
Memoranda/Mémorandums

Cervical cancer control in developing countries: Memorandum from a WHO meeting*

This memorandum summarizes the report of a WHO Consultation on the Control of Cervical Cancer in Developing Countries, held on 6–7 November 1994, in New Delhi, India. Evaluated was the current situation with regard to cervical cancer and the relevance of current practices in screening. New pragmatic approaches to cervical cancer were proposed that are relevant for developing countries; this includes empowerment of women to come forward, and visual inspection—"downstaging".

Introduction

Size of the problem

Cervical cancer is the commonest form of cancer that affects women in virtually all developing countries and the second commonest form of cancer that affects women in the world. Globally, there are an estimated 450 000 new cases each year, with 300 000 deaths. If the undiagnosed, early cases are taken into account, the number of new cases each year would be 900 000 worldwide. This is approximately the same as the total number of new cases of acquired immunodeficiency syndrome (AIDS) among males and females each year, but in contrast to AIDS, large numbers of women with cervical cancer are usually ignored.

* This Memorandum is based on the report of a WHO Consultation on the Control of Cervical Cancer in Developing Countries, held in New Delhi, on 6–7 November 1994. The participants were as follows: P. Blake, London, England; A. Beltram, Tlalpan, Mexico; K. Chaudhry, New Delhi, India; Z.M. Chirenge, Harare, Zimbabwe; H.S. Cronjé, South Africa; D.K. Das, Delhi, India; F. Geldenhuys, Johannesburg, South Africa; M.K. Hakama, Tampere, Finland; J.B. Halil, Kuala Lumpur, Malaysia; C.M. Jagdish, Bangalore, India; H.C. Kitchener (*Rapporteur*), Aberdeen, Scotland; S.P. Kohli, New Delhi, India; S. Krishnamurthy, Karnataka, India; I.N. Mitra, Bombay, India; P. Naud, Porto Alegre, Brazil; I. Oliver, London, England; A.E. Prasad, Bangalore, India; N. Rehman, Dhaka, Bangladesh; C.R. Ramachandran, New Delhi, India; A. Roxas, Manila, Philippines; L.H. Samarage, Galle, Sri Lanka; A. Sehgal, New Delhi, India; L. Shamsuddin, Dhaka, Bangladesh; V. Singh, New Delhi, India; R.P. Symonds (*Rapporteur*), Glasgow, Scotland; E. Vallikad, Bangalore, India; F. Welsch, Bethesda, MD, USA; Z.M. Zain, Kuala Lumpur, Malaysia. *WHO Collaborating Centre:* A.B. Miller (*Chairman*), Toronto. *WHO Secretariat:* S. Nazeer (*Secretary*), J. Stjernswärd (*Co-chairman*).

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Reprint No. 5709

State of the art

Cervical cancer is both preventable and curable, provided it is detected at an early stage. In developed countries 80% of cervical cancer cases detected are cured because of early detection. However, in developing countries 80% of cervical cancer cases are incurable at the time of detection, if they are detected at all. Five out of six women with cervical cancer live in developing countries, which possess only 5% of the global resources for cancer control. There are few, if any, cytology screening programmes with a coverage sufficient to have an impact in developing countries; standard radiotherapy is often not available.

A realistic, pragmatic approach to cervical cancer control has to be sought for developing countries, coupled with the provision of curative therapy and palliative care and pain relief.^a Over the years WHO has advocated "downstaging" (visual inspection of the cervix) as a more realistic approach to active coverage in developing countries^{b,c} than, e.g., cytology screening; however, its sensitivity and specificity remain to be evaluated in controlled studies. One of the purposes of the consultation was to initiate and coordinate such studies. Another approach that is highly relevant in developing countries is to educate women about the early warning signals of cervical cancer and to inform them that the disease is curable if diag-

^a *National cancer control programmes: policies and managerial guidelines.* Geneva, World Health Organization, 1995.

^b **Stjernswärd J et al.** Plotting a new course for cervical cancer screening in developing countries. *World health forum*, 1987, **8**: 42–45.

