

Cervical Cancer Prevention in Low-Resource Settings

This policy statement has been prepared by The Society of Obstetricians and Gynaecologists of Canada, The Society of Gynecologic Oncology of Canada, and The Society of Canadian Colposcopists, and approved by the Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To help care providers understand the current status of cervical cancer in low-resource countries.

Options: The most effective and practical options for cervical screening and treatment in low-resource countries are evaluated.

Outcomes: Improvement in rates of prevention and early detection of cervical cancer in low-resource countries.

Evidence: PubMed or Medline, CINAHL, and The Cochrane Library were searched for studies published in English between January 2006 and December 2009. Results were restricted to systematic reviews, randomized control trials/controlled clinical trials, and observational studies. Grey (unpublished) literature was identified through searching the websites of health technology assessment and health technology assessment-related agencies, clinical

practice guideline collections, clinical trial registries, and national and international medical specialty societies.

Values: The quality of evidence was rated using the criteria described in the Report of the Canadian Task Force on Preventive Health Care. Recommendations for practice were ranked according to the method described in that report (Table).

Recommendations

1. All girls 9 years old or over should have access to the cervical cancer vaccine before they become sexually active. (I-A)
2. Cervical cancer screening by visual inspection with acetic acid is suggested for low-resource settings acceptable. Cervical cytology or human papillomavirus testing may also be used when practical. (II-2B)
3. Cryotherapy is a safe, effective, and low-cost therapy that should be included in pre-invasive cervical cancer treatment. (III-B)
4. All countries should have a documented cervical cancer prevention strategy that includes public education built on existing outreach programs. (III-C)
5. Countries should define a centre or centres of excellence for the management of cervical cancer. (III-C) Because these units would serve a larger population, they would be able to identify leaders and develop their skills, and would be able to invest in costly radiation equipment.
6. All women with cervical cancer should have access to pain management. (III-C)

INTRODUCTION

Cervical cancer is the third most common cancer in the world, with 2.3 million prevalent cases and 510 000 incident cases each year.¹ Annually, 288 000 women die of cervical cancer, and 80% of these deaths occur in low-resource countries.² Much has been written about maternal mortality, but little is said about mortality from cervical cancer, even though the rates are very similar. Nearly two thirds of healthy years lost by women in developing countries are lost because of cervical cancer and not, as is often supposed, because of problems related to reproductive health.³ This is particularly disturbing because cervical cancer is a preventable disease.

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Human papillomavirus is the causative agent for cervical cancer. Women come into contact with the virus usually through sexual encounters. The low-risk HPV types like 6 and 11 cause genital warts. The oncogenic or high-risk HPV types like 16 and 18 result in cellular changes (dysplasia) that, if not identified through screening and treated, may result in cervical cancer. Exposure can be minimized through vaccination of young women. Vaccination is most effective if given to young women before they become sexually active (primary prevention). Precancerous cellular changes can be identified through screening, assessment of test-positive cases, and treatment (secondary prevention). The goal of secondary screening is to prevent cancer, but it may also identify cervical cancer at an earlier stage, which will increase the likelihood that treatment will be successful. Many women in low-resource countries die from cervical cancer because it is not identified until symptoms appear. These may include vaginal bleeding, foul smelling discharge, pelvic or leg pain, or kidney failure. The likelihood that cervical cancer will be cured once symptoms occur is much lower than when the disease is identified at an earlier stage. This policy statement reviews the spectrum of cervical disease from primary prevention to palliation.

VACCINATION

The development of carcinoma of the cervix is related to the persistence of one of the oncogenic types of HPV.⁴ Vaccination against HPV sub-types 16 and 18 has the potential to prevent up to 70 % of invasive cancers of the cervix worldwide.⁵ Both a bivalent vaccine (16, 18) and a quadrivalent vaccine (6, 11, 16, 18) are currently commercially available.

