

Clinical trials of cancer screening in the developing world and their impact on cancer healthcare

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Several research and training initiatives were organized by the International Agency for Research on Cancer (IARC) in collaboration with national institutions in countries such as Angola, Brazil, Burkina Faso, China, Republic of Congo, Guinea, India, Mali, Mauritania, Nepal, Niger, Peru, Tanzania and Thailand among others, to address feasible and effective means of early detection and prevention of cervical, breast and oral cancers. The impact of these activities, that involved over 600 000 participants and more than 1200 healthcare personnel trained on strengthening the local health services in terms of infrastructure, human resources and service delivery aspects in host countries and other regions, is addressed here. These studies, inbuilt in appropriate health services platforms, have resulted in the development and sustenance of several continuing point of care services of screening and treatment in most host countries, particularly in sub-Saharan Africa, and have catalysed regional early detection programmes in India, China and Thailand. The IARC collaborative studies have evolved into major focal points of training and extending services in many countries. The large evidence base, resulting from ours and other studies is likely, in due course, to facilitate much wider scaling up of screening and treatment services through organised programmes.

introduction

The impact of a programme of cancer screening studies and clinical trials, addressing specific research questions on healthcare systems in the developing world, will depend critically upon a high level of awareness of the potential for impact. In addition to the direct outcomes, i.e., answering specific research questions, it is interesting and worthwhile to measure the wider effect of such programmes in terms of the effect on the development of national policies and disease control globally, as well as the direct impact the studies may have on development of human resources, infrastructure and scaling up of programmes in the settings/countries where the research studies were implemented. The general perception about health research programmes, particularly in developing countries, is that the research is conducted with a narrow aim of answering a research question and once this is done, the programme is wound up and everything stops. In addition, the perception is that there is no continuity of activities and that research programmes per se do not contribute to improving skills, infrastructure and health care delivery in the settings where they were conducted.

The International Agency for Research on Cancer (IARC) of the World Health Organization (WHO) has a long tradition of conducting cancer prevention research. A good example of this is the Gambia Hepatitis Intervention Study (GHIS) established in 1986 in collaboration with the government of The Gambia and the Medical Research Council, UK, to evaluate the protective effectiveness of infant hepatitis B immunization in

the prevention of chronic liver disease, particularly, hepatocellular carcinoma. This long-term IARC study has improved the capacity of health services in the host country, notably by strengthening the national immunization services generally, including the coverage of hepatitis B vaccination. This has resulted in a high coverage by vaccines within the expanded programme of immunization and a reduction in the prevalence of hepatitis B surface antigen [1].

IARC has organized a number of cross-sectional studies and randomized clinical trials in developing countries over the last two decades to evaluate various screening options in order to facilitate development of cost-effective strategies and suitable public health policies for early detection and control of cervical, breast and oral cancers, which constitute a major burden of cancers in low- and medium-resource countries [2–8]. The studies were conducted, or are still on-going, in countries with wide ranging socio-economic and technological development such as Laos, Burkina Faso and India. For many years IARC conducted an active programme of screening studies in low- and medium-resource countries such as Angola, Burkina Faso, Guinea, India, Laos, Mali, Mauritania, Nepal, Niger, Republic of Congo and Tanzania. Right from the beginning, these studies were organised with the aims not only of answering research questions, but also contributing to improving the infrastructure and skilled human resources of the local health services. The impact of these studies on the cancer health services in the provinces/regions/countries where they were organized, or are on-going, is briefly discussed in this chapter.

IARC screening studies

A brief description of the different IARC research initiatives and training courses, in collaboration with national investigators and institutions in different countries in the prevention and early detection of cervical, oral and breast cancers, is given in Tables 1 and 2 and the locations of these research activities are shown in Figure 1. The research objectives of these studies are to provide data on the accuracy, reproducibility, efficacy, benefits, harmful effects and cost-effectiveness of different screening interventions for cervical, oral and breast cancers, in reducing deaths and in improving the quality of life in different settings, thus leading to rational utilization of health care resources in designing, implementing, monitoring and evaluating screening programmes. The ultimate aim is to guide the development of public health policies in implementing screening in a range of health care settings, particularly in low-resourced countries.

