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## COMMENTARY

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# Screening and Management of PreCancerous Lesions To Prevent Cervical Cancer in Low-Resource Settings

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### Abstract

Cervical cancer is a leading cause of cancer death among women in low-resource settings, but it is completely preventable by screening for and treating precancerous lesions. In this article, the current approaches to screening, confirmation, and treatment of precancerous lesions of the cervix are reviewed from the perspective of low-resource settings. Cervical cytology is compared to visual inspection with acetic acid (VIA) for screening women to detect precancerous lesions. The use of colposcopy to confirm findings in women with positive screening test results and various treatment methods are discussed. With one examination, cytology appears to detect fewer precancerous lesions than VIA, but VIA has a lower specificity and labels proportionately more women falsely positive. When available, colposcopy may be used to obtain directed biopsies from abnormal areas of the cervix to pathologically confirm the findings in women with positive screening tests. Treatment with cryotherapy appears to be a safe, acceptable, and effective procedure for the majority of precancerous lesions. Lesions that are not suitable for cryotherapy because of endocervical canal involvement or large size are amenable to outpatient treatment by loop electrical excision procedure (LEEP). HIV/AIDS and immune system suppression are associated with more rapid CIN progression and HIV-positive women generally have high recurrence rates of CIN after treatment. Women *tempora* may more readily transmit the virus after cryotherapy and, therefore, they require counseling regarding abstinence and condom use. Highly active antiretroviral therapy (HAART) may cause CIN to regress and may decrease the risk of cervical cancer in HIV-infected women. Cost-effectiveness modeling using South African data shows that use of a single lifetime VIA test and immediate cryotherapy saves costs compared to cytology or to no screening. VIA and cryotherapy are appropriate services for low-resource settings. Colposcopy and LEEP services should be available on a referral basis.

**Key Words:** Screening - cervical cancer - cervical intraepithelial neoplasms - low-resource settings - prevention - colposcopy - cryotherapy - LEEP

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### Introduction

More than 80 percent of the 470,000 new cases of cervical cancer identified annually occur among women in developing countries and cervical cancer kills nearly 200,000 women in these countries every year (Ferlay et al., 2001). This inequity is particularly tragic because precancerous lesions exist for approximately 15 years during which time cervical cancer could be readily prevented if low-resource countries possessed more effective programs aimed at screening for and treating precancerous lesions. Precancerous lesions are precursors of cancer and are variously referred to as cervical intraepithelial neoplasia

(CIN), squamous intraepithelial lesions, or dysplasia. Few women in developing countries have access to effective screening and treatment for CIN. Consequently, years later they may develop cervical cancer from untreated precancer and present at an advanced stage with symptoms. At the Eldoret Hospital in Kenya for example, 95 percent of patients presenting with symptoms of cervical cancer are FIGO (International Federation of Gynecology and Obstetrics Staging System) stage II and above (Were and Buziba, 2001). This paper discusses the current understanding of the natural history of cervical neoplasia and the screening and treatment interventions that are effective for cancer prevention.

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## Natural History of Cervical Cancer

Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide and is the primary cause of cervical cancer (Koutsky, 1997). There are over one hundred types of HPV, but only certain types are oncogenic. The cumulative lifetime incidence of acquiring oncogenic types of HPV is 70 to 80 percent in many countries, but less than 10 percent of these women develop precancerous lesions or cervical cancer. However, the risk of more severe lesions increases with age (Koutsky, 1997). Where resources are limited, screening for precancerous lesions should be attempted once or twice in a woman's life between the ages of 30 and 50 years (Sankaranarayanan et al., 2001).

## Key Components in an Effective Cervical Screening Program

Women's participation in screening, test accuracy and reproducibility, rapidity with which results are available, and test acceptability and affordability to women influence the effectiveness of a cervical cancer prevention program (Herdman and Sherris, 2000). Screening is performed on asymptomatic women in the attempt to identify women who are at increased risk of having precancerous cervical lesions. By discovering lesions before they become cancerous, the treatment needed is much less invasive, and cancer can be avoided.

A major factor influencing the success of any cervical prevention program is the willingness of women at risk to be screened. Without adequate participation rates among the women at risk (called program coverage), the screening, treatment, follow-up, and subsequent impact of a screening program is weakened. The vaginal examination is a potential barrier that program planners and providers need to be aware of, since many women feel embarrassed, ashamed, or fearful (Dzuba et al., 2002).

High test sensitivity (its ability to correctly identify abnormal) is important if women are to be screened only once or twice in their lifetime. High test specificity (its ability to correctly identify normals) is important in ensuring that women are not falsely labeled as diseased, causing them unnecessary anxiety and wasting scarce health care resources on unnecessary diagnostic and treatment procedures. In order to assure equity of service delivery, tests should be reproducible, meaning that results can be replicated reliably in various settings.