Efficacy of vaccination is best when the vaccine is given prior to the onset of sexual activity and prior to exposure to HPV. Vaccines do not appear to influence pre-existing infections.⁶ Cross reactivity of the vaccine in preventing persistent infection with less common but closely related oncogenic vaccine strains has been shown and may provide an improvement in expected efficacy.⁷

The major barrier to vaccination implementation in the developing world is cost. Even if the cost of vaccination is lowered, the price is well beyond the health budgets in much of the developing world. Many non-government organizations are working towards providing vaccine access for the developing world:

In December 2006, the World Health Organization released a set of guidelines to help health workers around the world prepare for the vaccine's introduction, noting that the mobilization of "resources for strengthening health systems and purchasing human papillomavirus vaccines, both nationally and internationally, must be a priority and there must be innovative ways to finance HPV (vaccine) introduction."⁸

Recommendation

1. All girls 9 years old or over should have access to the cervical cancer vaccine before they become sexually active. (I-A)

CERVICAL SCREENING

Secondary prevention for cervical cancer involves identifying women with cervical intraepithelial neoplasia 2/3 and treating it to prevent the occurrence of cancer. Currently available tests include cytology evaluation, visual tests, and tests for HPV infection. It is recognized by both the World Health Organization and the Alliance for Cervical Cancer Prevention that in settings of limited resources, the best public health strategy will encompass (1) age specific screening, at least once in a woman's lifetime⁹ and (2) follow-up and treatment for those with positive screening results.

There are several recognized obstacles to cytology-based screening, including the need for required laboratory infrastructure, trained specialists for processing and reporting, quality control, and a system of communication to the women screened so that they may receive sufficient treatment. The necessity for multiple visits with cytology-based screening results in significant loss to follow-up.¹⁰⁻¹²

Improved cost-effectiveness has been observed with direct visual inspection.^{10,11} Visual inspection after the application of 3% to 5% acetic acid solution on the cervix does not require any laboratory structure. Sensitivity is consistent with or better than conventional cytologic testing. However, specificity is lower, and there is a risk of overtreatment.¹³⁻¹⁵ VIA is easy to learn, and health care workers can be trained

ABBREVIATIONS

ACCP	Alliance for Cervical Cancer Prevention
CIN	cervical intraepithelial neoplasia
VIA	visual inspection with acetic acid

Table 1. Key to evidence statements and grading of recommendations, using the ranking of the Canadian Task Force on Preventive Health Care

Quality of evidence assessment*	Classification of recommendations†
I: Evidence obtained from at least one properly randomized controlled trial	A. There is good evidence to recommend the clinical preventive action
II-1: Evidence from well-designed controlled trials without randomization	B. There is fair evidence to recommend the clinical preventive action
II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group	C. The existing evidence is conflicting and does not allow to make a recommendation for or against use of the clinical preventive action; however, other factors may influence decision-making
II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category	D. There is fair evidence to recommend against the clinical preventive action
III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees	E. There is good evidence to recommend against the clinical preventive action
	L. There is insufficient evidence (in quantity or quality) to make a recommendation; however, other factors may influence decision-making

*The quality of evidence reported in these guidelines has been adapted from The Evaluation of Evidence criteria described in the Canadian Task Force on Preventive Health Care.⁴²

†Recommendations included in these guidelines have been adapted from the Classification of Recommendations criteria described in the The Canadian Task Force on Preventive Health Care.⁴²

within 5 to 10 days.¹⁶ In low-resource countries, VIA is the best option for cervical cancer testing.

HPV testing currently has limited use in low-income countries. It requires laboratory infrastructure, trained technicians, and storage facilities. However, HPV testing offers a reproducible profile of women who are at high risk of developing precancerous or cancerous lesions. When used alone, or in combination with VIA, HPV DNA testing has shown great promise.^{17–19} A large cluster randomized trial conducted in India, addressed the role of screening in women 30 to 59 years old. The trial consisted of 4 groups: women screened by cervical cytology, by VIA, or by HPV testing, and a control group. Only HPV testing was seen to significantly reduce the number of cervical cancers and the number of deaths (HR 0.52; 95% CI 0.33 to 0.83).²⁰ Over an 8-year period, there was no significant reduction in numbers of advanced cervical cancers or deaths with a single cytology test or VIA. (Likely the lower sensitivity and specificity of cytology or VIA would require more frequent testing to rule out false negative cases.) Efforts are underway to develop an affordable rapid biochemical HPV test (careHPVtest, Qiagen), with improved sensitivity and almost immediate results that would enable single-visit disease prevention.

