Cervical Cancer: Screening and Therapeutic Perspectives

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Key Words

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Abstract

Cervical cancer is a major cause of mortality and premature death among women in their most productive years in low- and medium-resourced countries in Asia, Africa and Latin America, despite the fact that it is an eminently preventable cancer. While cytology screening programmes have resulted in a substantial reduction of cervical cancer mortality in developed countries, they have been shown to have a wide range of sensitivity in most routine settings including in developing countries. Although liquid-based cytology improves sample adequacy, claims on improved sensitivity remain controversial. Human papillomavirus testing is more sensitive than cytology, but whether this gain represents protection against future cervical cancer is not clear. Recently, in a randomized trial, the use of visual inspection with 4% acetic acid was shown to reduce cervical cancer incidence and mortality. Cryotherapy and large loop excision of the transformation zone are effective and safe treatment methods for cervical intraepithelial neoplasia. The clinical stage of cancer is the single most important prognostic factor and should be carefully evaluated in choosing optimal treatment between surgery and radiotherapy, with or without chemotherapy. At the public health level, health care infrastructure,

affordability and capacity for initiating and sustaining vaccination and screening programmes are critical factors in cervical cancer control. On the other hand, an informed practitioner can utilize the multiple opportunities in routine primary care interactions for prevention, screening, early detection and prompt referral for treatment.

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Introduction

Cervical cancer is an important global public health problem. It accounted for an estimated 493,000 incident cases, 1.4 million prevalent cases and 273,000 deaths in the world around the year 2002, constituting approximately 8% of the global burden of cancer among women (table 1) [1]. Developing countries accounted for four fifths of this global burden, reflecting the grim reality of the lack of effective control measures in many high-risk countries. It is a major cause of mortality and premature death among women in their most productive years in low- and medium-resourced countries in Asia, Africa and Latin America, despite the fact that it is an eminently preventable cancer. If effective prevention interventions are not implemented, over 1 million new cervical cancer cases will be diagnosed annually by the year 2030. While early detection of asymptomatic precancerous le-

Table 1. Cancer of the uterine cervix: incident cases, deaths and 5-year prevalence in 18 world regions in 2002

Region	Cervix cancer burden		
	cases	deaths	5-year prevalence
World	492,800	273,200	1,409,200
More developed countries	83,400	39,500	309,900
Less developed countries	409,400	233,700	1,099,300
Eastern Africa	33,900	27,100	57,200
Middle Africa	8,200	6,600	13,900
Northern Africa	8,100	6,500	14,000
Southern Africa	7,600	4,400	13,100
Western Africa	20,900	16,700	35,700
Caribbean	6,300	3,100	18,400
Central America	17,100	8,100	49,300
South America	48,300	21,400	139,200
Northern America	14,600	5,700	58,200
Eastern Asia	61,100	31,300	191,900
South-Eastern Asia	42,500	22,500	132,500
South Central Asia	157,700	86,700	446,100
Western Asia	4,400	2,100	13,700
Eastern Europe	30,800	17,100	107,700
Northern Europe	5,600	2,800	21,100
Southern Europe	10,600	4,100	40,900
Western Europe	12,700	5,600	49,200
Oceania	2,000	800	6,500

sions by screening and their effective treatment lead to the prevention of invasive cervical cancer and premature death from it, the fact that cervical cancer is caused by persistent infection by one or more of the 15 oncogenic human papilloma virus (HPV) types [2] provides the exciting opportunity for prevention through vaccination. We will briefly discuss the role of screening for preneoplastic disease, early clinical diagnosis and treatment of invasive cancer in the control of cervical cancer, with particular reference to low-resource countries where lack of effective screening programmes, early diagnosis and diagnostic/treatment facilities have resulted in high cervical cancer death rates.

Cervical Cancer Incidence and Mortality

There is a more than eightfold difference between the highest and lowest incidence rates of cervical cancer worldwide (fig. 1) [1, 3]. In sub-Saharan Africa, Central and South America, South Asia and South-East Asia, age-standardized incidence rates of cervix cancer exceed 25

per 100,000 in many countries. Rates lower than 7 per 100,000 women are observed in middle-eastern countries, while these are lower than 10 per 100,000 women in most developed countries [1, 3]. A large variation in survival from cervical cancer is observed among countries due to the differences in clinical stages at presentation and the level of development of cancer-related health services in different countries. Five-year survival rates of less than 25% are reported for black patients in Uganda [4] and Zimbabwe [5]; survival ranged between 30 and 50% in Cuba, India, and Philippines, 50 and 60% in Thailand and mainland China [6], and 65% in Singapore [7]. Rates ranged between 60 and 75% in developed countries [8, 9].

Estimated age-adjusted cervical cancer mortality rates ranged between 3 and 8 per 100,000 women in most developed countries and 10–25 per 100,000 women in most developing countries [1]. The high mortality in developing countries is due to advanced clinical stage at presentation and to the fact that a significant proportion of patients does not avail of or complete prescribed courses of treatment due to deficiencies in treatment availability, accessibility and affordability. There is reason to suspect that the burden of disease in some of the high-risk countries, particularly in sub-Saharan Africa, is underestimated given the inadequacy of diagnostic and treatment services and lack of reliable cancer information systems.

