med. 2005;353(2):2158–68.
95. Arbyn M, Sasieni P, Meijer CJ, Clavel C, Koliopoulos G, Dillner J. Chapter 9: Clinical applications of HPV testing: a summary of meta-analyses. Vaccine. 2006;24 Suppl 3:S78–89.
96. Salmeron J, Lazcano-Ponce E, Lorincz A, Hernandez M, Hernandez P, Leyya A, et al. Comparison of HPV-based assays with papanicolaou smears for cervical cancer screening in Morelos State, Mexico. Cancer Causes Control. 2003;14:505–12.
97. Sellors JW, Lorincz AT, Mahony JB, Mielzunska I, Lutwun A, Roth P. Comparison of self-collected vaginal, vulvar and urine samples with physician-collected cervical samples for human papilloma virus testing to detect high grade squamous intraepithelial lesions. Can Med Assoc J. 2000;163:513–8.
98. Nobbenhui MA, Helmerhorst TJ, van den Bruie AJ, Rozendaal L, Jaspaars LH, Voorhorst FJ. Primary screening for high risk HPV by home obtained cervicovaginal lavage is an alternative screening tool for unscreened women. J Clin Pathol. 2002;55:435–9.
99. Longatto-Filho A, Toletli-Martins C, Hammes L, Etlinger D, Pereira SM, Erzen M. Self sampling for human papillomavirus (HPV) testing as cervical cancer screening option. Experience from the LAMS study. Eur J Gynaecol Oncol. 2008;29(4):327–32.
100. Petignat P, Faltin DL, Bruchim I. Are self-collected samples comparable to physician-collected cervical specimens for human papillomavirus DNA testing? A systematic review and meta-analysis. Gynecol Oncol. 2007;105:530–5.
101. Pengsaa P, Sriamporn S, Kripetcharat O. A comparison of cytology with Pap smears taken by a gynaecologist with a self-sampling device. Asian Pac J Cancer Prev. 2003;4:99–102.
102. Barbee L, Kobetz E, Menard J. Assessing the acceptability of self-sampling for HPV among Haitian immigrant women: CBPR in action. Cancer Causes Control. 2010;21:421–31.
103. Balasubramanian A, Kulasingam SL, Baer A. Accuracy and cost-effectiveness of cervical cancer screening by high-risk human papillomavirus DNA testing of self-collected vaginal samples. J Low Genit Tract Dis. 2010;14:185–95.

104. Howe SI, Vargas DE, Granada D, Smith JK. Cervical cancer prevention in remote rural Nicaragua: a program evaluation. Gynecol Oncol. 2005;99 Suppl 3:232–5.
105. Mwanahamuntu MH, Sahasrabuddhe VV, Kapambwe S, Praendler KS, Chibwesha C, Mkumba G, et al. Advancing cervical cancer prevention initiatives in resource-constrained settings: insights from the cervical cancer prevention program in Zambia. PLoS Med. 2011;8(5):e1001032.
106. Mitchell MF, Tortolero-Luna G, Cook E, Whittaker L, Rhodes-Morris H, Silva E. A randomized clinical trial of cryotherapy, loop electrosurgical excision for treatment of squamous intraepithelial lesions of the cervix. Obstet Gynaecol. 1998;92:737–44.
107. Howe DT, Vincenti AC. Is large loop excision of the transformation zone (LLETZ) more accurate than colposcopially directed punch biopsy in the diagnosis of cervical intraepithelial neoplasia? Br J Obstet Gynaecol. 1991;98(6):588–91.
108. Pretorius RG, Belinson JL, Burchette RJ, Hu S, Zhang X, Qiao YL. Regardless of skill, performing more biopsies increases the sensitivity of colposcopy. J Low Genit Tract Dis. 2011;15(3):180–8.
109. Pretorius RG, Bao YP, Belinson JL, Burchette RJ, Smith JS, Qiao YL. Inappropriate gold standard bias in cervical screening studies. Int J Cancer. 2007;121(10):2218–24.