Recommendation

2. Cervical cancer screening by visual inspection with acetic acid is suggested for low-resource settings acceptable. Cervical cytology or human papillomavirus testing may also be used when practical. (II-2B)

TREATMENT OF DYSPLASIA

Screening will have no benefit unless it is followed by effective treatment for those with disease. Conventional treatment for CIN consists of local ablative therapies such as cryotherapy, laser ablation, and excisional methods such as loop electrosurgical excision procedure, laser cone, and cold knife cone biopsy. These procedures have been proven to be equally effective in treating CIN. The choice of modality depends on the size and severity of the lesion, costs, procedure simplicity, patient preferences, and the ability to analyze a tissue specimen.²¹ In general, patients treated with ablative therapy should have no evidence of invasive disease and no suspicion of glandular disease. They should also have concordant cytology and histology, and it must be possible to visualize the entire transformation zone.

Conventional cervical screening programs in industrialized countries have been very successful in preventing cervical cancer; however, these programs are impractical and unaffordable in low-resource settings. Women in many developing countries have limited access to health services because they live far away from health centres and cannot leave their homes or cannot afford to pay for travel. The proportion of women who are screened but do not return for treatment is reported to be as high as 80%, which interferes with the effectiveness of the cervical screening program.²² These women need access to treatment options that are safe, effective, and affordable. These options must be practical and sustainable and must take into account local resources, geography, and disease prevalence. One

safe, acceptable, and cost-effective approach to cervical cancer prevention in low-resource settings is the “screen and treat” or “single-visit approach.”^{10,23–25} This uses a detection method, such as visual inspection of the cervix with acetic acid followed by an immediate treatment with cryotherapy for all eligible women. It has a high acceptance rate by patients.²⁶ Efficacy has been demonstrated by both a low occurrence of lesions on follow-up VIA and a reduction in the lifetime risk of cancer.

Cryotherapy is a safe and effective method of treating precancerous lesions and can be delivered by a range of health providers, including non-physicians (e.g., trained nurses and midwives).^{24,25} It is generally less effective for severe lesions and those that cover $\geq 75\%$ of the cervix and/or extend into the endocervical canal. Women with these lesions should be referred to a colposcopy clinic for evaluation and alternative treatment.

In summary, using a screening test followed by cryotherapy has the advantage that precancerous lesions can be resolved at the primary care level without the need for sophisticated equipment or highly specialized medical personnel. This approach also ensures that women receive immediate treatment and reduces the chance that they will be lost to follow-up care, which often occurs as a result of multiple referrals and referrals to secondary level care centres.

Recommendation

3. Cryotherapy is a safe, effective, and low-cost therapy that should be included in pre-invasive cervical cancer treatment. (III-B)

SCREENING PROGRAM

In order to mount an effective screening program, several conditions must be met.²⁷ First, to warrant screening, it should have been shown that cervical cancer is prevalent in the population and that there is interest in screening. Second, the screening test should be accurate, practical, acceptable, highly sensitive (those with disease are most likely to have a positive test), and highly specific (negative test means there is no disease), and it should have a high predictive value (those with a positive test are most likely to have disease). Several screening tests are available that range in sensitivity and specificity and cost. In a large randomized trial, Sankaranarayanan et al.²⁰ have shown that a single lifetime screening using HPV testing followed by intervention for test-positive cases can prevent cervical cancer. Third, to be efficacious, treatments must have a high compliance rate and should prevent the cancer. All forms of treatment for CIN prevent cervical cancer. Cryotherapy is the most cost-effective treatment. Fourth, the program

should reach a high proportion of the women for whom it is intended. Finally, the health care system should be capable of coping with screening and treatment of test-positive cases. In implementing a cervical cancer screening program, it is important that specific plans be developed according to resources, culture, beliefs, and health care systems.

Recommendation

4. All countries should have a documented cervical cancer prevention strategy that includes public education built on existing outreach programs. (III-C)

CANCER

The rates of cervical cancer in developed countries are 5 per 100 000 women compared with 25 per 100 000 in low-resource countries. The high mortality rates are due to the advanced stage at presentation, affected women being unable to complete therapy, lack of available treatment, and unaffordable therapy.²⁸

The WHO has promoted the development of tertiary care centres providing surgery and radiotherapy, including brachytherapy. It considers the management offered by these tertiary centres to be the only recommended treatment for cervical cancer, with surgery confined to early (stage I) cancers and performed by surgeons trained in gynaecologic cancer care.²⁹ It also recommends that radiotherapy, including brachytherapy, be considered for all stages of cervical cancer. Hypofractionation—radiation treatment in which the total dose of radiation is divided into large doses and treatments are given less than once a day—can stop bleeding and offer significant pain relief in advanced cancer when oral morphine is logistically impractical and impossible to administer.