To achieve this aim, long-term follow-up research studies were organized. The study designs include randomized controlled screening trials, cross-sectional studies, descriptive studies, and demonstration projects (Table 1). The design, conduct and results from many of these studies have already been published and can be found, as well as details of on-going studies, on the IARC's Screening Group (SCR) website (<http://screening.iarc.fr>). Training courses and centres have been organized and set up in the context of these studies and several printed and digital manuals have been produced to support the training initiatives.

impact of IARC cervical cancer screening studies on the health services in sub-Saharan African countries

A high burden of cervical cancer is experienced in sub-Saharan African countries with estimated age-standardized incidence rates exceeding 32 per 100 000 women and where around 75 000 women develop and 50 000 die from it annually [9]. Cervical cancer constitutes the number one cancer among women in these countries and over 90% of cancer cases present in advanced clinical stages with poor prospects of cure. Almost all sub-Saharan countries, with the exception of South Africa, have among the most extremely poorly developed cancer health services in terms of infrastructure for early detection, treatment and follow-up care and trained human resources in the world. In at least thirty countries, there is no possibility for most persons diagnosed with cancer to access and receive adequate care, due to the fact that these are not widely available and where some services are available, these are mostly concentrated in capital cities. For instance, clinically detected invasive cervical cancers would require clinical investigations such as histopathology, cystoscopy and x-ray imaging to adequately diagnose and stage the cancers to decide on treatment options. Subsequently, the treatment would require facilities providing for radical hysterectomy (in early stages), external plus intracavitary radiotherapy facilities (for early and moderately advanced cancers and for palliation in advanced cases) and the

possibility of administering cisplatin-based chemotherapy in addition to radiotherapy (for moderately advanced cervical cancers). In almost all countries, again except South Africa, access to radiotherapy services and most of the commonly used cancer chemotherapeutic agents is very limited.

This dramatic situation seems to be due to the absence of systematic long-term planning, to the lack of committing adequate financial resources and investments to the infrastructure and lack of augmenting human resources in the health services since countries obtained their independence. This is further compounded by the fact that the control of non-communicable diseases, particularly cancer, is accorded low priority, due to other competing health care priorities. Needless to say, there has been traditionally no investment in screening for cervical cancer in sub-Saharan African countries where, excluding South Africa, less than 200 000 cervical smears are taken annually. Until the beginning of the 21st century, there were no functioning colposcopy or treatment services with facilities for cryotherapy, cold coagulation and loop electrosurgical excision procedure (LEEP).

In the context of cervical cancer early detection and prevention, we organized cross-sectional studies to evaluate the accuracy of visual screening with acetic acid (VIA) and with Lugol's iodine (VILI) in detecting high-grade cervical intraepithelial neoplasia (CIN) and the feasibility, safety and acceptability of treatment of CIN with cryotherapy and LEEP in eight countries (Table 1) during 2000–2005 [2, 6, 7, 10]. Each country had only one single pathology laboratory with 1–3 pathologists, none had colposcopy or radiotherapy services, and radical hysterectomies for early cervical cancer management were not widely carried out. There were no screening services, and precancerous lesions were rarely detected and treated before the year 2000. As part of the studies, the pathology laboratories were well equipped (new microtomes, histokinettes, high-resolution microscopes, etc.) and technicians and pathologists were retrained and reoriented. The project sites were provided with sufficient numbers of specula, sharp biopsy punches, colposcopes, cryotherapy and electrosurgical equipment with smoke evacuators and instruments required for cold knife conisation (CKC) and radical hysterectomy. Nurses were trained in providing VIA and VILI and doctors and gynaecologists were trained in colposcopy, directing biopsies, cryotherapy, LEEP, CKC and radical hysterectomy.

All these activities were supported by the Bill & Melinda Gates Foundation through the Alliance for Cervical Cancer Prevention (ACCP) of which IARC was a member. Other than Mauritania, where the study failed to take off mainly due to the difficulties in coordination among various hospitals and local investigators, in the other seven countries 48 500 women aged 30–59 years were screened and investigated with colposcopy during the study period. Women participated enthusiastically in the studies indicating wide community acceptance. Biopsies were directed in 4301 women, 1776 women with CIN1 to 3 were detected and 1091 treated; the accuracy, feasibility, safety and acceptability of the visual tests were reported. This research programme helped in the development of skills in cervical visual screening, colposcopy and management of precursor lesions and improvement of histopathology services in these seven countries.

