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Commentary

Prevention of Cervical Cancer in Africa: A Daunting Task?

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ABSTRACT

Africa has a high estimated incidence of cervical cancer, thus requiring the development of an effective prevention strategy. Cytology-based screening is beyond the capacity of many African countries, hence the need for alternatives. Visual inspection of the cervix after application of 3-5% acetic acid (VIA) is a promising screening test, with similar sensitivity to that of cytology but lower specificity. The same accounts for other VIA methods using magnification devices, visual inspection after the application of Lugol's iodine, or human papilloma virus (HPV) DNA testing, all proposed alternatives to cervical cancer prevention screening tests. Vaccination against HPV is the most promising strategy for the prevention of cervical cancer, but a wider variety of HPV types than currently being investigated must be considered for the development of the multivalent vaccine preparations required in Africa. Other considerations in developing an effective prevention programme include full public sector investment and achieving acceptability of a vaccine against a sexually transmitted infection targeted for adolescents. Unfortunately, however, if HPV vaccines are developed the initial impact of prophylactic vaccines will be delayed for many years. Alternative strategies should, therefore, be promoted in parallel. There are several approaches to cervical cancer prevention and their evaluation should be comprehensive and coordinated to achieve short and long-term public health benefits in different programme settings. (*Afr J Reprod Health* 2003; 7[2]: 7-12)

RÉSUMÉ

Prévention du cancer du col en Afrique: une tâche intimidante? Il y a une haute incidence estimée du cancer du col, exigeant ainsi l'élaboration d'une stratégie de prévention efficace. Le dépistage à base cytologique est au-dessus de la capacité de bien de pays africains, ce qui justifie la nécessité des alternatifs. L'inspection visuelle du col suite à l'application de 3-5% d'acide acétique (IVA) demeure un test de dépistage prometteur dont la sensibilité est identique à celle de la cytologie, mais qui a une spécificité plus faible. Voilà ce qui justifie les autres méthodes IVA qui se servent des mécanismes de grossissement de l'inspection visuelle suite à l'application de la solution de Lugol ou du virus de papillome humain (VPH), du test d'ADN, tous les alternatifs aux tests de dépistage pour la prévention du cancer du col qui ont été proposés. La vaccination contre le VPH est la stratégie la plus prometteuse pour la prévention du cancer du col, mais il faut étudier une plus grande variété de types VPH pour mieux développer la production polyvalente des vaccins dont a besoin en Afrique. D'autres considérations à l'égard de l'élaboration d'un programme efficace de la prévention comprennent un investissement dans le secteur public et le succès au niveau de l'acceptabilité d'un vaccin contre une infection sexuellement transmissible qui vise les adolescents. Malheureusement, pourtant, si les vaccins VPH sont élaborés, l'impact initial des vaccins prophylactiques sera retardé pour beaucoup d'années. Il faudrait donc promouvoir d'autres stratégies en parallèle. Il y a plusieurs approches à la prévention du cancer du col et il faut que leur évaluation soit compréhensive et coordonnée pour réaliser à court et à long terme des bénéfices de la santé publique dans des cadres des divers programmes. (*Rev Afr Santé Reprod* 2003; 7[2]: 7-12)

KEY WORDS: Cervical cancer, prevention, screening, cytology, visual inspection, HPV, DNA detection, health awareness, vaccines

INTRODUCTION

Cancer of the cervix is the most common cancer among women in the developing countries. It accounts for more than 80% of all cases worldwide.¹ Africa as a region has one of the highest incidence rates in the world, and five of the seven countries with the highest rates are in eastern or southern Africa.² The number of deaths from cervical cancer worldwide is estimated at 230,000 per year.³ Many of those who die are relatively young women, as the peak incidence occurs among women in their forties. Mortality is highest in countries that are least equipped to deal with the problem. Many patients in Africa come for examination when the tumour is far advanced and inoperable, radiation is rarely available, and even palliative care is often of poor quality.