Natural History of Cervical Cancer

Compared to many other human cancers, the natural history of cervical neoplasia is much better understood. The direct precursors to invasive squamous carcinoma are the high-grade cervical intraepithelial neoplasia (CIN grades 2 and 3). One third to a half of these may progress to invasive cervical cancer over a period of 5–15 years, while most low-grade CIN (CIN 1) regress spontaneously and only 10–15% persist or progress to high-grade lesions. Adenocarcinoma in situ is the precursor lesion for invasive adenocarcinoma. Persistent infection with one or more of the oncogenic types of HPV causes cervical neoplasia [2]. Over 99% of cervical cancer cases and their precursors are caused by persistent infection with HPV, an infection of the surface epithelium that is mostly asymptomatic. Women are mostly infected with HPV in their teens, twenties, or early thirties and it is estimated that 50–80% of women may be infected after sexual debut in their lifetime. Most HPV infections are transient and 80% of them resolve within 2 years, but some women in-

Fig. 1. Incidence and mortality rate of cervical cancer in selected regions. ASR = Age-standardized incidence rates.

ected with one or more of the high-risk types develop persistent infections. Persistent genital HPV infection can lead to high-grade CIN (CIN 2–3) and adenocarcinoma in situ, which, left undetected and untreated, can lead to both invasive squamous cell carcinomas and adenocarcinoma. Of the more than 100 HPV types identified, one or more of the 15 so-called high-risk types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73 and 82) are associated with cervical neoplasia [2]. In a pooled analysis of 3,085 cases of cervical cancer in 11 studies from 25 countries, the overall HPV prevalence was 96% where HPV 16 and 18 accounted for 70% and the next six most common types accounted for 19% of cases [10]. In a meta-analysis involving 14,595 cases of invasive cervical cancer, 87% contained one or more of the oncogenic HPV

genotypes that cause cervical cancer; the frequency of HPV in cervical cancer specimens ranged from 86 to 94% in different regions of the world [11]. Almost the same estimates were found in a meta-analysis of 85 published studies [12].

Prevention by Vaccination

The estimated HPV 16/18 positive fraction in cervical cancer and high-grade CIN is approximately 70 and 50%, respectively, which equates to 350,000 potentially preventable cervical cancers annually by vaccination against HPV 16 and 18 [1, 12]. Thus, there is a vast potential to reduce HPV-related morbidity and mortality by HPV

vaccination. Currently, monovalent (HPV 16), bivalent (HPV 16, 18) and quadrivalent (HPV 6, 11, 16, 18) HPV L1 virus-like particle vaccines have been developed and evaluated [13–21]. The results from these studies indicate, with remarkable consistency, that a regimen of three intramuscular injections of HPV vaccine offers HPV-naïve women a very high level of protection (~99%) from infections and CIN associated with the HPV types included in the vaccine. The vaccines were safe and well tolerated with relatively few side effects [13–21]. While HPV vaccination holds great promise, there are still several challenges that need to be resolved before it can be widely implemented in high-risk developing countries [22]. These challenges include current high costs of the vaccines, affordability, feasibility, acceptability, logistics of vaccine delivery (in view of the need for three doses spread over 6 months, improved strategies and vaccine platforms to reach out to pre- or early-adolescent girls), long-term immunogenicity and efficacy in preventing cervical neoplasia, cross-protection against HPV types not targeted by the vaccine antigens and the efficacy of different, more logistically feasible dose regimes in inducing and maintaining immunogenicity and long-term protection against cervical neoplasia. Prophylactic vaccination is likely to provide important future health gains if vaccination is offered to girls before onset of sexual activity. However, cervical screening should still be continued because the risk of being infected with the oncogenic HPV types or of acquiring CIN due to an HPV type other than 16 or 18 remains.

Screening for Cervical Cancer

Screening involves application of a relatively simple, inexpensive test to a large number of asymptomatic women in order to classify them as likely or unlikely of having the disease of interest. The screen-positive women are subsequently investigated to rule out cervical neoplasia and those confirmed with disease are treated. The objective of cervical screening is to prevent invasive cervical cancer by detecting and treating women with high-grade CIN 2 and 3 lesions and the effectiveness of screening is evaluated by the extent of reduction in cervical cancer incidence and mortality following screening. The critical components of successful cervical screening are high coverage of target women with accurate, quality-assured screening tests, screen-positive women with diagnostic investigations and women with confirmed cervical neoplasia with treatment and follow-up care. However, orga-

nized and effective population-based cervical cancer screening programmes have not yet been implemented in most developing countries due to several barriers, such as competing health care priorities, and limited, understaffed, under-resourced and overstretched primary health care facilities [23]. Needless to say, cancer diagnostic treatment and palliative care services are even more limited in many of these countries.

Screening Methods for Cervical Neoplasia

Conventional cervical cytology, liquid-based cytology (LBC), HPV testing and visual screening after application of acetic acid (VIA) or Lugol's iodine (VILI) are the currently available tests for the early detection of CIN. The most widely used and evaluated screening test is conventional cytology and, in recent years, the other tests have been increasingly evaluated in different settings. The accuracy and efficacy of these tests in preventing cervical cancer will be discussed briefly.

Conventional Cytology

Cytology (Pap smear) screening involves collection of cervical cell samples from the cervical epithelium using a wooden spatula or a brush, preparation and fixation of the smear by a doctor or a nurse followed by staining, reading and reporting of the results by a cytotechnician and a cytopathologist. Cytology requires a laboratory infrastructure, with internal and external quality control measures to process slides and microscopy, and a system to communicate the results to those concerned. High-quality training, continuing education, and proficiency testing of personnel are essential to ensure reliable and efficient testing.