Table 1. Major IARC Screening Group studies on cancer prevention and early detection according to cancer site

Cervical cancer	
<i>Primary prevention</i>	
India	Multicenter cluster-randomized clinical trial of 2 versus 3 doses of quadrivalent human papillomavirus (HPV) vaccine involving 20 000 girls to evaluate the feasibility, effectiveness, safety and acceptability of the two-dose HPV vaccination regimens (selected districts in Maharashtra, Tamil Nadu, Gujarat, Andhra Pradesh, Haryana, Sikkim and Mizoram States) [8]
<i>Early detection</i>	
Cross-sectional studies	
Sub-Saharan Africa Congo, Mali, Niger, Guinea, Burkina Faso, Tanzania, Angola	Multicenter cross-sectional studies in Africa to evaluate the test characteristics of cervical screening tests such as visual inspection with acetic acid (VIA) and visual inspection with Lugol's iodine (VILI) [2, 6, 7, 10] Study design involved providing colposcopy to each woman and directing biopsies in those with colposcopic abnormalities. The aim was to generate skills in colposcopy, processing and reporting biopsies, improving histopathology services, providing treatment for cervical intraepithelial neoplasia (CIN) and early invasive cancer by radical hysterectomy
India Kerala, Mumbai, New Delhi, Kolkata, Jaipur, Hyderabad START Project: Osmanabad District	To evaluate the test characteristics of cervical screening tests such as VIA, magnified visual inspection with acetic acid (VIAM), VILI, conventional cytology and HPV testing; to evaluate the safety, acceptability and effectiveness of field based treatment for CIN [2, 27–41] Screening Technologies to Advance Rapid Testing for cervical cancer prevention (START). To develop rapid, accurate and affordable biochemical tests to screen for cervical cancer by HPV-DNA testing. Collaboration with Programme for Appropriate Technology in Health (PATH), USA, Nargis Dutt Memorial Cancer Hospital (NDMCH), Barshi, India and Tata Memorial Cancer Hospital (TMH), Mumbai, India and the Cancer Institute of the Chinese Academy of Medical Sciences (CICAMS), Beijing, China [8]
Nepal Bhaktapur, Bharatpur, Banepa	To evaluate the accuracy of visual screening and the efficacy of cryotherapy to cure cervical precancerous lesions [8]
Cluster randomized controlled trials	
India Osmanabad District	Trial involving 140,000 women to evaluate the efficacy and cost-effectiveness of a single-round of visual, cytology and HPV screening in reducing cervical cancer incidence and mortality in Osmanabad district, India in collaboration with the Tata Memorial Hospital, Mumbai and the Nargis Dutt Memorial Cancer Hospital, Barshi, India [5, 37, 39, 43, 44]
Dindigul District	Trial involving 80 000 women to evaluate the efficacy and cost-effectiveness of a single-round of visual screening in reducing cervical cancer incidence and mortality in Dindigul district, India in collaboration with the Christian Fellowship Community Health Centre, Ambillikai and the Cancer Institute (WIA), Chennai, India [4, 36, 42, 45]
<i>Treatment of precancerous lesions</i>	
India Barshi, Ambillikai, Trivandrum	Follow-up studies to evaluate the safety, acceptability and effectiveness of cryotherapy, cold coagulation and loop electrosurgical excision procedure (LEEP) in the treatment of CIN [36–39]
Oral cancer	
<i>Early detection</i>	
India	Cluster randomized controlled trial involving 200,000 persons to evaluate the effectiveness of oral visual screening in reducing oral cancer mortality in Trivandrum district, India in collaboration with the Regional Cancer Centre, Trivandrum, India [3, 46–51]
Cuba	Descriptive and analytic evaluation of the oral cancer screening programme in Cuba [68, 69]
Breast cancer	
<i>Early detection</i>	
India	Cluster randomized controlled trial involving 120 000 women to evaluate the role of interventions 'package' consisting of breast awareness and clinical breast examination (CBE) in reducing breast cancer mortality in collaboration with Regional Cancer Centre, Trivandrum, India [8, 52]

Table 2. Training courses on early detection and treatment of cervical cancer (1999–2009)