110. Cagle AJ, Hu SY, Sellors JW, Bao YP, Lim JM, Li SM, et al. Use of an expanded gold standard to estimate the accuracy of colposcopy and visual inspection with acetic acid. Int J Cancer. 2010;126(1):156–61.
111. Pretorius RG, Kim RJ, Belinson JL, Elson P, Qiao YL. Inflation of sensitivity of cervical cancer screening tests secondary to correlated error in colposcopy. J Low Genit Tract Dis. 2006;10(1):5–9.
112. Pretorius RG, Zhang WH, Belinson JL, Huang MN, Wu LY, Zhang X. Colposcopically directed biopsy, random cervical biopsy, and endocervical curettage in the diagnosis of cervical intraepithelial neoplasia II or worse. Am J Obstet Gynecol. 2004;191(2):430–4.
113. Sellors JW, Sankaranarayanan R. Colposcopy and treatment of cervical intraepithelial neoplasia: a beginner's manual. Lyon, France: IARC;2003/2004.
114. Chamot E, Kristense S, Stringer JSA, Mwanahamuntu MH. Are treatments for cervical precancerous lesions in less-developed countries safe enough to promote scaling up of cervical screening programs? A systematic review. BMC Womens Health. 2010;10:1–11.
115. Castro W, Gage J, Gaffikin L, Ferreccio C, Sellors J, Sherris J. Effectiveness, safety and acceptability of cryotherapy: a systematic literature review. Cervical cancer prevention: issues in depth, No. 1. Alliance for Cervical Cancer Prevention; 2003.
116. Blumenthal PD, Lauterbach M, Sellors JW, Sankaranarayanan R. Training for cervical cancer prevention programs in low-resource settings: focus on visual inspection with acetic acid and cryotherapy. Int J Gynecol Obstet. 2005;89(Supp 2):S30–7.
117. Seamans Y, Loesel C, Jeronimo J, Sellors J, Castle PE. Effect of cough technique and cryogen gas on temperatures achieved during simulated cryotherapy. BMC Womens Health. 2007;7:16.
118. Soutter WP, De Barros Lopes A, Fletcher A, et al. Invasive cervical cancer after conservative treatment for cervical intraepithelial neoplasia. Lancet. 1997;349:978–80.
119. Alvarez RD, Helm CW, Edwards RP, et al. Prospective randomized trial of LLETZ versus laser ablation in patients with cervical intraepithelial neoplasia. Gynecol Oncol. 1994;52:175–9.
120. Kyrgiou M, Koliopoulos G, Martin-Hirsch P, Arbyn M, Prendiville W, Paraskevaidis E. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. Lancet. 2006;367(9509):489–98.
121. Arbyn M, Kyrfiou M, Raifu AO, Koliopoulos G, Martin-Hirsch P, Prendiville W. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia; metaanalysis. BMJ. 2008;337:a1284.
122. Crane JMG. Pregnancy outcome after loop electrosurgical excision procedure: a systematic review. Obstet Gynecol. 2003;102:1058–62.
123. Pfaendler KW, Mwanahamuntu MH, Sahasrabuddhe VV, Mudenda V, Stringer JS, Parham GP. Management of cryotherapy-ineligible women in a "screen-and-treat" cervical cancer prevention program targeting HIV-infected women in Zambia: lessons from the field. Gynecol Oncol. 2008;110(3):402–7.
124. Bruinsma FJ, Quinn MA. The risk of preterm birth following treatment for precancerous changes in the cervix: a systematic review and meta-analysis. BJOG. 2011;118(9):1031–41.
125. Denny L, Kuhn L, De Souza M, Pollack AE, Dupree W, Wright Jr TC. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. JAMA. 2005;294(17):2173–81.
126. Sankaranarayanan R, Rajkumar R, Esmy PO. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. Br J Cancer. 2007;96(5):738–43.
127. Alliance for Cervical Cancer Prevention (ACCP). New evidence on the impact of cervical cancer screening and treatment using HPV DNA tests, visual inspection, or cytology. http://www.rho.org/files/ACCP_screening_factsheet_July09.pdf. [cited 2009 July].