In most routine settings, cytology has been shown to have a wide range in sensitivity in detecting cervical neoplasia. The sensitivity to detect CIN 2 and 3 lesions ranged from 47 to 62% and the specificity from 60 to 95% in reviews of several studies [24, 25]. There have been several cross-sectional studies in developing countries assessing the accuracy of cytology, in which the sensitivity varied from 31 to 78% and the specificity from 91 to 96% (table 2) [26]. Verification bias was minimized in some of these studies by providing reference standard investigations to all participants.

Large-scale population-based cytology screening programmes have resulted in a dramatic reduction in the burden of cervical cancer in the past five decades in the developed countries of Europe, North America, Japan,

Australia and New Zealand by early detection and effective treatment of cervical precancerous lesions [23, 27]. The marked reduction in the incidence of and mortality from cervical cancer before and after the introduction of cytology screening in developed countries has been interpreted as strong non-experimental, observational evidence for the effectiveness of cytology screening programmes [27]. Following the introduction of widespread cytology screening in developed countries since the 1960s, cervical cancer mortality rates have declined at a remarkable rate. Cervical cancer incidence has been reduced by as much as 80% where the cytology screening quality, coverage and follow-up of women are high. The highest reduction in cervical cancer incidence was in the 30–49 age groups where the focus of screening was the most intense. Organized screening with systematic call, recall, follow-up and surveillance systems have shown the greatest effect (e.g. Finland, Iceland), while using fewer resources than the less organized programmes (e.g. USA, France).

Establishing quality-assured cytology screening programmes with national coverage is beyond the capacity and resources of many developing countries in view of the infrastructure for testing, trained personnel for reading, quality assurance and the organization required. Cytology screening has failed to reduce cervical cancer burden by any great extent in Latin American countries including Cuba, Brazil, Mexico, Peru, and Colombia [23]. The main reasons for the lack of success in these countries were a combination of suboptimal cytology testing, lack of quality assurance, poor coverage of women at risk and inadequate follow-up of screen-positive women with diagnosis and treatment. While poor-quality cytology is a reflection of several challenges in providing quality-assured testing, the lack of coverage for diagnosis and treatment is related to the inadequate health care infrastructure, human resources and programme logistics. Cytology is a resource-intensive technology and, unfortunately, it is not possible to commit sufficient financial and human resources to fulfil the optimal requirements. These would be for collection of cervical cells, slide preparation, staining, reading and reporting, as well as quality control measures, to ensure good-quality cytology with optimal accuracy in low-resource countries.

A critical appraisal of reasons for the failure or suboptimal performance of cytology screening and the difficulties in organizing cytology screening in low- and medium-resourced countries have prompted the search for, and evaluation of, alternative screening tests such as VIA, VILI and HPV DNA testing and paradigms that require

Table 2. Characteristics of cervical screening tests for detecting CIN 2 and 3 lesions in cross-sectional studies

Test	Sensitivity, %	Specificity, %
Cytology	31–78	91–96
HPV testing	61–100	62–96
VIA	37–95	49–97
VILI	44–92	75–85

one single or two visits to complete the screening and diagnosis/treatment processes [23, 26, 27]. This has also led to the reorganization of existing cytology programmes and more effective utilization of resources in some countries such as Brazil, Chile, Costa Rica, South Korea, Mexico, Singapore, Thailand and Uruguay. Reorganization of the programme in Chile has been associated with decline in cervical cancer mortality in recent years [28]. The incidence and/or mortality rates are currently declining in Costa Rica, Hong Kong, Singapore, Taiwan, Mexico, Uruguay and South Korea due to widespread screening in the health services.

Liquid-Based Cytology

LBC relies on a uniform thin layer of cervical cells without debris prepared from processing a fluid medium containing the cervical cells. The advantages of LBC include an increased possibility of a more representative and complete transfer of cervical cells from the sampling device to the slide and improved microscopic readability due to the elimination of problems such as poor fixation, air-drying artifact, uneven thickness of the cellular spread, debris due to blood and inflammatory cells, and overlapping of cells. Cell suspension remaining after the preparation of the smear may be used for additional testing procedures such as HPV testing. It is a more expensive test than conventional cytology and requires additional instrumentation to prepare the smears. LBC is reported to improve sample adequacy and increase the sensitivity of cervical cytology in comparison with conventional cytology [25, 29].

In a recent review of 56 studies, LBC and conventional cytology were compared in terms of the percentage of slides classified as unsatisfactory in each cytology category and the accuracy of detection of high-grade disease [30]. Data were examined for studies overall and in strata to examine the effect of study quality on results. The median difference in the percentage of unsatisfactory slides between LBC and conventional cytology was 0.17%. The

classification of high-grade squamous epithelial lesions varied according to study quality ($p = 0.04$), with conventional cytology classifying more slides in this category than did LBC in high-quality studies ($n = 3$) only. In medium-quality ($n = 30$) and high-quality studies, LBC classified more slides as atypical squamous cells of unknown significance (ASCUS) than did conventional cytology when compared with low-quality studies ($n = 17$; $p = 0.05$). This review does not lend support to claims of better performance by LBC.

In a randomized trial in Italy, LBC showed no significant increase in sensitivity for CIN 2 or worse lesions (relative sensitivity 1.17, 95% confidence interval 0.87–1.56), whereas the positive predictive value was reduced (relative positive predictive value vs. conventional cytology 0.58, 0.44–0.77) [31]. LBC detected more lesions of grade 1 or more (relative sensitivity 1.68, 1.40–2.02), with a larger increase among women aged 25–34, but did not detect more lesions of grade 3 or more (relative sensitivity 0.84, 0.56–1.25). The relative frequency of women with at least one unsatisfactory result was lower with LBC (0.62, 0.56–0.69).

