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CHAPTER 6

Secondary prevention of cervical cancer

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Visual inspection with Lugol's iodine (VILI);
Screen and treat

Abstract Cervical cancer continues to be the commonest cause of death among women in developing countries, largely due to the failure to initiate or sustain effective cytology-based screening programs. Experience from countries with successful screening programs indicates that target age and the extent of coverage of the target group are key indicators of success in reducing cervical cancer. Alternative methods for the secondary prevention of cervical cancer have been evaluated in numerous studies over the past 10 years in different countries. These include visual inspection with acetic acid and linking screening to treatment. Although longitudinal data are scanty, these alternative approaches have been shown to be feasible, acceptable, and effective in reducing cervical cancer.

1. Introduction

Cervical cancer continues to be a major public health threat to women in many low- and medium-resourced countries in South and Central America, sub-Saharan Africa, and South and Southeast Asia where it is still the leading cancer among women [1–3]. The high burden of cervical cancer in these countries is due both to a high prevalence of human papillomavirus (HPV) infection (>10% in women aged 30 years or older) and the lack of effective screening programs [1,2]. Of the 493,000 newly diagnosed cases, 1.4 million prevalent cases, and 273,000 deaths worldwide in the year 2002, more than 80% occurred in the low- and medium-resourced countries of South Asia, East Asia, sub-Saharan Africa, and Latin America (Table 1) [3]. In developing countries, a large proportion of cervical cancers are diagnosed in advanced stages, with poor rates of survival (Figure 1) [4].

Primary prevention of a disease requires warding it off before the pathogenic process can occur. In the case of cervical cancer, this would require that infection of the cervix with HPV (a necessary although not sufficient cause of cervical cancer) be prevented. It could be achieved either by complete abstinence from sexual activity or with a vaccine. Secondary prevention stops the progression of disease once it has already started. A good example of secondary prevention is cytologic screening to detect cervical cancer precursors, followed by treatment to prevent progression to cancer.

There have been no randomized trials to evaluate the impact of screening on cervical cancer incidence and mortality, and all data on the effect of screening have come from cohort and case-control studies. However, the marked reduction in the inci-

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

Region	Cancer of the cervix		
	No. of cases	No. of deaths	5-year prevalence
Worldwide	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

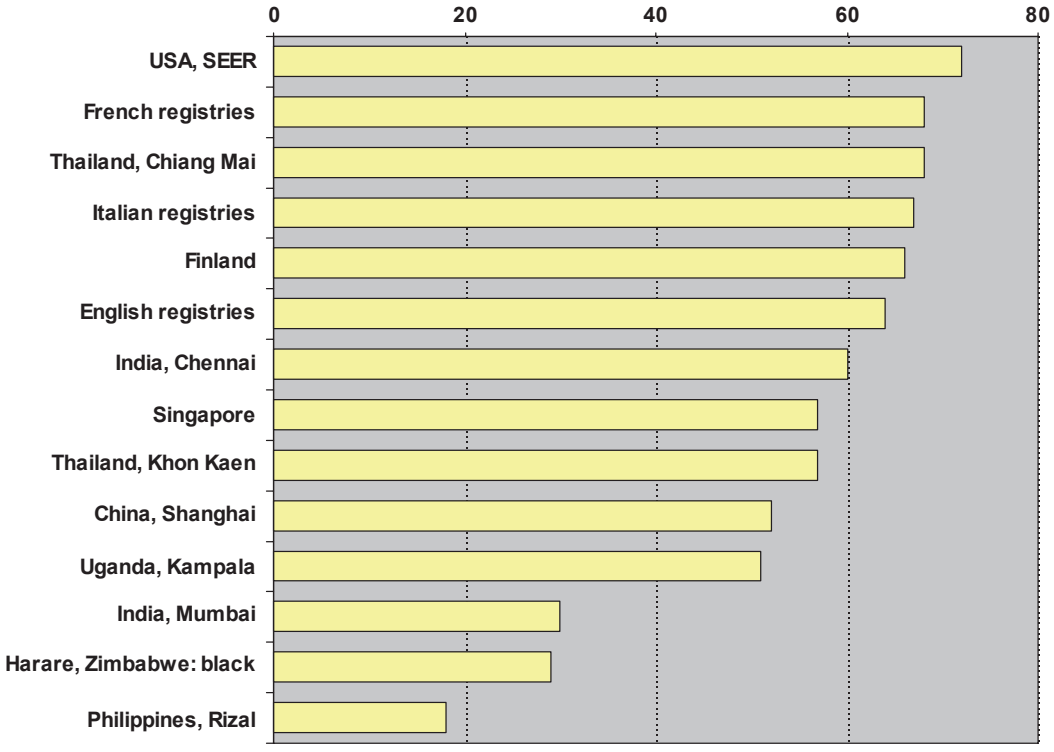

Figure 1 Cancer of the uterine cervix: 5-year relative survival around 1990. SEER indicates Surveillance, Epidemiology and End Results program.

dence of and mortality from cervical cancer following the introduction of cytologically based screening programs in a variety of developed countries has been interpreted as strong nonexperimental support for organized cervical cancer screening programs [5].