The International Atomic Energy Agency's Programme of Action for Cancer Therapy in collaboration with the WHO and International Agency for Research in Cancer has been active in providing radiotherapy technology and expertise to low- and middle-income countries. These resources are essential to the implementation of a cancer control program.³⁰ The International Atomic Energy Agency recently completed a project in Tanzania, one of the world's 10 poorest nations, setting up a centre of excellence for the treatment of cancer patients.³¹ This involved the purchase of a single radiotherapy machine to treat 20 000 new cancer patients per year. The cost for the cobalt machine and the training of staff was $> \$1$ million.³²

In summary, it is essential to develop a cancer control strategy that incorporates cancer screening and diagnosis

and treatment of pre-invasive and invasive cancers. It is also critical to incorporate a palliative care program for pain management. Radiotherapy plays a critical role not only in the treatment of advanced cancers but also in the palliative setting.³³

Recommendation

5. Countries should define a centre or centres of excellence for the management of cervical cancer. (III-C)
Because these units would serve a larger population, they would be able to identify leaders and develop their skills, and would be able to invest in costly radiation equipment.

PALLIATIVE CARE

In low-resource countries, women with cervical cancer usually present at an advanced stage, when curative treatment is not an option. In this situation there are issues that require health care team input.³⁴ Pain related to nerve impingement or bony metastases can be managed with anti-inflammatory medication and, if that is not effective, with long-acting opioids. Significant vaginal bleeding can be managed by palliative radiation. Foul smelling vaginal discharge can be minimized with oral or vaginal metronidazole suppositories. Urinary obstruction can be managed with urinary stents, but patients should be informed that intractable pain, bleeding, and discharge may be averted or minimized if no intervention is made and death results from uremia.

Recommendation

6. All women with cervical cancer should have access to pain management. (III-C)

CHALLENGES IN IMPROVING EXISTING PROGRAMS AND INITIATING NEW ONES

Considerable resources and a high level of program coordination are needed to implement a widespread cervical screening program with components expected in industrialized countries: testing, treatment, quality assurance, follow-up, and information dissemination. These programs are impractical and unaffordable in a low-resource setting, but women in these settings deserve access to safe, effective, and affordable services to prevent cervical cancer. If these services are to be provided, it is important to understand the strengths and weaknesses of any existing cervical cancer prevention program and the capacity of the health system in general before planning interventions and providing benchmarks against which to measure change. The following must be taken into consideration.

1. Competing Health Needs

Developing countries have the significant burden of many diseases that must be managed within a limited public health care budget. For example, in 2002, the leading cause of death in sub-Saharan Africa was infectious disease (e.g., AIDS and malaria) followed by maternal or perinatal complications. Together they were responsible for approximately 70% of all deaths in women.³⁵ Unfortunately, countries in this region, have also some of the world's highest death rates from cervical cancer, for example, 67 per 100 000 people in Harare, Zimbabwe and 40.8 per 100 000 in Kampala, Uganda.³⁶ Other regions with high cervical cancer mortality rates are in Central and Latin America, where the proportional mortality due to cervical cancer is as high as 53.5 per 100 000 in Haiti.³⁷

2. Limited Human and Financial Resources

Under-developed primary health care structures and limited financial, equipment, and human resources are major problems in most countries in Eastern and Southern Africa and Central America, which are the regions with the highest incidences of cervical cancer.

Cervical cancer prevention services include counselling, a screening test, and pre-cancer treatment for women who test positive, which must be provided by trained and competent medical personnel. Resources must be designated to the program if it is to provide consistent and reliable services and continuity of care over time.