^c **Stjernswärd J.** National training of radiotherapists in Sri Lanka and Zimbabwe: priorities and strategies for cancer control in developing countries. *International journal of radiation oncology, biology, physics*, 1990, **19**: 1275–1278.

Memorandum

nosed early enough.^d It is an open question as to what will come first — effective cytology screening coverage, as is the case in developed countries, or a vaccine for primary prevention. For a cost-effective, basic prevention programme it would seem rational to combine activities against sexually transmitted diseases (STDs), AIDS, and cervical cancer.

Problems

In developing countries the major problems associated with cervical cancer are the following: lack of knowledge among women about its symptoms; a fatalistic attitude towards cancer, in general, and lack of awareness about the possibility of a cure; shortage of health care facilities in rural areas, with often total lack of standard therapies; and male dominance and ignorance, combined with a low priority for women's health issues.

Early detection and screening have been successful in reducing morbidity and mortality from cervical cancer in some developed countries, but not in others. Lack of effect is most often due to poor management and implementation of inappropriate policies with mainly young women being screened and insufficient coverage of older women.^e

In most developing countries a purposeful coverage of all women at risk through cytological screening will not be possible for decades to come, because of the paucity of economic and technically competent manpower resources and inadequate quality assurance for smear tests.

Solution

Empowering women with knowledge about cervical cancer — its early warning signals, such as intermenstrual, postcoital or postmenopausal bleeding, foul discharge, its curability if diagnosed early — combined with the availability of adequate therapies could have a major impact. In developing countries the incidence of cervical cancer is often equal to mortality. Experience in Nordic countries shows that before the introduction of any formal cytology screening programme the proportion of advanced disease among invasive cancers decreased significantly when therapy became available and women had been made aware about the condition. Mortality decreased much more than that resulting from

the later introduction of cytology screening.^{d,f} In developing countries a major effect on cervical cancer would therefore be expected using such an approach.

Appropriate management and effective early detection and referral policies along with availability of standard therapy are vital for reducing morbidity and mortality from cervical cancer.

International Study Group

An International Study Group on the control of cervical cancer in developing countries has been set up to analyse and evaluate the feasibility and validity of various low-cost strategies for cervical cancer screening in low resource settings compared with cytology. The group aims, in particular, to emphasize the effect of health education and empowerment of women and of the clinical downstaging approach, which involves simple visual inspection of the cervix of asymptomatic women to detect cervical cancer at an earlier, curable stage. Most probably the study findings will be available long before a purposeful level of cytology screening coverage in the majority of developing countries. It is intended that the group will meet regularly to pursue its aims to develop protocols for improving early detection of cervical cancer in developing countries and hence increase the prospects of cure.

Objectives

The primary objectives of the study group are to compare the effect of health education, the empowerment of women with knowledge about cervical cancer, and visual inspection (downstaging) versus cytology and to evaluate the relative contributions of each.

The secondary objectives are shown below:

- to accelerate improvements by coordinating efforts;
- to evaluate scientifically health education materials for their effect;
- to produce education models and a visual tumour atlas jointly, in order to avoid duplication;^g
- to identify and support study participants;
- to standardize the study protocols;

^d **Stjernswärd J.** Downstaging — strategies for cancer control programmes in developing countries; *Cancer care*, 1994, 1: 11.

^e **Miller AB.** *Cervical cancer screening: managerial guidelines*. Geneva, World Health Organization, 1992.

^f **Portén J et al.** Strategies for global control of cancer. *International journal of cancer*, 1995, 60: 1–26.

^g *Cervical cancer screening: technical guidelines*, 2nd edit. Geneva, World Health Organization, 1996 (in press).

- to identify funding resources;
- to provide epidemiology and biostatistical support, which are essential for a conclusive study; and
- to provide a forum for regular meetings to establish protocols, exchange information, share experiences, and hold discussions in the presence of world experts.