Although cervical cancer is preventable with early diagnosis and treatment, in many

developing countries it has been difficult to establish and maintain effective screening programmes.⁴ Initiation and maintenance of cytology-based screening programmes involving sexually active women every 1-5 years have probably resulted in a large decline in cervical cancer incidence and mortality over the last 40-50 years in many industrialised countries.⁵ However, implementing such programme in areas with inadequate health service coverage and low appreciation of preventative medicine means first overcoming issues such as access to the population, acceptability and availability of the screening examinations, quality of the specimen collection and evaluation, follow-up and treatment, the considerable cost and resource implications, and demands of competing health needs.

NATURAL HISTORY

Cervical cancer generally develops slowly over a period of 10-15 years. It is preceded by detectable and treatable precursor conditions in which certain cells in the cervix develop abnormal characteristics but are not yet cancerous. Broadly known as cervical dysplasia, these pre-cancerous abnormalities are classified according to severity. One classification system refers to the abnormal conditions as cervical intraepithelial neoplasia (CIN), while under a newer system (the Bethesda system), they are known as squamous intraepithelial lesions (SIL). Low grade SIL includes early cellular abnormalities and mild dysplasia (comparable to CIN I). Low grade SIL regresses spontaneously in about 60% of women within two to three years and generally does not require treatment. High grade SIL (comparable to CIN II or III) is more likely to progress to cancer if untreated; 30-70% progresses to invasive cancer within 10 years and, therefore, generally requires treatment. These factors are important to consider in planning a screening and treatment programme, particularly where resources are limited.

HUMAN PAPILLOMA VIRUS AND OTHER RISK FACTORS

A causal link between human papilloma virus (HPV), a sexually transmitted infection (STI), and the development of cervical cancer has been established. It is estimated that over 99% of cancers worldwide contain HPV DNA.⁶ Commonly accepted risk factors for HPV and, hence, for cervical cancer include a history of other STIs, early onset of sexual activity, more than one sexual partner and/or a partner with more than one sexual partner. Other possible cervical cancer risk factors include early childbearing, high parity, tobacco use, use of oral contraceptives, genital schistosomiasis and nutritional factors such as low intake of vitamins A, C, E, carotenoids and folate.^{7,8} Some of the other cervical cancer risk factors identified are closely interrelated, making it difficult not only to assess the relative importance of these factors but also to know whether they have an independent effect. Both genital HPV and HIV are STIs and may interact, but the nature of such interaction has not been determined. Most studies show an association of HIV with HPV and SIL, but published data from Africa do not (yet) support an increased risk of cervical cancer in women with HIV. However, prospective studies show an association between

HIV and persistent HPV, leading to possible subsequent development of cervical dysplasia.⁹

CERVICAL CYTOLOGY SCREENING

Cervical cytology is considered to be a very specific test for high-grade precancerous lesions or cancer. Even if the quality of collection and smearing of cells, fixation and staining of smears, and reporting by well-trained technicians and cytopathologists is good, its sensitivity of around 60% is still relatively moderate.^{5,10} A high screening frequency is then needed to detect a missed high grade lesion during the subsequent rounds, and a screening frequency of once every one to five years has considerable cost and resource implications. Women found to have low grade lesions typically are asked to return for a follow-up smear every six months so that progression or regression of the abnormality can be monitored. Women who have a high grade lesion are then evaluated using a colposcope and biopsy to confirm diagnosis before treatment is initiated. Colposcopy services in low resource settings are often insufficient to meet the demand. Furthermore, colposcopes may not always function properly, they are expensive and not easy to repair or replace. Follow-up is often problematic due, for example, to transportation difficulties of specimen; long delays between screening, diagnosis and treatment; inability to contact women with abnormal cytology results; and difficulty in convincing women of the need for further evaluation and treatment.