A comprehensive analysis of data from several of the largest screening programs in the world con-

ducted by the International Agency for Research on Cancer (IARC) and published in 1986 showed that well-organized screening programs were effective in reducing cervical cancer incidence and mortality [5]. In the Nordic countries, following the introduction of nationwide screening in the 1960s, cumulative mortality rates for cervical cancer showed a falling trend. The greatest fall was in Iceland (84% from 1965 to 1982), where the screening interval was the shortest and the target age range the widest. The smallest reduction (11%) was in Norway, where only 5% of the population had been part of organized screening programs [6]. In Finland, Sweden, and Denmark the falls in cumulative mortality were 50%, 34%, and 27%, respectively. The greatest reduction in cervical cancer incidence was in women aged between 30 and 49 years, for whom the focus of screening was the most intense.

The association between mortality trends and coverage of the female population by organized screening was found to be most pronounced when the proportional reductions in the age-specific rates were related to the ages targeted by the screening programs. The age-specific trends indicated that the *target age range* of a screening program was a more important determinant of risk reduction than the *frequency* of screening within the defined age range. This finding was in agreement with the estimates of the IARC working group, that for screening intervals of up to 5 years, the protective effect of organized screening was high throughout the targeted age group ($>$80%) [7]. It is therefore apparent that the success or failure of screening programs in decreasing cervical cancer incidence and mortality is largely reflected in (1) the extent to which the population at risk is screened; (2) the target age of women screened; and (3) the reliability of cytology services used in the programs.

Screening tests for cervical cancer such as cytologic evaluation, visual tests, and tests for HPV infection are all capable of identifying women with a high probability of having cervical intraepithelial neoplasia (CIN), squamous intraepithelial lesions (SIL), or preclinical invasive cancer. The objective of cervical screening is to prevent invasive cervical cancer by detecting and treating women with CIN 2/3 lesions (high-grade cervical cancer precursor lesions), and the effectiveness of screening is evaluated by the reduction in cervical cancer incidence and mortality observed following screening. The critical components of cervical screening are the following: screening tests of good quality and, in screen-positive women, prompt diagnostic investigations such as colposcopically directed biopsies; appropriate treatment; and post-treatment follow-up to detect persistence or recurrence of disease. Ensuring high levels of participation, sufficient health care infrastructure and human resources, and linkage of the critical screening components in an organized fashion are essential for the success of screening programs [8]. The inability to implement effective cytologic screening and the perceived lack of applicable alternative approaches have delayed the introduction of cervical cancer prevention programs in developing countries by several decades.

2. Cytologic screening

Cervical cancer prevention efforts worldwide have so far relied on screening sexually active women with conventional cytologic tests to detect precancerous lesions, and then treating the lesions. Cytologic screening involves the collection of cervical cells, slide preparation, staining, reading, and finally reporting. It therefore requires a laboratory infrastructure; trained cytotechnologists and pathologists for processing slides and reporting; internal and external quality control; and a system for communicating the results to the women. High-quality training, continuing education, and proficiency testing of personnel are essential to ensure reliable testing. When all these requirements are addressed, cytologic testing has been shown to be moderately sensitive and highly specific in detecting CIN 2/3 lesions. However, in most routine settings, the testing has been shown to be poorly sensitive — with a wide sensitivity range — in detecting cervical neoplasia. In recent reviews, the sensitivity to detect CIN 2/3 lesions ranged from 47% to 62% and the specificity from 60% to 95% [1,9—11]. In several cross-sectional studies from developing countries assessing the accuracy of cytologic screening, the sensitivity varied between 44% and 78% and the specificity between 91% and 96% [12].

In most developing countries, cytologic screening is accessible only to a relatively small proportion of women relying mostly on private-sector providers. For instance, in a large country such as India, currently fewer than 1,000,000 cervical smears are taken annually. A lack of adequate financial resources and trained staff, effective referral mechanisms and adequate laboratory facilities, and an adequately developed health care infrastructure for diagnosis and treatment, along with many competing healthcare priorities, have hampered the organization of effective cytologic screening programs in resource-poor countries. Cytology-based screening programs were introduced from the 1960s to the 1980s in Cuba, Mexico, Chile, Brazil, Costa Rica, Peru, and other developing countries in South and Central America, but these programs have had min-

imal or no impact on the cervical cancer burden probably because they were largely unorganized [2]. Too few women receiving testing, diagnosis, and treatment; suboptimal quality of testing, with no quality control; low level of financial coverage; and low follow-up participation on the part of the women at risk have contributed to the apparent failure of these programs. In Peru, a recent study found that only 23% of the screen-positive women had adequate diagnostic work-up and treatment, as required [13].