128. Goldie SJ, Kuhn L, Denny L, Pollack A, Wright TC. Policy analysis of cervical cancer screening strategies in low-resource settings: clinical benefits and cost-effectiveness. JAMA. 2001;285(24):3107–15.

129. Goldhaber-Fiebert JD, Goldie SJ. Estimating the cost of cervical cancer screening in 5 developing countries. Cost Eff Resour Alloc. 2006;4:13.
130. Suba EJ, Murphy SK, Donnelly AD, Furia LM, Huynh ML, Raab SS. Systems analysis of real-world obstacles to successful cervical cancer prevention in developing countries. Am J Public Health. 2006; 96(3):480–7.
131. Organization WH. Cancer prevention (Chap. 16). In: Dos Santos Silva I, editor. Cancer epidemiology. Lyon: IARC Nonserial Publication; 1999. p. 355–83.
132. Arbyn M, Rebolj M, de Kok IM, Fender M, Becker N, O'Reilly M, et al. The challenges of organising cervical screening programmes in the 15 old member states of the European Union. Eur J Cancer. 2009;45(15):2671–8.
133. Anttila A, Nieminen P. Cervical cancer screening programme in Finland with an example on implementing alternative screening methods. Coll Antropol. 2007;31 Suppl 2:17–22.
134. Lynge E, Clausen LB, Guignard R, Poll P. What happens when organization of cervical cancer screening is delayed or stopped? J Med Screen. 2006;13(1): 41–6.
135. de Kok IM, van der Aa MA, van Ballegooijen M, Siesling S, Karim-Kos HE, van Kemenade FJ, et al. Working Group Output of the Netherlands Cancer Registry. Trends in cervical cancer in the Netherlands until 2007: has the bottom been reached? Int J Cancer. 2011;128(9):2174–81.
136. Franco EI, Duarte-Franco E, Frenzy A. Early detection of cervical cancer with visual inspection methods. Salud Publica Mex. 2003;45(Supp 3):S5367–75.
137. Arrossi S, Paolino M, Sankaranarayanan R. Challenges faced by cervical cancer prevention programs in developing countries: a situational analysis of program organization in Argentina. Rev Panam Salud Publica. 2010;28(4):249–57.
138. Perkins RB, Langrish SM, Stern LJ, Burgess JF, Simon CJ. Impact of patient adherence and test performance on the cost-effectiveness of cervical cancer screening in developing countries: the case of Honduras. Womens Health Issues. 2010;20(1): 35–42.
139. Yabroff KR, Washington KS, Leader A, Neilson E, Mandelblatt J. Is the promise of cancer-screening programs being compromised? Quality of follow-up care after abnormal screening results. Med Care Res Rev. 2003;60(3):294–331.
140. Yabroff KR, Kerner JF, Mandelblatt JS. Effectiveness of interventions to improve follow-up after abnormal cervical cancer screening. Prev Med. 2000;31(4): 429–39.
141. Kelly AW, Fores CM, Wollan PC. A program to increase breast and cervical cancer screening for Cambodian women in a Midwestern community. Mayo Clin Proc. 1996;71:437–44.
142. Pearlman DN, Clark MA, Rakowski W, Ehrich B. Screening for breast and cervical cancers: the importance of knowledge and perceived cancer survivability. Health. 1999;28:93–112.
143. Gupta A, Kumar A, Stewart DE. Cervical cancer screening among South Asian women in Canada: the role of education and acculturation. Health Care Women Int. 2002;23:123–34.
144. Francis SA, Nelson J, Liverpool J, Soogun S, Mofammere N, Thorpe RJ. Examining attitudes and knowledge about HPV and cervical cancer risk among female clinic attendees in Johannesburg, South Africa. Vaccine. 2010;28(50):8023–42.
145. Idestrom M, Milsom I, Ellstrom AA. Knowledge and attitudes about the pap smear screening program. A population-based study of women aged 20–59. Acta Obstet Gynecol Scand. 2002;81: 962–7.
146. Waller J, Mccaffery K, Wardle J. Beliefs about the risk factors for cervical cancer in a British population sample. Prev Med. 2004;38:745–53.