Data on demand and acceptability of cervical cytology screening programmes are rare. A South African anthropological study found that the common perception is that a cervical smear is primarily diagnostic and not preventative. The general perception that cancer of the "womb" is inevitably fatal also made this a powerful disincentive to be screened for many women.¹¹ Few women in a study in Kenya were aware that early diagnosis and treatment of pre-cancerous lesions greatly improve the probability of a successful cure and prevention of cancer.¹² Often, limited information is provided to women and as a result they may have wrong perceptions. In addition, there might be cultural barriers including fear of pelvic examinations, and there is the issue of general accessibility and quality of health care services including routine gynaecological care. It is common to find clinics that are without trained personnel and laboratories. They may also not have fresh water, electricity, slides, spatulas and many of the other basics that are necessary for cytology-based screening programmes.¹³

Cytology Alternatives

Several recent studies have demonstrated that direct visual inspection of the cervix with acetic acid 3B5% (VIA) is a reliable, reasonably sensitive and cost-effective alternative to

cytology screening.^{10,14,15} VIA using magnification devices and visual inspection after the application of Lugol's iodine are being investigated.¹⁶ It requires a lower level of infrastructure and provides immediate results and possibility to treat immediately. However, the relatively low specificity, possibly related to high prevalence of STIs, is a problem with danger of over-treatment.¹⁷ Another unknown factor is how well VIA performs when genital schistosomiasis is prevalent. Standardised initial training and continuing education programmes including supervision and mechanisms for quality control will need to be developed if wide scale VIA screening is to be introduced. There is also no study yet showing that a VIA screening programme reduces cervical cancer incidence and mortality.

HPV DNA testing of health worker obtained cervical samples has sensitivity for detection of high grade lesions or cervical cancer that is equivalent or superior to that of cytology. A recent South African survey indicated that HPV testing of self-administered vaginal swabs was as sensitive as cytology screening for detecting high grade cervical disease in women aged 35 years and above.¹⁸ HPV detection in urine specimens is another promising method removing the obstacle on the need for a gynaecological examination.¹⁹

HPV DNA testing is also not (yet) cheap. Theoretically, the polymerase chain reaction (PCR) needed is not a difficult technique and generates large amounts of target DNA by using known oligonucleotide primers and heat stable DNA polymerase. It is a very sensitive technique, which is also its drawback. Contamination of specimens in the laboratory can be a major problem, hence the need to use positive and negative controls. The sensitivity of PCR throws up another problem: minute quantities of viral DNA can be detected. Is a positive result for high-risk HPV based on a tiny amount of DNA as clinically significant as a positive result from a larger amount of DNA remains an unanswered question.

As with VIA, HPV testing also has the disadvantage of relatively low specificity compared to cytology.¹⁷ Studies are needed to evaluate carefully the medical and programmatic side effect of over-treating significant numbers of women without cervical disease and the efficacy of outpatient modalities when performed by mid level health care workers in the absence of colposcopic guidance in a low resource setting. Moreover, to determine the comparative cost-effectiveness of the different screening tests and approaches in reducing mortality from cervical cancer in low resource settings, formal cost-effective modelling using country-specific costs needs to be performed.¹⁰

What should not be forgotten is that health education and promotion, as well as behavioural change programmes directed at HIV and other STIs might equally prevent cervical cancer, although the evidence is inconclusive.^{20, 21}

Treatment

For cervical cancer screening to result in reduced morbidity and mortality, effective treatment and/or follow-up must also be available. In many resource poor settings, the only treatments available at present are cold knife cone biopsy and hysterectomy. Use of these methods certainly results in severe over-treatment of many women. They are associated with significant complications and side effects and require significant infrastructural support for anaesthesia, equipment and in-patient care, and they are costly. Of interest for use in low resource settings (due to their effectiveness, low incidence of side effects, low cost, lack of requirement for general anaesthesia and relatively technical simplicity) are loop electrosurgical excision procedure (LEEP) and cryotherapy. Cryotherapy destroys abnormal normal cells by using a low temperature probe (-60° to -90°C) to freeze the transformation zone. Liquid nitrogen or carbon dioxide are the most commonly used refrigerants because they produce sufficiently low temperatures and are readily available and inexpensive, particularly carbon dioxide. Cryotherapy causes virtually no bleeding and little or no pain. A recent study from rural Thailand showed that a single visit approach with VIA and immediate cryotherapy appears safe, acceptable and feasible.²² The most common side effect of cryotherapy is profuse watery discharge for 2-3 weeks, and women are at risk for infection until the epithelium is completely healed. Another disadvantage of cryotherapy is that a specimen is not obtained for histological evaluation. The disadvantages of LEEP or excision of the epithelium with cauterisation are the requirements for electricity, the higher costs along with the technical expertise required compared to cryotherapy, and the risk of bleeding complications. Studies are needed to establish the efficacy of cryotherapy and LEEP when performed without colposcopy.