A model protocol^h for a controlled randomized study was presented and agreed upon. It is designed to evaluate the applicability and cost-effectiveness of different approaches to the early detection of cervical cancer in developing countries, especially health education and cytology versus downstaging, and to evaluate the relative contribution of each.

Four study arms should be employed, with a sample size of at least 5000 women in each arm, targeting women aged 35–65 years. The intervention pattern in each arm is shown below.

- Arm I: Control arm.
- Arm II: Health education only (empowerment of women).
- Arm III: Health education + visual inspection.
- Arm IV: Health education + Pap-smears.

Country experiences

Outlined below is an analysis of the situation with regard to cervical cancer in selected countries.

United Kingdom

Until recently, the cervical screening programme in the United Kingdom had failed to have a significant impact on cervical cancer, largely because it comprised nonsystematic, opportunistic screening with too few women aged over 35 years being screened. This situation has now been turned around, however, by a government initiative that introduced computerized call/recall, tackled quality assurance in laboratories, and paid general practitioners for meeting coverage targets.

An overall fall in incidence of 15% had been reported recently, but a rise in incidence was being seen among young women. Unless the programme, which now costs US\$ 100 million per annum, results in a substantial reduction in deaths following these

initiatives, its credibility in terms of cost-effectiveness will be questionable. In considering the proposals for under-resourced countries it is relevant to keep the United Kingdom experience in mind, and avoid a dogmatic noneffective cytology screening as the only relevant solution for the very different situation that prevails in such countries.

South Africa

In South Africa as a whole, although the health infrastructure is good and the new government favours primary health care, the problems posed by distance, poor communication, and ignorance remain. While treatment and laboratory facilities were not problems, screening and follow-up coverage of the black population certainly were.

Cape Town. A protocol has been piloted in Cape Town, which is primarily designed to eliminate referral problems. The protocol involves an educational programme in the target area for 2–3 weeks backed up by a mobile clinic, where a trained nurse takes smears that are processed on the spot. If a high-grade cytological abnormality is found, colposcopy + acid solution and treatment by diathermy loop excision are performed. If a low-grade abnormality is found, a repeat smear is undertaken 6 months later. If the smear is normal, another is taken 10 years later (the national proposal is for smears at 30, 40, and 50 years of age). In the pilot project thus far, 86 abnormal smears were identified in 2600 screened women, the level that would be expected in the population involved. The project is currently being supported by an independent development trust.

Orange Free State. A parallel effort is being carried out in Orange Free State. Different methods of identifying precancerous lesions of the cervix were first evaluated in terms of cost, low expertise required, immediate diagnosis, as well as sensitivity and specificity. Of these, affordability and immediate diagnosis were held to be particularly important. Cytology, cervicography, and a clinical test involving application of a solution of acetic acid to the cervix were evaluated; of these, the acetic acid test had a higher sensitivity than the other two (though it was much less specific), as well as being cheap and instantaneous (Table 1).

The primary objective is to screen 80% of the target population over a 3-year period, beginning in one district. The protocol involves primary screening by acetic acid testing at 30, 40, and 50 years of age. If the primary test is abnormal, cervicography (held to be more cost-effective than repeat cytology) will be performed, and if the results are abnormal, treat-

^h *Prevention and detection of cervical cancer in developing countries: model protocol for a pilot study.* Unpublished WHO document CAN 1995.1.

Memorandum

Table 1: **Comparative sensitivity and specificity of cytology, cervicography and the acetic acid test, Orange Free State**

	Sensitivity (%)	Specificity (%)
Cytology	27	98
Cervicography	51	93
Acetic acid test	65	43

ment by colposcopy and diathermy loop excision will be carried out. Where resources were scarce, this could be scaled down to acetic acid testing, and if the results are abnormal, the cervix treated using cryosurgery, although its limited specificity (40–50%) would necessitate a large number of treatments.

India

It is important to emphasize that the Indian population is essentially rural, largely of low social class, many of whom are poorly informed in general and about health care in particular, especially women. Of India's population of approximately 900 million a total of 700 million cannot afford health care, and these are the very people who need to be targeted.