The apparent lack of impact of cervical cytology programs and the difficulties in organizing such programs in low- and medium-resourced countries have prompted 2 developments in recent years. One is the search for affordable and effective alternative screening tests and the other concerns the reorganization of programs and the more effective utilization of resources in countries such as Chile, Costa Rica, and Brazil [2,8,14]. Program reorganization of in Chile has been associated with some decline in cervical cancer mortality in recent years [14].

The notification of results to women, as well as the 3 visits (1 each for testing, diagnosis, and treatment) required for cytologic screening, have posed major programmatic and logistic challenges. Therefore, one of the guiding principles has been to evaluate simple, inexpensive alternative tests that allow the screening and treatment processes to be completed in 1 or 2 visits.

3. Visual screening

The need for optimal cervical screening tests, and the fact that most of the precancerous and early cancerous lesions are visible to the naked eye after application of diluted acetic acid and Lugol's iodine solution, have prompted an extensive evaluation of visual screening tests in comparison with conventional cytologic assessment in recent years. Visual inspection after application of a 3% to 5% solution of acetic acid (VIA) — also known as direct visual inspection (DVI), the acetic acid test (AAT), or cervicoscopy — is the most widely evaluated visual screening test. A higher concentration of intracellular proteins in cervical neoplasia leads to the dense acetowhitening effect following the acetic acid application.

VIA involves naked-eye inspection of the uterine cervix, lit up by a bright torch light or a halogen focus lamp, 1 to 2 minutes after diluted acetic acid has been applied by means of a cotton swab or a spray. A positive VIA test result is characterized by well-defined acetowhite areas close to the squamocolumnar junction (SCJ) or by the white color of a cervical growth or the entire cervix [15]. Anything that does not meet the criteria of a positive test result, including the absence of acetowhite lesions; faint, ill-defined, translucent acetowhite areas; faint acetowhitening of endocervical polyps; nabothian cysts; acetowhite dots; and prominent SCJ is categorized as negative. Acetowhitening is not specific to cervical neoplasia and may occur in immature squamous metaplasia and in inflamed or regenerating cervical epithelium. Acetowhite areas associated with CIN are localized in the transformation zone and are usually well demarcated and dull white, and early cancerous growths turn intensely opaque.

VIA is an easy-to-learn, inexpensive method that requires minimal equipment rather than a laboratory infrastructure and yields real-time results — making it possible to diagnose and treat in the same session. Physicians, nurses, midwives, and paramedical health workers can be rapidly trained to provide VIA in courses of 5 to 10 days [16]. Motivated providers can learn the practice of VIA with the help of manuals, atlases, and the wide range of teaching materials now available for training personnel [15—17]. For all these reasons, VIA shows promise as a viable and implementable method of secondary prevention of cervical cancer in low-resource settings.

The test characteristics of VIA have been evaluated in several cross-sectional studies in developing countries. These studies involving together more than 150,000 women have reported promising results, supporting VIA as an alternative to cervical cytology in these settings. The sensitivity of VIA to detect CIN 2 and 3 lesions and invasive cervical cancer varied from 49% to 96% and the specificity varied from 49% to 98% in these studies [1,12]. Conventional cytologic assessment was concurrently evaluated in most of the studies, and VIA sensitivity was found to be similar to that of the cytologic assessment or better although its specificity was found to be consistently lower. However, many of these studies suffered from the verification bias that occurs when only a subset of the screened individuals is subject to diagnostic reference investigations (against a “gold standard”) to establish final disease status. Thus, the estimates for sensitivity and specificity must be corrected to account for individuals with unknown final disease status. Most studies evaluating visual testing for cervical neoplasia have reported sensitivity rates greater that 60% and specificity rates greater that 70% for the detection of high-grade cervical neoplasia. After adjusting for the effects of verification bias, pooled estimates regarding the sensitivity and specificity of VIA to detect high-grade CIN ranged between 62% and 80%

for sensitivity and between 77% and 84% for specificity.

Whether low-level magnification (a magnification of 2 to 4) could improve the diagnostic accuracy of VIA by eliminating a proportion of false-positive appearances due to squamous metaplasia and inflammatory conditions has been investigated in cross-sectional studies [12]. However, magnification did not improve the test performance above naked-eye viewing and no improvement in the detection rate of high-grade lesions or cancers was observed using magnification.