The length of time it takes to obtain test results greatly impacts program success. If results are available within two hours of screening, women can be adequately counseled and those with positive tests can be offered immediate management that may include further examination, treatment, or referral, as appropriate. This prevents the loss to follow-up that typically occurs if women are asked to return at a later time for results of their screening test. Lastly, screening and management must be affordable to women

and the health care system.

## Cervical Cytology

Conventional cytology (Pap smear) has been used successfully for over 50 years in developed countries to reduce cervical cancer incidence and mortality. Given adequate resources and within the context of a well-organized screening program, cytology can be a practical, affordable, and accurate screening method. An additional advantage is that a cytology slide provides a permanent record that can be referred to for quality control purposes. However, a systematic overview and meta-analysis have shown that even in expert hands, cytology has a sensitivity of 51 percent for identifying CIN of any grade or cancer, and a specificity of 98 percent (AHCPR, 1999). The high specificity of cytology means that very few normal women are falsely labeled as positive. But on the other hand, the low sensitivity means that women must be screened periodically to ensure that precancerous lesions are eventually identified. Most developing countries lack microscopes and trained laboratory pathologists and technologists to read smears. In addition, inadequate information systems and delays with transporting specimens and reports also pose challenges. For these reasons, implementing effective cytology-based screening programs is not feasible for the foreseeable future in most developing countries. The difficulty of providing high-quality cytology-based services is what has prompted interest in alternative screening approaches.

## Visual Inspection with Acetic Acid (VIA)

Screening using VIA is based on the naked-eye identification of abnormal epithelial tissue, especially precancerous lesion, which turn white one minute after washing the cervix with 3 to 5 percent acetic acid (vinegar). The acetowhite areas are caused by the coagulation of cellular proteins that are increased in precancerous cells. Equipment needed includes a good light source (torch), vinegar, cotton swabs, a vaginal speculum, and examination gloves. Results are scored as VIA-negative, VIA-positive, or suspicious for cancer (Sellors et al., 2002).

Two methodologically rigorous, cross-sectional studies on a total of approximately 4,000 women showed that the sensitivity and specificity of VIA for biopsy-proven CIN 2 or 3 are approximately 74 percent and 69 percent, respectively (U. of Zimbabwe/JHPIEGO Cervical Cancer Project, 1999; Belinson et al., 2001). Only about 1 in 7 of all VIA-positive women had CIN 2 or 3 (U. of Zimbabwe/JHPIEGO Cervical Cancer Project, 1999; Belinson et al., 2001). Major advantages of VIA are that minimal supplies and equipment are required, training of providers can be accomplished in one week, and nurses and midwives can perform and interpret this screening test (Sellors et al., 2003). The screening test result is immediately available, making it theoretically possible to provide treatment, if necessary,

or to plan further management at the same visit. VIA and cytology both rely on considerable quality-control mechanisms for optimal performance, and in expert hands, the reproducibility of VIA is similar to cytology (Sellors et al., 2002).

## Colposcopy

Ideally, women with positive screening test results (cytology, VIA) would then have a diagnostic examination by colposcopy to confirm the presence of a lesion and to determine how the lesion should be treated. Sometimes this is not feasible, and a single-visit approach for screening and immediate cryotherapy of screen-positive women may be used (Goldie et al., 2001; Gaffikin et al., 2003).

Colposcopy is the magnified visual examination of the ectocervix, the transformation zone, the squamocolumnar junction, and the lower endocervical canal. The cervix is washed with 3 to 5 percent acetic acid solution and then inspected using binocular magnification (4X to 20X) with a variable light source. The primary purpose of colposcopy is to rule out the presence of cervical cancer and to guide the taking of a biopsy of any abnormal-looking tissue. A colposcopist should keep a permanent record and a drawing of the cervical findings on every patient. A colposcopy service requires expensive, fragile equipment that needs maintenance, electrical power, providers with specialized training, surgical instruments, and pathology services (Sellors and Sankaranarayanan, 2003).

During colposcopy, the cervix is first washed with normal saline and carefully inspected, usually under high power with a green filter, for abnormal blood vessels underlying the epithelium. Next, the cervix is washed with 3 to 5 percent acetic acid and inspected at least one minute later for any abnormal acetowhite areas in the transformation zone or the columnar epithelium. As a last step in the examination, Lugol's iodine can be applied to the cervix and the cervix inspected as was done with acetic acid. Abnormal areas are graded according to their color density, borders, blood vessels, and whether they take up a dark brown stain when Lugol's iodine is applied to the cervix (Sellors and Sankaranarayanan, 2003).