In India, cytology lacks sensitivity owing to the high incidence of cervicitis, and it was held that the South African approach could be a useful model.

Delhi. A team at the Indian Council for Medical Research (ICMR), Delhi, has undertaken cervical photography using a 300-mm lens. It is claimed that the photographs obtained are only slightly inferior to cervicography if a "ring"-type flash unit is used.

Bangalore. In Bangalore, a study was conducted over a 3-year period using visual inspection by a nurse as the means of early detection. If the nurse found that the cervix was abnormal, the woman was transferred to the primary health care (PHC) system. The aim was to achieve a downshift in cervical cancer stage by activating or mobilizing the PHC system.

Four interventions were instituted in four areas; the coverage of the target population was such that, of the entire targeted study population, 15.7% received education on cervical cancer and 7.8% had undergone visual inspection. The results demonstrated a very low population coverage and poor patient compliance. The number of cancers identified was in proportion to the population screened, but no results are yet available on downshifting. The reasons for noneffectiveness or noncompliance were ascribed to under-resourcing and the unwillingness of women to avail themselves of the programmes, as well as their refusal to be examined.

The factors in the PHC system that contributed to the poor coverage were lack of innovation and incentives, with the tasks of an already overworked PHC staff. The coverage was better at centres where the primary health care was being delivered by a local self-governing body rather than in the WHO/ICMR areas, where the existing PHC centres had to be used, with insufficient incentives for the staff (often the female medical officers) to collaborate actively in the study.

Nordic countries

Swedish and Finnish data show that cervical cancer deaths had fallen in these countries very significantly prior to screening, presumably due to better health awareness among women, which led to earlier stage presentation and availability of free treatment. The subsequent contribution of screening to a fall in mortality from the disease was much less. The finding that professional and public education had such a marked effect on cervical cancer mortality has an important message for developing countries, and in such countries health awareness and education should be priorities.

Prospective studies

Below are outlined details of various prospective studies on cervical cancer screening in selected countries.

Zimbabwe

In Zimbabwe most of the population lives in a rural setting, with district hospitals in the cities and primary health centres staffed by nurses all over the country. Most women live within 10km of such a clinic.

The study will involve recruiting 15 000 women, with 5000 in one of three arms; education intervention alone; education intervention and visual inspection; and education intervention and cytology. Any women in the first arm with symptoms of cancer will be examined for abnormalities. Each arm will function in a different part of Mashonaland Central province, an area containing a homogeneous population. It is planned to include also a control arm, i.e., with no health education intervention, in order to evaluate the effect of health education, which probably in itself could have a major impact.

United Kingdom

At the Royal London Hospital it is proposed to set up an integrated prostate and cervical cancer screen-

ing programme in association with the family planning clinic and the school education programme on the common risk factors for both these diseases and AIDS. The aim is to tackle the contribution of males to cervical cancer.

India

In Bombay a study has been designed to answer whether downstaging can be achieved. The aim is to change significantly the current distribution of cervical cancer from 70% in stages 3 and 4 to a level of 30%. The study will also investigate downstaging of oral and breast cancer. The sample size will be 35000, randomized to each arm.

In order to increase its cost-effectiveness, the study is linked to the expanded programme on immunization (EPI) in Bombay. A database of 1 million Bombay families currently exists and this will be used to identify a target population. Half the effort will be undertaken by dedicated health workers with the remainder being carried out by EPI staff.

The protocol involves randomization to one of two arms: either no intervention or visual inspection of the mouth, breast, and cervix annually for 5 years. The outcomes will be changes in disease stage and mortality. This is viewed as a study defining the effectiveness of downstaging.

Bangladesh

In Dhaka, it is believed that efforts on cervical cancer screening should revolve around gynaecologists and it is intended to compare the findings from visual inspection alone versus those from a non-intervention control group.