It is not feasible to implement LBC in many low-resource settings. Although some countries have changed to LBC for cervical screening, controversy remains. The impact of LBC on cancer incidence and mortality remains to be established, as does its cost-effectiveness.

HPV Testing

The fact that cervical neoplasia is caused by persistent infection with oncogenic types of HPV has led to the evaluation of HPV testing as a primary screening test for cervical neoplasia. HPV testing is the most objective and reproducible of all currently available cervical screening tests. The sensitivity of HPV testing in detecting CIN 2 and 3 lesions varied from 66 to 100% and the specificity varied from 62 to 96% in several cross-sectional studies (table 2) [26, 32, 33]. In a recent meta-analysis of 25 studies comparing HPV testing to cytology for the detection of high-grade CIN in primary cervical cancer screening, the pooled sensitivity of HPV testing by hybrid capture 2 (HC2) test, polymerase chain reaction, cytology (ASCUS or worse) and cytology (LSIL or worse) was 90, 80.9, 72.7 and 61.6%, respectively, and the pooled specificity was 86.5, 94.7, 91.9 and 96.0%, respectively [32]. The ratio of the sensitivity of HC2 to cytology (ASCUS) was 1.25 (95% CI = 1.20–1.29), and the corresponding specificity ratio was 0.97 (95% CI = 0.96–0.98). The ratio of the sensitivity of combination of HC2 and cytology (ASCUS) to HC2 alone was 1.05 (95% CI = 1.04–1.06) and the ratio of the

specificity 0.95 (95% CI = 0.94–0.96). For women over 30 years, the sensitivity of HC2 was 94.8% and the specificity 86.0%. The combination of HC2 and cytology has the highest sensitivity and lowest specificity. The sensitivity of HPV testing reported from developing country settings has been somewhat lower than that reported from studies in developed countries [26].

In randomized trials, HPV testing has greater sensitivity for the detection of CIN as compared with Pap testing [34–36]. In a randomized trial in Sweden, 12,527 women aged 32–38 years were randomly assigned to have HPV test plus cytology (intervention group) or a Pap test alone (control group) [34]. The relative frequency of CIN 2 or 3 or cancer detected at enrollment in the intervention group was 51% greater than the proportion of women in the control group. At subsequent screening examinations over 4 years, the proportion of women in the intervention group who were found to have CIN 2 or 3 lesions or cancer was 42% less and the proportion with CIN 3 lesions or cancer was 47% less than the proportions of control women. In a randomized trial in Canada involving 10,154 women aged 30–69 years, the sensitivity of HPV testing for CIN 2 or 3 was 94.6%. These used the conservative definition based on confirmation by histological and, in addition, loop electrosurgical excision procedure (LEEP) investigations. On the other hand, the sensitivity of Pap testing was 55.4% (95% CI, 33.6–77.2; $p = 0.01$) [35]. The specificity was 94.1% for HPV testing and 96.8% for Pap testing. The sensitivity of both tests used together was 100%, and the specificity was 92.5%. In a randomized trial in the Netherlands, 8,575 women aged 29–56 years were assigned to receive combined cytological and HPV DNA testing and 8,580 women (control group) conventional cytological testing only. CIN 3 or worse lesions detected at baseline in the intervention group was 70% more than in the control group (68 vs. 40, $p = 0.007$) [36]. The number of CIN 3 or worse lesions detected in the subsequent round was lower in the intervention group than in the control group (24/8,413 vs. 54/8,456, 55% decrease, 95% CI 28–72; $p = 0.001$). The number of CIN 3 or worse lesions over the two rounds did not differ between groups, implying that HPV DNA testing leads to earlier detection of CIN 3 or worse lesions.

Although self-sampling for HPV DNA testing seems to be a viable screening option and potentially promising for use in under-resourced areas or for women who are reluctant to participate in screening programmes, evidence supporting it is limited [37]. Further definitive research is needed to clarify the use of self-sampling for HPV DNA testing for the purpose of increasing screen-

ing rates, especially in women who are never or seldom screened.

In low-resource settings, where repeated testing of women at risk for cervical neoplasia may not be feasible, HPV testing may provide an objective method of identifying and investing the limited resources on women at risk for disease [26]. However, it is currently more expensive (20–30 USD) than other screening tests and requires sophisticated laboratory infrastructure including testing equipment, storage facilities for samples and trained technicians. Further developments in terms of less expensive testing and less sophistication in infrastructure and equipment requirements are essential to make HPV testing feasible in low-resource settings. Efforts are now underway to develop simple, affordable, rapid and accurate HPV testing methods for use in low- and medium-resource settings.

In summary, compared to cytology, HPV testing is substantially more sensitive for prevalent CIN 2 or worse lesions, but significantly less specific. Whether this gain represents overdiagnosis or protection against future high-grade CIN or cervical cancer is not clear. Reduced incidence of or mortality from invasive cervical cancer among HPV-screened subjects compared to cytologically screened subjects has not yet been demonstrated and a cluster-randomized trial is addressing this issue in India [38]. Interim results from this trial showed similar detection rates of CIN 2 and 3 lesions per 1,000 screened women among those screened by cytology or HPV testing [38]. The reason for this lack of difference in detection rate is not obvious at present. HPV testing, reportedly, does not add significant psychological distress when combined with cytology in routine primary cervical screening [39].