## Treatment

Cryotherapy is a first-line method of choice for women diagnosed with precancerous cervical lesions (Castro et al., 2003). To perform cryotherapy, a health care provider, using a vaginal speculum, applies acetic acid or, preferably, Lugol's iodine to the cervix to clearly outline the borders of the lesion. A metal probe that becomes very cold due to the passage of a refrigerant gas through it, is placed on the ectocervix, covering the transformation zone. The cervical tissue is frozen (at less than -40 degrees Celsius) and thawed twice during the 15-minute procedure to eradicate the lesion. Women generally are requested to return to the health facility for a check-up approximately 3 months and 1 year after the

cryotherapy. There are mild side effects, which include mild cramping, profuse, watery vaginal discharge for about 1 month, and spotting or light bleeding for 1 to 2 weeks. Cryotherapy is easily taught to providers, it is inexpensive, and it is 80 to 90 percent effective in treating even high-grade precancerous lesions (CIN 2 and 3) (Castro et al., 2003). While cryotherapy can be used to treat most lesions, it should not be used to treat lesions that extend into the endocervical canal and is less effective for large lesions that cover more than 3 quadrants of the cervix (Sellors and Sankaranarayanan, 2003).

LEEP, also referred to as large loop excision of the transformation zone, is an alternative to cryotherapy. LEEP uses a thin wire, electrified with a high frequency, high voltage current, to excise the entire transformation zone and part of the endocervical canal. LEEP is more versatile than cryotherapy, since LEEP can be used to treat large lesions and lesions that extend up to 1.6 cm into the endocervical canal. It is 90 to 95 percent effective in treating precancerous lesions, but in contrast to cryotherapy, LEEP requires more extensive provider training and has a slightly higher risk of side effects and complications, such as severe bleeding. LEEP requires an electrosurgical generator, a smoke evacuator, and the injection of local anesthetic into the cervix. Since a tissue specimen is always obtained, it is an opportunity for pathologic confirmation of the diagnosis and adequacy of excision (Sellors and Sankaranarayanan, 2003).

Cold cone biopsy is a surgical procedure that is performed in a hospital by a gynecologist with a special scalpel and general anesthesia. Cold conization removes the entire circumference of the transformation zone and most of the cervical canal. It is an alternative to cryotherapy and LEEP and is especially useful if a lesion extends past 1.6 cm into the endocervical canal and is not amenable to LEEP. When microinvasive cancer (FIGO stage I a) is suspected, cold conization is commonly used to examine the tissue in the endocervical canal to gauge the maximum depth and extent of invasion in order to plan the appropriate therapy. Cone biopsy may lead to serious complications, including bleeding, infection, and (rarely) spontaneous miscarriage or prolonged labor due to cervical stenosis.

## HIV is an Important Consideration

Because of the high prevalence of HIV infection in many low-resource settings, it is important to note the association of HIV infection and the degree of immune suppression with more rapid progression of CIN (Abercrombie and Korn, 1998; Chirenje et al., 2002). Additionally, HIV-positive women generally have high recurrence rates of CIN after treatment and should be followed up closely. Highly active antiretroviral therapy (HAART) may cause CIN to regress and may decrease the risk of cervical cancer in HIV-infected women (Moore et al., 2002). Often the HIV status of a patient or their partner is not known, so providers need to educate women about minimizing the risk of HIV transmission during the one month that the cervix takes to heal after

treatment. Advising abstinence and the provision of condoms are sensible practices at the time of counseling for treatment of precancer (Sellors and Sankaranarayanan, 2003).

## Cost Modeling can Aid Program and Policy Development

Mathematical modeling of the cost effectiveness of a single lifetime screening is one way to estimate what the costs and consequences would be if different screening strategies were used in low-resource settings where HIV-1 is endemic. Using South African data, VIA screening of women at age 35 years, followed by cryotherapy of screen-positive women without colposcopic confirmation, would reduce the incidence of cervical cancer by 26 percent and be a cost saving compared to doing nothing. A cytology-based program would have reduced incidence by 19 percent at a cost of \$81 per year of life saved (Goldie et al., 2001). While findings from cost modeling can provide valuable insights, a variety of medical, ethical, cultural, and practical considerations also are important in making appropriate decisions regarding allocation of scarce health resources.

## Conclusions

Adequate coverage of women aged 30 to 50 (the age group generally at increased risk of CIN 2 and 3) is essential to maximize the impact of any prevention program on cervical cancer incidence and mortality rates. VIA has advantages over conventional cytology as a cervical precancer screening strategy in low-resource settings. Women who are VIA-positive may be treated immediately at the same visit or referred for colposcopic confirmation prior to treatment. Ablation of precancerous lesions by cryotherapy can be performed by nurses and is effective treatment for most lesions, except those that are too large or those that involve the endocervical canal. As an adjunct to referral services for colposcopy, LEEP can be used by physicians to excise precancerous lesions that are not suitable for cryotherapy. Careful follow-up to detect treatment failure is essential. Cold conization and hysterectomy require the use of general anesthesia and an operating theatre and are seldom necessary for the treatment of precancerous lesions if cryotherapy and LEEP services are established (Ngwalle et al., 2001). HIV/AIDS and its implications regarding CIN progression and recurrence rates and post-treatment transmission of the disease itself must be taken into consideration when developing screening and treatment protocols. Finally, mathematical modeling of costs of different screening strategies in South Africa suggests that VIA can be a cost-saving strategy.

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