Vaccines

Given the long record of viral vaccines as a cost-effective approach to preventing life-threatening infections, an effective vaccine directed against the major oncogenic HPV types could have tremendous impact on the global cervical cancer burden, particularly if made available to developing countries. In many developing countries, it has been difficult to establish and maintain effective screening programmes. On the other hand, these countries have, in many instances, developed comprehensive vaccination programmes, which, with appropriate adjustments, could prove to be instrumental in cervical cancer prevention.

There is growing consensus that a safe, effective and accessible prophylactic and possibly curative HPV vaccine will offer the best solution to significantly reduce cervical cancer mortality especially in resource poor countries. There is consensus that virus-like particles (VLP) are the immunogens of choice for prophylactic vaccines.²³ Recombinant viral L1 capsid protein from HPV, which contains no viral DNA and is therefore non-infectious and safe, forms virus-like particles. VLPs stimulate the production of antibodies that bind and neutralise the infectious virus, and studies in animal models indicate that protection

induced by prophylactic immunisation is efficacious, long-lasting and type-specific. Human trials with L1 VLPs have shown safety, excellent tolerability and high immunogenicity. A recent randomised controlled trial of a HPV type 16 VLP vaccine reduced the incidence of both HPV-16 infection and HPV-16 related CIN.²⁴ However, vaccine candidates currently under evaluation are mainly targeting HPV types 16 and 18, which account for the majority of cancer cases in industrialised countries. Limited epidemiological data available suggest that a much wider variety of HPV types are involved in the pathogenesis of cervical neoplasia in developing countries.²⁵⁻²⁸ All these HPV types must be considered for the development of multivalent vaccine preparations capable of inducing an immune response to a variety of HPV vaccines. As this is unlikely to be very profitable, public sector commitment and spending are needed. The fact that HPV infection is a sexually transmitted infection may pose an obstacle to the acceptance of a prophylactic HPV vaccine. Positioning an STI vaccine raises sensitive social issues especially when it will be targeted at adolescents to ensure protection before the onset of sexual activity. Meanwhile, effective HPV vaccines are not yet available, and if they are developed the initial impact of prophylactic HPV vaccines will be delayed for ten or twenty years, while the existing infections continue to progress to cancer.

CONCLUSION

Prevention of cervical cancer in Africa seems daunting, even overwhelming, but the scale of the problem means we cannot ignore it. Instead, a practical and pragmatic strategy is required.

There are several approaches to cervical cancer prevention, and only their comprehensive and coordinated evaluation will deliver short and long-term public health benefits in different programme settings. Cytology-based screening programmes for cervical cancer have not been a success; they are difficult to initiate and perhaps even more difficult to maintain. The choice of a screening test in countries that plan to initiate new programmes should be based on the comparative performance characteristics of the test, costs, technical requirements, the laboratory and local health infrastructure, and awareness and perceptions within the community. In very resource poor countries, of which there are many in Africa, this might lead to a minimum package of a one-visit strategy of VIA with immediate cryotherapy treatment once in a lifetime, e.g., in the high risk age group of women between 35 and 50 years. This strategy ignores the low specificity of VIA and accepts over-treatment. However, advocates of this approach will point out that cytological and colposcopic services are unlikely to become available in many resource poor settings in the foreseeable future. They also believe that invasive cervical cancer represents a serious health problem for women, which needs to be dealt with immediately. The development and testing of the efficacy and effectiveness of vaccines directed against the major oncogenic HPV types for cervical cancer in Africa has high priority.

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