Visual inspection with Lugol's iodine (VILI) involves naked-eye examination to identify mustard-yellow areas on the cervix after application of the solution. VILI depends on the interaction between iodine and glycogen. The columnar epithelium does not change color after iodine application. On the other hand, a healthy mature squamous epithelium is characterized by an abundance of glycogen and turns dark brown or black following application of iodine, whereas abnormal squamous epithelium contains little or no glycogen and takes on a mustard-yellow color. The VILI test results are reported immediately after application of iodine. A positive result is based on the definite appearance of a mustard-yellow area on the cervix close to the SCJ, or the os, or on a cervical growth [15].

Recently VILI was evaluated in cross-sectional studies in India, sub-Saharan Africa, and Latin America [20,21]. A multicenter study in India and Africa involving approximately 49,000 women concurrently evaluated VIA and VILI by independent providers using a common protocol [20]. The pooled sensitivity and specificity to detect high-grade CIN were 92% and 85%, respectively, for VILI vs. 77% and 86% for VIA — indicating a higher sensitivity for VILI but similar specificity for VILI and VIA in this study. In contrast, in a Latin American study involving about 3000 women, VILI was found to have a sensitivity of 53% and a specificity of 78% to detect high-grade CIN [21].

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 with treatment of screen-positive women [22,23]. In this approach, screen-positive women without clinical evidence of invasive cancer, and satisfying the criteria for ablative therapy, are immediately treated with cryotherapy without confirmatory colposcopic or histologic investigations. The safety, acceptability, and feasibility of the single-visit approach combining VIA and cryotherapy has been demonstrated in a study in rural Thailand [22]. Of 5999 women tested by trained nurses using VIA, 798 (13.3%) had positive results. And of 618 women eligible for immediate cryotherapy, 609 (98.5%) accepted the treatment. Overall, 756 women received cryotherapy (either immediately or later), with no major complications recorded, and only 33 (4.4%) of the treated women returned for a perceived problem. At the 1-year follow-up visit, the rate of negative VIA test results was 94.3%. This program has been expanded in several provinces in Thailand.

Recently, a randomized controlled trial involving 6550 women in South Africa reported on the safety and efficacy of 2 screen-and-treat approaches (visual screening followed by cryotherapy or HPV testing followed by cryotherapy) for cervical cancer prevention [23]. All participants were screened using HPV testing or VIA and then randomized to 1 of 3 groups: cryotherapy for those who had a positive HPV test result; cryotherapy for those who had a positive VIA test result; or delayed treatment regardless of the result of the VIA or HPV test. Six months after randomization, the prevalence of histologically confirmed CIN 2/3 lesions (there were no cancers) was significantly lower in the 2 screen-and-treat groups compared with the delayed-treatment group. At 6 months, CIN 2/3 was diagnosed in 0.8% of the women in the HPV DNA group (95% confidence interval [CI], 0.4—1.2%) and 2.2% (95% CI, 1.5—2.9%) in the VIA group compared with 3.6% (95% CI, 2.7—4.4%) in the delayed-treatment group ($P < 0.001$ and $P = 0.02$ for the HPV and VIA groups, respectively). A subset of women underwent a second colposcopic examination 12 months after enrollment. At 12 months the cumulative detection of CIN 2/3 was 1.4% (95% CI, 0.8—2.0%) in the HPV DNA group, 2.9% (95% CI, 2.1—3.7%) in the VIA group, and 5.4% (95% CI, 4.3—6.5%) in the delayed-treatment. No major complications were reported in this study.

A recent study that assessed the cost-effectiveness of a variety of cervical-cancer screening strategies in India, Kenya, Peru, South Africa, and Thailand reported that screening women once in their lifetime, at the age of 35 years, with a 1-visit or 2-visit screening and treatment strategy involving VIA, reduced the lifetime risk of cancer by approximately 25% to 36% and cost less than $500 per year of life saved [24]. Relative cancer risk declined by an additional 40% with 2 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, according to the Commission on Macroeconomics and Health. The study concluded that VIA and treatment in 1 or 2 clinical visits is one of the cost-effective alternatives to conventional 3-visit cytology-based screening programs in low-resource settings.

4. Conclusion

Although a working group of the IARC concluded that the evidence for VIA and VILI is only limited [1], fairly consistent findings in cross-sectional studies, randomized trials, and cost-effectiveness studies indicate that visual tests are useful early detection tests for cervical neoplasia in low- and medium-resourced clinical settings, particularly where good-quality cytologic and HPV testing is not available. However, adequate training and close monitoring of testing is essential to ensure the quality of the visual test.

HPV testing is the most reproducible of all cervical screening tests and is a promising new technology for cervical cancer prevention. 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. However, HPV testing is currently more expensive (20–30 US$) than other screening tests and requires sophisticated laboratory infrastructure that includes testing equipment, storage facilities for samples, and trained technicians. These requirements make HPV testing nonviable in developing countries at this stage. Lower testing costs and less sophisticated infrastructure and equipment requirements are essential to make HPV testing feasible in low-resource settings.

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