Visual Screening

Naked eye visibility of most precancerous and early cancerous lesions after application of dilute acetic acid or Lugol's iodine solution and the need for affordable, simple cervical screening tests have prompted the evaluation of visual screening tests in comparison with conventional cytology in recent years. VIA, also known as direct visual inspection (DVI), or as acetic acid test (AAT), or cervicoscopy, is the most widely evaluated visual screening test.

VIA involves naked eye inspection of the cervix using a bright torch light or a halogen focus lamp, 1–2 min after the application of 3–5% acetic acid using a cotton swab or a spray. A positive test is characterized by well-defined acetowhite areas close to the squamocolumnar junction or to the external os or on the entire cervix or a cervical growth turning acetowhite [40]. Immediate results fol-

lowing VIA allow diagnostic investigations and/or treatment in the same session as screening. A range of personnel including doctors, nurses, midwives, and paramedical health workers can be rapidly trained in providing VIA in short training courses of 4–10 days [41]. A wide range of teaching materials is now available for training personnel in carrying out VIA competently [40, 42, 43]. However, it is a subjective test that suffers from high false-positive rates and low to moderate specificity and reproducibility. Quality assurance procedures for VIA are yet to be standardized and assuring consistent high performance can be challenging under field conditions and requires constant monitoring and frequent retraining of test providers.

The sensitivity of VIA to detect CIN 2 and 3 lesions and invasive cervical cancer varied from 37 to 95% and the specificity varied from 49 to 97% in several cross-sectional studies in developing countries (table 2) [26]. The wide range in accuracy parameters of VIA in different studies underscores the subjective nature of the test, the varying competency of test providers, and the varying quality of reference standards used to establish the true positive disease. When conventional cytology was concurrently evaluated, the sensitivity of VIA was found to be higher than or similar to that of cytology, but had lower specificity [26]. It appears that VIA has an average sensitivity around 55% and specificity around 85% to detect high-grade CIN in experimental study settings.

The immediate availability of test results following visual testing has opened up the option of 'screen and treat' or 'single visit' approach to ensure a high compliance to treatment of screen-positive women. In this, screen-positive women with no clinical evidence of invasive cancer and satisfying the criteria for ablative therapy are immediately treated with cryotherapy, without confirmatory investigations such as colposcopy or histology. The safety, acceptability, and the feasibility of combining VIA and cryotherapy in a single-visit approach have been demonstrated in rural Thailand [44], Ghana [45], Guatemala [46] and South Africa [47]. VIA-based screen and treat programmes are currently operational in 15 provinces in Thailand. In a randomized controlled trial in South Africa, VIA followed by cryotherapy resulted in a 37 and 46% lower prevalence of CIN 2–3 lesions at 6 and 12 months follow-up compared with a control group [47]. In this study, cryotherapy for HPV test-positive women resulted in much higher decline in the prevalence of CIN 2–3 at 6 and 12 months (77 and 74%, respectively). It was concluded that both screen-and-treat approaches are safe and result in a lower prevalence of high-grade cervical

cancer precursor lesions compared with delayed evaluation at both 6 and 12 months.

Currently, the efficacy and effectiveness of VIA screening in reducing cervical cancer incidence and mortality are being addressed in randomized controlled trials in India [38, 48]. In a cluster-randomized controlled trial, of the 114 study clusters in Dindigul district, 57 were randomized to a single round of VIA by trained nurses and 57 to a control group [48]. Of the 49,311 eligible women aged 30–59 years in the VIA group, 31,343 (63.6%) were screened; 30,958 women in the control group received routine care. During the 7 years following the beginning of screening, there were 167 cervical cancer cases and 83 cervical cancer deaths in the intervention group, compared with 158 cases and 92 deaths and in the control group [incidence hazard ratio 0.75 (95% CI 0.55–0.95) and mortality hazard ratio 0.65 (95% CI 0.47–0.89)] [48]. These results show a 25% reduction in cancer incidence and a 35% reduction in cancer mortality. The greatest reduction in incidence and mortality rates were observed for the 30- to 39-year age group, which makes biological sense, since the transformation zone where cervical neoplasia occurs is fully exposed on the ectocervix in young women, enabling VIA to detect the abnormalities. The convincing reduction in disease burden and the feasibility justify the use of VIA screening both in clinical and public health settings in developing countries. However, good training of providers and sustained quality assurance are vital for VIA screening to succeed in preventing cervical cancer in developing countries. It is possible that the protection from a single screening may diminish with time and further follow-up in this study will document the evolution of invasive disease incidence over time. However, the protection observed 6 years from the beginning of VIA screening in this study is important from a public health point of view for low resource settings. VIA may also be a suitable screening approach for the underserved socio-economically disadvantaged populations who are currently not covered by the existing cytology screening programmes in developed countries.

Studies evaluating low-level magnification for visualization of acetowhite changes have shown that it does not improve accuracy over that of naked eye visualization [26, 49]. VILI involves naked eye examination of the cervix, to identify mustard-yellow lesions in the transformation zone of the cervix, after application of Lugol's iodine [40]. The VILI test results are reported immediately after application of iodine. A positive result is based on the appearance of definite mustard-yellow area on the cervix close to the squamocolumnar junction or the os or on a

cervical growth. The sensitivity of VILI varied between 44 and 92% and specificity between 75 and 85% in cross-sectional studies (table 2) [26, 50–52].