Philippines

In the Philippines, cervical cytology is too expensive for a nationwide programme and an alternative strategy was required. The Ministry of Health is producing a proposal to obtain funding from the World Bank based on a modification of the Zimbabwe protocol discussed above. A study design of three arms is planned: 15000 women per arm to evaluate visual inspection versus education, versus a combination of both these plus cervical cytology. The outcomes will include improvements in knowledge, coverage, and rates of detection of cervical cancer and cervical intraepithelial neoplasia.

Brazil

A planned study in southern Brazil will compare visual inspection plus cervical cytology versus visual

inspection alone, with 6000 women in each arm. Women would be screened every 3 years with a 5-year follow-up.

Malaysia

In Malaysia, cervical cancer control has been made a priority under the national cancer control programme. A protocol similar to that of Zimbabwe will be implemented in Kelantan State and a cervical cancer register established. It is intended to study a total of 15000 women aged 35–59 years. A fulltime position for 3 years for an epidemiologist–biostatistician has been created for this purpose.

Recommendations

- Cervical cancer needs to be recognized as a major but soluble, health problem among women in most developing countries.
- Empowerment of women through health education about cervical cancer, its signs and symptoms, and its curability could have a major impact. There is a great need to enhance women's awareness of their own reproductive health in order to make them come forward willingly for early detection tests and therapy.
- Appropriate management and effective early detection and referral policies along with availability of standard therapy are vital to reduce the morbidity and mortality from cervical cancer.
- Controlled studies to evaluate ways of most effectively empowering the women are urgently needed.
- In developing countries, downstaging cervical cancer by visual inspection and the possibility of achieving coverage with quality controlled cytology screening need to be evaluated.
- Early detection should not be carried out in isolation, and other clinical aspects should also be addressed simultaneously, such as the availability of treatment for any STDs found, treatable cancers, and incurable cases. Thus, clear policies, including referral systems, for therapy and palliative care should also be established.
- For an effective primary prevention approach, it seems rational to combine efforts against STDs, AIDS, and cervical cancer.

Résumé

Lutte contre le cancer du col utérin dans les pays en développement: Mémorandum d'une réunion de l'OMS

Le cancer du col utérin est la forme la plus fréquente de cancer féminin dans la quasi-totalité des pays en développement et, à l'échelle mondiale, la deuxième forme de cancer chez la femme. On dénombre chaque année dans le monde environ 450 000 nouveaux cas et 300 000 décès dus à ce cancer. Si on tient également compte des cas précoces non diagnostiqués, on arrive à au moins 900 000 nouveaux cas par an.

Cette affection est à la fois évitable et curable, à condition d'être détectée à un stade précoce. Dans les pays développés, 80% des cas détectés sont guéris grâce au dépistage précoce; en revanche, dans les pays en développement, 80% des cas ne sont pas détectés ou sont déjà incurables au moment de la détection.

Il est nécessaire de parvenir à une approche réaliste de la lutte contre le cancer du col utérin dans les pays en développement, approche qui doit être assortie de la fourniture d'un traitement curatif, de soins palliatifs et d'un traitement de la douleur. L'OMS encourage le dépistage précoce simplifié, par inspection visuelle du col utérin, comme alternative au dépistage cytologique pour la recherche active des cas dans les pays en développement. La sensibilité et la spécificité de cette approche doivent encore être évaluées lors d'études contrôlées; l'un des buts de la Consultation était de mettre en place et de coordonner de telles études. L'éducation des femmes concernant les signes d'alerte précoces du cancer du col et la possibilité de guérir la maladie si elle est diagnostiquée suffisamment tôt est également du plus grand intérêt dans les pays en développement.