3. Lack of Understanding and Limited Commitment

In many countries, the burden of disease from cervical cancer is underestimated because of unreliable/incomplete record keeping. As well, there is also a poor understanding of the considerable benefits of effective prevention through screen-and-treat programs. Changing this situation requires support from national policy-makers (ministries of health and politicians) to improve national programs. Integrating cervical cancer prevention services with existing services will prevent the creation of programs that are difficult to sustain without significant external funding. Involvement of local stakeholders is vital to ensure that the program meets the needs of individuals and communities. Starting with a program in a small defined area is more practical and more likely to succeed than a nationwide launch. A small scale limited approach allows better monitoring of quality of care and adaptation and refinement of systems for the local setting.

4. Political Instability

Transition between governments in low-resource countries often implies significant changes in national policies. Such changes (especially after an election) can result in reversals or modifications of policy decisions and can destabilize the implementation of a cervical screening program.

5. Dedicated Staff

After a project is initiated, local staff are often highly motivated to recruit and screen large numbers of women. When the screening program is integrated into routine services, a larger number of staff may have responsibility for screening. At this point, the service quality can become inconsistent, especially if there is no program leader. Designated program funding is necessary to maintain dedicated staff who manage the services and facilitate consistency. This also ensures high-quality screening and maintenance of skills.

6. Geographical

A challenge in initiating a program is achieving high coverage over a wide area. Success is more likely if a program begins by focusing on a small geographic area, which will allow better coverage and assessment of the program's feasibility and performance before expansion.

7. Insufficient Resources to Provide Treatment for the Additional Newly Diagnosed

Implementing a successful cervical cancer prevention program, targeted to unscreened populations, will substantially increase the number of known cancer cases. In most low-resource settings, there are limited resources to deal with this increased cancer load. Even if cancer treatment is unavailable initially, there is still a significant benefit to implementing a screening program and managing precancerous disease.

8. Sociocultural

Cervical cancer is caused by a sexually transmitted virus. Diagnosis may be accompanied by a stigma because it may be assumed that people who have sexually transmitted infections are promiscuous. Other social issues are the hesitancy of women to have a pelvic examination with a speculum, especially when the examination is performed by a male health care provider. Promoting the value of cervical cancer screening and dispelling myths should involve both the general population and the health care providers.

SUCCESSSES

The benefits secondary prevention of cervical cancer using cervical screening have been known for several decades. Despite this, cervical cancer is the second leading cause of death, with 80% of cases occurring in low-resource countries. A breakthrough in strategies to prevent cervical cancer in this environment came in 1999, when the Alliance for Cervical Cancer Prevention was formed. Five organizations made up this alliance: EngenderHealth, The International Agency for Research on Cancer, Jhpiego (an international non-profit health organization affiliated with Johns Hopkins University), The PanAmerican Health Organization and Program in Advanced Technology in Health.^{38,39} They defined the key research questions and began advocating for greater global and nation interest. There was progress in the following 4 areas:

1. Screening

The ACCP reinforced the importance of oncogenic HPV testing as the most sensitive and specific test but determined that technical and infrastructure requirements would make it difficult to implement. Work moved forward on the development of a low-cost rapid HPV screening test. One of the landmark pieces of work at this time was the cost-effectiveness study by Goldie et al.¹⁰ that looked at cervical cancer screening strategies in India, Kenya, Peru, South Africa, and Thailand. The most cost-effective strategies were those requiring fewer visits, once in a lifetime screening at age 35 years, using VIA or DNA test. This led to a 25% to 36% decrease in lifetime risk of cervical cancer at a cost of < \$500/per year of life saved.⁴⁰ In the interim, a large study in India and Africa showed that VIA has equivalent sensitivity to but lower specificity than cytology.¹⁵ Sankaranarayanan et al.⁴⁰ identified the importance of working on a defined project in a defined area.

2. Treatment

The single visit approach of screen and treat with cryotherapy is preferable to the multi-visit protocol.

3. Community Outreach

A cervical screening program should be built on existing outreach and community education programs that provide health and prevention messages, and it should include community leaders and generate community involvement.

4. Advocacy

Developing recognition of the problem will help get commitment to solve it. The ACCP has shown that creativity and flexibility with a well-focused use of resources

can decrease the burden of cervical cancer in low-resource countries.⁴¹

This document is intended to help care providers understand the current status of cervical cancer in low-resource countries, from prevention to screening, management of pre-invasive and invasive disease, and palliation. Partnerships between Canadian health care providers and their compatriots in other countries can improve care for women who are affected or who are at risk of being affected by oncogenic HPV.

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