Cost-Effectiveness of New Paradigms of VIA/HPV Screening

Cost effectiveness studies based on data from India, Kenya, Peru, South Africa, and Thailand indicate that the most cost-effective strategies for cervical screening are those approaches requiring the fewest visits, leading to improved follow-up testing and treatment [53, 54]. Screening women once in their lifetime, at the age of 35 years, with a one- or two-visit screening strategy involving VIA or HPV testing in cervical cell samples reduced the lifetime risk of cancer by approximately 25–36%, and cost less than 500 dollars per year of life saved [54]. Relative cancer risk declined by an additional 40% with two screenings (at 35 and 40 years of age), resulting in a cost per year of life saved that was less than each country's per capita gross domestic product, a very cost-effective result [54].

Treatment of Cervical Cancer Precursor Lesions

Principles of Treatment of CIN

The treatment of CIN has evolved from in-patient procedures like hysterectomy and cold knife conization towards more conservative, yet safe and effective approaches such as destruction (ablation) or removal (excision) of the entire transformation zone of the cervix including the extension into the crypts (average depth 5 mm). Ablative therapy can be done by cryotherapy, carbon dioxide laser or cold coagulation. Excisional techniques include large loop excision of the transformation zone (LLETZ), also known as LEEP, needle excision of the transformation zone (NETZ) and laser excision, cold knife conization and hysterectomy. Currently, cold knife conization under local or general anaesthesia is reserved for the treatment of micro-invasive cancer where evaluation of the margin is of prime importance. For adenocarcinoma in situ and previous failed treatment, NETZ may be a better choice. Hysterectomy should be reserved only for a select few cases of CIN coexisting with associated gynaecological conditions requiring removal of the uterus.

CIN 2 and CIN 3, being true cervical cancer precursors, should always be treated. CIN 1 lesions should be treated if follow-up cannot be ensured (as in most low-resource settings) or the lesion persists for 2 years or worsens in grade or size [1]. In the case of CIN associated

with pregnancy, the woman is reassessed 6 months after delivery to allow the uterus and cervix to involute and treatment is decided based on clinical findings at that time. We limit our discussion of treatment techniques to cryotherapy and LLETZ [55].

Cryotherapy

Cryotherapy using nitrous oxide or carbon dioxide refrigerant is the simplest, safest and most widely practised ablative treatment that can be carried out by a wide range of health care personnel like nurses, general practitioners and specialists. Any grade of CIN can be treated by cryotherapy provided that the entire lesion is visible and occupies less than three fourths of the transformation zone; it does not extend into endocervix or vagina; no suspicion of glandular or invasive disease and the entire lesion can be adequately covered by the cryoprobe [55]. Adequate punch biopsies should be obtained from the abnormal area prior to ablative therapy. Freezing should be done in two cycles of 3 min with 5 min of thawing in between (double-freeze technique) [55]. Cryotherapy is a safe procedure with no significant operative morbidity. Cure rates following cryotherapy have reported to vary between 86 and 95% for all grades of CIN, 91 and 100% for CIN 1, 75 and 96% for CIN 2 and 70 and 92% for CIN 3 lesions [56, 57]. This impressive success rate of cryotherapy, like any other excision treatment for CIN, may fall over a long period. Pooled analysis of studies comparing laser ablation and cryotherapy failed to demonstrate any significant difference in the frequency of residual disease (odds ratio: 0.96; 95% CI: 0.67–1.36) [58] and there was no statistically significant difference in cure rates of ectocervical CIN lesions following cryotherapy, laser ablation, LEEP and cone biopsy [59]. There is no reason to suspect that high cure rates can be achieved for ectocervical lesions occupying less than three fourths of the transformation zone by cryotherapy. Cryotherapy is an important and effective work horse for treating ectocervical CIN in the low- and medium-resource countries, where most women do not have the means or luxury to access excisional methods of treatment. Realities are very different in different parts of the world.

Large Loop Excision of the Transformation Zone (LLETZ or LEEP)

All CIN lesions including the glandular abnormalities can be treated by LLETZ. A wire loop electrode powered by an electrosurgical unit is used to remove the entire transformation zone, containing the entire lesion, under colposcopic control and under local anaesthesia. The

heat from a high-voltage electrical arc between the operating electrode and tissue allows the operator to cut by vaporizing the tissue. Once the specimen has been removed and placed in formalin, any bleeding points are carefully fulgurated using a ball electrode. Extensive ablation of the treatment crater should be avoided because this may interfere with the early detection of inadequately treated occult invasive disease. The excision of transformation zone treats the abnormality effectively and provides a specimen for detailed histological evaluation. The width of the loops ranges from 10 to 20 mm and the depth ranges from 8 to 15 mm. The appropriate size of the loop is chosen to achieve adequate depth and width of cut depending on the size and position of the lesion.

Though infrequent, excessive bleeding may occur during or immediately after surgery. Usually such bleeding can be controlled by diathermy fulguration or by applying Monsel's paste. Rarely, lateral suturing may be required. No significant differences in the frequencies of primary or secondary haemorrhage following LLETZ and laser ablation have been observed in randomized trials [60–62]. Up to 20% of the post-LLETZ biopsy specimens may have disease at the margin and such women have a high risk of post-treatment recurrence [63, 64]. While every effort should be taken to avoid incomplete excision, some of the cases with deep positive margins would be safer with a second treatment, but most will need close follow-up [63, 64]. The risk of recurrence is higher if the endocervical margin has residual disease. The failure rate of LLETZ varies between 4 and 18% in various studies [58, 62, 64]. High-grade post-treatment disease occurred in 597 of 3,335 (18%) women who had incomplete excision versus 318 of 12,493 (3%) women with complete excision in a recent meta-analysis [64]. The randomized trials that compared residual disease at follow-up did not observe any significant difference between LLETZ, laser conization or knife conization [59]. In a randomized controlled trial comparing NETZ with LEEP involving 347 women with CIN, more women in the NETZ arm had clear histological margins (85 vs. 75%) and produced more specimens in one piece (97.5 vs. 29.5%) [65].