L'autonomisation des femmes grâce à l'information sur le cancer du col utérin—portant sur les signes d'alerte précoces comme les saignements intermenstruels, postcoïtaux ou postménopausiques et les écoulements vaginaux malodorants, et sur la possibilité de guérir cette maladie si elle est diagnostiquée suffisamment tôt—associé à la possibilité de disposer de traitements appropriés, pourrait avoir un impact majeur sur la maladie. Dans les pays en développement, l'incidence du cancer du col égale souvent sa mortalité. En revanche, dans les pays nordiques, avant même l'adoption de tout programme officiel de dépistage cytologique, la proportion de cas avancés parmi les cancers invasifs a baissé de façon importante, plus encore qu'après l'adoption du dépistage, lorsqu'un traite-

ment est devenu disponible et que les femmes ont reçu une information sur la maladie. Dans les pays en développement, on pourrait par conséquent attendre d'une telle approche un important effet sur les cancers du col.

Un groupe d'étude international sur la lutte contre le cancer du col utérin dans les pays en développement a été constitué en vue d'analyser et d'évaluer la faisabilité et la validité de différentes stratégies à faible coût de dépistage du cancer du col dans un contexte de faibles ressources, par rapport au dépistage cytologique. Le groupe cherchait en particulier à souligner l'effet de l'éducation sanitaire et de l'autonomisation des femmes, et celui de l'approche consistant en un dépistage précoce simplifié, avec une simple inspection visuelle du col utérin chez les femmes asymptomatiques, afin de dépister le cancer du col à un stade précoce, et curable. Il est probable que dans la plupart des pays en développement, les résultats de l'étude seront disponibles bien avant l'introduction du dépistage cytologique à grande échelle.

Un protocole type pour les études randomisées contrôlées a été préparé et approuvé par les membres du groupe. Ce protocole vise à évaluer l'applicabilité et le rapport coût/efficacité de différentes approches de la détection précoce du cancer du col utérin dans les pays en développement, en particulier l'éducation sanitaire et le dépistage cytologique, par rapport au dépistage précoce simplifié, en vue d'évaluer leur contribution relative.

L'étude comptera quatre branches, avec des échantillons d'au moins 5000 femmes par branche, et sera axée sur les femmes sexuellement actives âgées de 35 à 65 ans, comme indiqué ci-dessous.

- Branche I: Lutte
- Branche II: Education sanitaire seule (autonomisation de la femme).
- Branche III: Education sanitaire + inspection visuelle.
- Branche IV: Education sanitaire + frottis et test de Papanicolaou.

Le groupe d'étude a formulé les recommandations suivantes:

- Le cancer du col utérin doit être reconnu en tant que problème de santé majeur mais soignable chez les femmes de la plupart des pays en développement.
- L'autonomisation des femmes, grâce à l'éducation sanitaire concernant la maladie, ses symptômes et ses possibilités de traitement, pourrait avoir un impact majeur sur les cancers du col. Il est indispensable d'améliorer l'information des femmes dans le domaine de la santé en matière de

reproduction afin de les encourager à se présenter pour des tests de dépistage précoce et à suivre un traitement.

- Une prise en charge appropriée, et une politique efficace de détection précoce et d'orientation, assorties de la possibilité de disposer d'un traitement standard, sont indispensables pour réduire la morbidité et la mortalité dues au cancer du col utérin.
- Il est urgent d'entreprendre des études contrôlées afin d'évaluer le moyen le plus efficace de mobiliser les femmes contre la maladie.
- Dans les pays en développement, il est nécessaire d'évaluer par des études contrôlées le dépistage précoce simplifié du cancer du col par inspection visuelle et les moyens de parvenir à une

bonne couverture par un dépistage cytologique de qualité suffisamment contrôlée.

- Le dépistage précoce ne doit pas être effectué isolément. D'autres aspects cliniques doivent être envisagés simultanément, par exemple la possibilité de traitement de toute maladie sexuellement transmissible observée, des cancers pouvant être soignés et de la prise en charge des cas incurables. Il faut par conséquent établir également des politiques claires, comportant des systèmes d'orientation, pour les soins thérapeutiques et palliatifs.
- Pour une approche de prévention primaire efficace, il convient d'associer les efforts de lutte contre les maladies sexuellement transmissibles, le syndrome d'immunodéficience acquise (SIDA) et le cancer du col utérin.