147. Yucel U, Ceber E, Ozenturk G. Efficacy of a training course given by midwives concerning cervical cancer risk factors and prevention. Asian Pac J Cancer Prev. 2009;10:437–42.
148. Waller J, McCaffery K, Forrest S, Szarewski A, Cadman L, Wardle J. Awareness of human papillomavirus among women attending a well women clinic. Sex Transm Infect. 2003;79(4):320–2.
149. Lambert EC. College student's knowledge of human papillomavirus and effectiveness of a brief educational intervention. J Am Board Fam Pract. 2001; 14(3):178–83.
150. Ramirez JE, Ramos DM, Clayton L, Kanowitz S, Moscicki AB. Genital human papillomavirus infection: knowledge, perception of risk, and actual risk in a nonclinic population of young women. J Womens Health. 1997;6(1):113–21.
151. Gakidou E, Nordhagen S, Obermeyer Z. Coverage of cervical cancer screening in 57 countries: low average levels and large inequalities. PLoS Med. 2008;5(6):e132.
152. Gage JC, Ferreccio C, Gonzales M, et al. Followup care of women with an abnormal cytology in a low-resource setting. Cancer Detect Prev. 2003;27: 466–71.
153. Herdman C, Sherris J. Planning appropriate cervical cancer prevention programs. Seattle, WA: PATH. http://www.path.org/publications/files/cxca-planning-appro-prog-guide.pdf. 2000.
154. Murillo R, Almonte M, Pereira A, Ferrer E, Gamboa OA, Jeronimo J, et al. Cervical cancer screening programs in Latin America and the Caribbean. Vaccine. 2008;26 Suppl 11:L37–48.
155. Huchko MJ, Bukusi EA, Cohen CR. Building capacity for cervical cancer screening in outpatient HIV clinics in the Nyanza province of western Kenya. Int J Gynaecol Obstet. 2011;114:106–10.
156. Chirenje ZM, Rusakaniko S, Akino V, Millingo M. A randomised clinical trial of loop electrosurgical excision procedure (LEEP) versus cryotherapy in the treatment of cervical intraepithelial neoplasia. J Obstet Gynaecol. 2001;21(6):617–21.
157. Mwanahamuntu MH, Sahasrabuddhe VV, Praendler KS, Mudenda V, Hicks ML, Vermund SH, et al.

Implementation of 'see and treat' cervical cancer prevention services linked to HIV care in Zambia. AIDS. 2009;23(6):N1–5.
158. Parham GP, Mwanahamuntu MH, Pfaendler KS, Sahasrabuddhe VV, Myung D, Mkumba G, et al. eC3—A modern telecommunications matrix for cervical cancer prevention in Zambia. J Low Genit Tract Dis. 2010;14(3):167–73.
159. Choconta-Piraquive LA, Alvis-Guzman N, Hoz-Restrepo FDL. How protective is cervical cancer screening against cervical cancer mortality in developing countries? The Colombian case. BMC Health Serv Res. 2011;10(270):1–6.
160. Marcus AC, Crane LA, Kaplan CP, Reading AE, Savage E, Funning J, et al. Improving adherence to screening follow-up among women with abnormal Pap smears: results from a large clinic-based trial of three intervention strategies. Med Care. 1992;30(3):216–30.
161. Carmichael M. Not just an illness of the rich. Scientific America. March 2011. p. 66–70.
162. Engelstad LP, Stewart S, Otero-Sabogal R, Leung MS, Davis PI, Pasick RJ. The effectiveness of a community outreach intervention to improve follow-up among underserved women at highest risk for cervical cancer. Prev Med. 2005;41(3–4):741–8.
163. IARC. Handbook of cancer prevention, Cervix cancer screening, vol. 10. Lyon: IARC; 2005.
164. Park DM, Bray F, Ferlay J, Pissani P. Global cancer statistics, 2002. CA Cancer J Clin. 2005;55:74–108.
165. ACCP. Planning and implementing cervical cancer prevention and control programs. A manual for managers. http://whqlibdoc.who.int/paho/2004/a92126.pdf. 2004.