Early Detection and Treatment of Invasive Cervical Cancer

Public and professional awareness are important in the early detection and management of invasive cervical cancer. Ensuring availability and accessibility to basic di-

Table 3. Treatment methods for cervical cancer

Stage	Description of the stage of disease	Treatment modality	5-year survival, %
IA	invasive cancer identified only microscopically; invasion is limited to measured stromal invasion with a maximum depth of 5 mm and no wider than 7 mm <ul style="list-style-type: none"> – <i>stage IA₁</i>: measured invasion of the stroma 3 mm or less in depth and 7 mm or less in diameter – <i>stage IA₂</i>: measured invasion of stroma more than 3 mm but 5 mm or less in depth and 7 mm or less in diameter 	<i>stage IA₁</i> : cold knife conization or simple hysterectomy <i>stage IA₂</i> : radical hysterectomy and bilateral pelvic lymphadenectomy or radical trachelectomy for fertility preservation plus bilateral pelvic lymphadenectomy or intracavitary radiotherapy, 75–80 Gy to point A	90–95
IB	clinical lesions confined to the cervix or preclinical lesions greater than stage IA <ul style="list-style-type: none"> – <i>stage IB₁</i>: clinical lesions 4 cm or less in size – <i>stage IB₂</i>: clinical lesions more than 4 cm in size 	<i>stage IB₁</i> : radical hysterectomy and bilateral pelvic lymphadenectomy or radical radiotherapy (external radiotherapy plus intracavitary radiation) <i>stage IB₂</i> : radical radiotherapy to a total dose of 80–85 Gy to point A (external radiotherapy plus intracavitary radiation) with or without concurrent chemotherapy cisplatin or cisplatin/fluorouracil or radical hysterectomy and bilateral pelvic lymphadenectomy with or without postoperative total pelvic radiation therapy plus chemotherapy cisplatin or cisplatin/fluorouracil	80–85
II	stage II is carcinoma that extends beyond the cervix but has not extended onto the pelvic wall; the carcinoma involves the vagina but not as far as the lower third section <ul style="list-style-type: none"> – <i>stage IIA</i>: no obvious parametrial involvement; involvement of as much as the upper two thirds of the vagina – <i>stage IIB</i>: obvious parametrial involvement but not onto the pelvic sidewall 	<i>stage IIA</i> : radical radiotherapy (external radiotherapy plus intracavitary radiation) with or without concurrent chemotherapy cisplatin or cisplatin/fluorouracil or radical hysterectomy and bilateral pelvic lymphadenectomy with or without postoperative total pelvic radiation therapy plus chemotherapy <i>stage IIB</i> : radical radiotherapy (external radiotherapy plus intracavitary radiation) with or without concurrent chemotherapy with cisplatin or cisplatin/fluorouracil	50–65 for IIA disease 40–50 for IIB disease
III	carcinoma that has extended onto the pelvic sidewall and/or involves the lower third of the vagina; on rectal examination, there is no cancer-free space between the tumour and the pelvic sidewall; all cases with a hydronephrosis or non-functioning kidney are stage IIIB, unless they are known to be due to other causes <ul style="list-style-type: none"> – <i>stage IIIA</i>: no extension onto the pelvic sidewall but involvement of the lower third of the vagina – <i>stage IIIB</i>: extension onto the pelvic sidewall or hydronephrosis or non-functioning kidney 	radical radiotherapy (external radiotherapy plus intracavitary radiation) with or without concurrent chemotherapy with cisplatin or cisplatin/fluorouracil	25–30
IV	carcinoma that has extended beyond the true pelvis or has clinically involved the mucosa of the bladder and/or rectum <ul style="list-style-type: none"> – <i>stage IVA</i>: spread of the tumour onto adjacent pelvic organs such bladder or rectum – <i>stage IVB</i>: spread to distant organs 	<i>stage IVA</i> : radical radiotherapy (external radiotherapy plus intracavitary radiation) with or without concurrent chemotherapy with cisplatin or cisplatin/fluorouracil or palliative radiotherapy <i>stage IVB</i> : palliative radiotherapy or chemotherapy	<5

agnosis and treatment services is key to the success of treatment of invasive cervical cancer.

Early, preclinical invasive cervical cancers may be detected during colposcopic assessment of screen-positive women. As invasion progresses, symptoms manifest with characteristic clinical features, depending on the clinical spread of the disease. Awareness of symptoms and signs

of invasive cancer should prompt physical examination and investigations to rule out cancer. Clinical suspicion and speculum examination are important in the early detection of invasive cancer. Once a diagnosis of invasive cancer is made, it is mandatory to stage the clinical extent of disease, according to the International Federation of Gynaecology and Obstetrics (FIGO) classification, to

guide treatment and prognosis. The FIGO clinical staging is based on primary tumour size and the extent of the spread of disease in the vagina, parametrium and distant organs (table 3). Speculum, vaginal and rectal examination, chest X-ray and intravenous pyelography or abdominal ultrasound scanning are mandatory investigations for staging. In choosing optimal therapy, the clinical stage of cancer is probably the most fruitful, if not the most perfect, surrogate for tumour volume that can also be measured universally. Surgery and radiotherapy, with or without chemotherapy, are important treatment modalities for invasive cervical cancer (table 3).

Management of Micro-Invasive Cancer

The management of micro-invasive cancer depends on the depth of stromal invasion. The frequency of nodal metastases increases from <1% in stage IA₁ (stromal invasion <3 mm) to 7% in stage IA₂ (stromal invasion 3.1–5.0 mm) [64]. Stage IA₁ disease may be treated by cold knife conization alone or simple hysterectomy (table 3). If the margins of the cone are free of disease and the depth of invasion does not exceed 3 mm, no further treatment is necessary. However, conservative management with conization is not recommended in this stage in developing countries, due to difficulties in ensuring long-term follow-up and adequate histological examination of the resected specimen. Hysterectomy should be done if the margins are involved. Extrafascial hysterectomy is an option to treat stage IA₁ disease in women above 40 years who have completed child-bearing. Stage IA₂ carcinoma is treated by radical hysterectomy and bilateral pelvic lymphadenectomy (table 3). Radical trachelectomy involving pelvic laparoscopic lymphadenectomy followed by vaginal resection of cervix, parametrium and upper one third of the vagina may be performed in selected patients desirous of preserving fertility. To prevent premature delivery a prophylactic cerclage is placed at the isthmus. In medically unfit patients, brachytherapy alone providing a total dose of 75–80 Gy to point A is an equally effective alternative treatment option.

Management of Stage IB and IIA Cancer

There is no significant difference in outcome of patients with stage IB₁ and IIA cancer treated by irradiation alone or by radical hysterectomy. The cure rate for either modality of treatment is around 85% at these stages [67]. However, surgery is the treatment of choice because of the following advantages: preservation of ovarian function, vaginal pliability, function, and the availability of radiation as a reserved treatment option in case of recurrence.

The most frequently used surgical procedure for stages IB₁ and IIA cervical cancer is Wertheim's operation (radical abdominal hysterectomy with bilateral pelvic lymphadenectomy) with some modifications. The modifications are: the cardinal and the uterosacral ligaments are removed short of their distal extensions instead of dissecting them right up to their attachments to pelvic walls; the ureters are mobilized less, so as to keep the blood supply to the terminal part intact. Postoperative pelvic irradiation is given to patients with lymph node metastasis, positive vaginal margin, deep stromal invasion or extensive lymphovascular space involvement.

Alternatively stage IB₁ cancers may be treated with external-beam pelvic radiation therapy combined with intracavitary brachytherapy. Radical radiotherapy comprises of external beam radiotherapy to the pelvis, to a total dose of 45–48 Gray (Gy) in 4 weeks and intracavitary radiation 30–35 Gy to point A. Although low-dose rate brachytherapy, typically with cesium-137, has been the traditional approach, the use of high-dose rate therapy, typically with iridium-192, is rapidly increasing. High-dose rate brachytherapy provides the advantage of eliminating radiation exposure to medical personnel, a shorter treatment time, patient convenience and outpatient management. High-dose rate brachytherapy is comparable with low-dose rate brachytherapy in terms of local-regional control and complication rates [68, 69]. It is emphasized that the addition of intracavitary irradiation to external beam radiotherapy is associated with improved disease control and survival, as compared to external radiotherapy alone. Stage IB₂ tumours have higher chance of having pelvic and para-aortic lymph node metastasis and are considered unsuitable for surgery. Radiotherapy plus chemotherapy with cisplatin or cisplatin/5-fluorouracil is the treatment of choice for stage IB₂ disease [68].

Management of Stage II–IV Cancer

Radiotherapy plus concurrent chemotherapy with cisplatin or cisplatin plus fluorouracil has emerged as the treatment of choice for those with stages IIB and III cervical cancers [70–73]. Randomized clinical trials have confirmed that the combination of chemotherapy and radiotherapy is superior to pelvic radiation alone [68–71]. Concurrent chemotherapy may improve the outcome only if radical radiotherapy is fully and accurately administered.

The introduction of three-dimensional conformal radiotherapy and intensity-modulated radiotherapy have resulted in overall reduction in volume of normal tissue irradiated which may translate into overall reduction in

both acute and late treatment-related side effects. Further trials are necessary to evaluate this perspective and possible improved cure rates [74, 75].

Patients with stage IVA, who already have bladder and/or rectal involvement, may be treated with radical radiotherapy as for stage III patients. However, the possibility of urinary or faecal incontinence or vesicovaginal or rectovaginal fistula may be accentuated when the cancer regresses due to treatment, necessitating urethrostomy or colostomy.

Stage IVB cervical cancer is incurable with locoregional treatment such as radiotherapy due to involvement of distant organs or systemic treatment with chemotherapy. They are candidates for palliative radiotherapy and/or chemotherapy to control bleeding, excessive discharge and pain and for symptomatic management.

Conclusions

The long natural history of cervical cancer presents several opportunities in terms of prevention, screening, early detection and treatment of CIN to prevent invasive

cancer. Both screening and vaccination have the potential to save many lives. At the public health level, health care infrastructure, affordability and capacity for initiating and sustaining vaccination and screening programmes are critical factors in cervical cancer control. Whereas the individual practitioner can successfully use the opportunities provided by health care interactions of women to offer one or more of the several useful interventions to prevent invasive cancer or death from invasive cancer by early clinical diagnosis, prompt referral and ensuring appropriate and effective treatment are necessary. Such efforts by informed clinicians are critical particularly in countries with no organized public health programme of screening and early detection.

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