Country: year (course number per year)	Early detection ^a (number of participants)	Treatment ^b (number of participants)	Histo/cytopathology ^c (number of participants)
Africa			
Angola: 2002	13	13	
Congo: 2001; 2003	27		
Gabon: 2009	24	17	
Guinea: 2000; 2001 (2); 2002; 2003; 2007	67	64	
Mali: 2001; 2004	60		
Mauritania: 2002	18	18	
Morocco: 2009	22		
Tanzania: 2002; 2009	48	36	
Asia			
China: 2004; 2006; 2008	68	31	
India: 1999; 2000 (3); 2001 (5); 2002 (2); 2003 (2); 2006; 2007 (2); 2008 (2)	374	294	
Democratic Public of Laos: 2002	15	15	
Nepal: 2003	8	8	
Thailand: 2006; 2007	54	30	
Europe			
France: 2000; 2003	5	5	11
Oceania			
Vanuatu: 2007	10	10	
Total	808	543	11

^aVIA; VILI; HPV-DNA testing, colposcopy.

^bLEEP, cryotherapy, some radical surgery.

^cTraining and quality control.

It is important to mention that a number of research studies by other colleagues, which were complementary to our efforts, were ongoing at the same time and addressing cervical screening, for example in South Africa [11–19], Zimbabwe [20–22], Ghana [23], Kenya [24], Democratic Republic of Congo [25] and Zambia [26] among others.

Once our research studies were completed, our study sites became point of care screening service outlets by conducting regular cervical screening and treatment clinics in hospitals and health centres in and around the capital regions and have evolved as focal points of training in cervical cancer prevention. Many of the medical and nursing staff, who trained and worked as part of the cross-sectional studies, have evolved as master trainers in screening, diagnosis and treatment of CIN and impart their skills to other providers in their countries/regions. The governments of Angola, Guinea and Tanzania have supported the evolution of these cervical cancer screening training centres by supporting construction of the training facility premises, equipping them and providing support to ongoing training activities. Training more service providers and the awareness and demand created by the research studies have facilitated the organization of new point of care screening services in provinces and districts of Angola, Burkina Faso,

Mali, Guinea and Tanzania. Moreover, Angola, Mali, Tanzania and Guinea Conakry now have a budget line established for cervical screening services. Indeed, Mali intends to provide visual screening services in every health centre in the country. As part of these activities, 15 000–20 000 women are screened with visual screening and 300–400 women detected with high-grade CIN are treated annually since 2004 in the seven countries, which are supported mostly by local resources, although IARC does continue to provide technical/equipment assistance to these initiatives within their means.

The term ‘opportunistic screening’ is used when a test is offered to an asymptomatic subject attending health care services for reasons unrelated to that disease. It differs from ‘population-based screening programme’ defined as an organized integrated process where all activities along the screening pathway are planned, coordinated, monitored and evaluated.

Opportunistic screening services have evolved in countries such as South Africa, Zimbabwe, Zambia, Nigeria, Senegal, Uganda, Kenya, Malawi and Madagascar as a result of research studies conducted by other investigators in these countries in collaboration with international partners [11–26]. For instance, a programme in Zambia has resulted in large-scale availability of opportunistic visual screening services in Lusaka and surrounding areas covering both HIV-positive and -negative women and a substantial proportion of women with positive screens receive treatment and follow-up care.

Impact of cancer screening studies on cancer health services in the Indian sub-continent and other countries

A number of cross-sectional studies were conducted in India and Nepal in various locations (Table 1) to assess the performance of various cervical screening tests by different providers. These studies collectively involved more than 55 000 women aged 30–59 years and addressed important accuracy and treatment outcome issues associated with screening [2, 27–41]. Cross-sectional studies involving an additional 11 000 were conducted in Solapur district, Maharashtra to provide biological samples for the development of an affordable and rapid HPV test, which partly contributed to the validation and development of the careHPV™ (Qiagen, Gaithersburg, MD, USA) test. The randomized trials of cervical cancer screening evaluating the impact of a single round of intervention with visual inspection, cytology or HPV screening tests on cervical cancer mortality involved around 220 000 women aged 30–59 years who have been followed up now for 11 years [4, 5, 42–45]; randomized trials of oral and breast cancer screening involved around 320 000 participants (Table 1) [3, 46–52].

The above studies created considerable awareness among the public, health-care providers and policy makers on the need not only for early detection programmes for cervical, but also for oral and breast cancers and catalysed the development of widespread opportunistic screening services in various districts of states such as Kerala, Tamil Nadu, Andhra Pradesh, Maharashtra, Gujarat, West Bengal, Sikkim, Mizoram, among others, as well as in Nepal, Bangladesh and in selected provinces

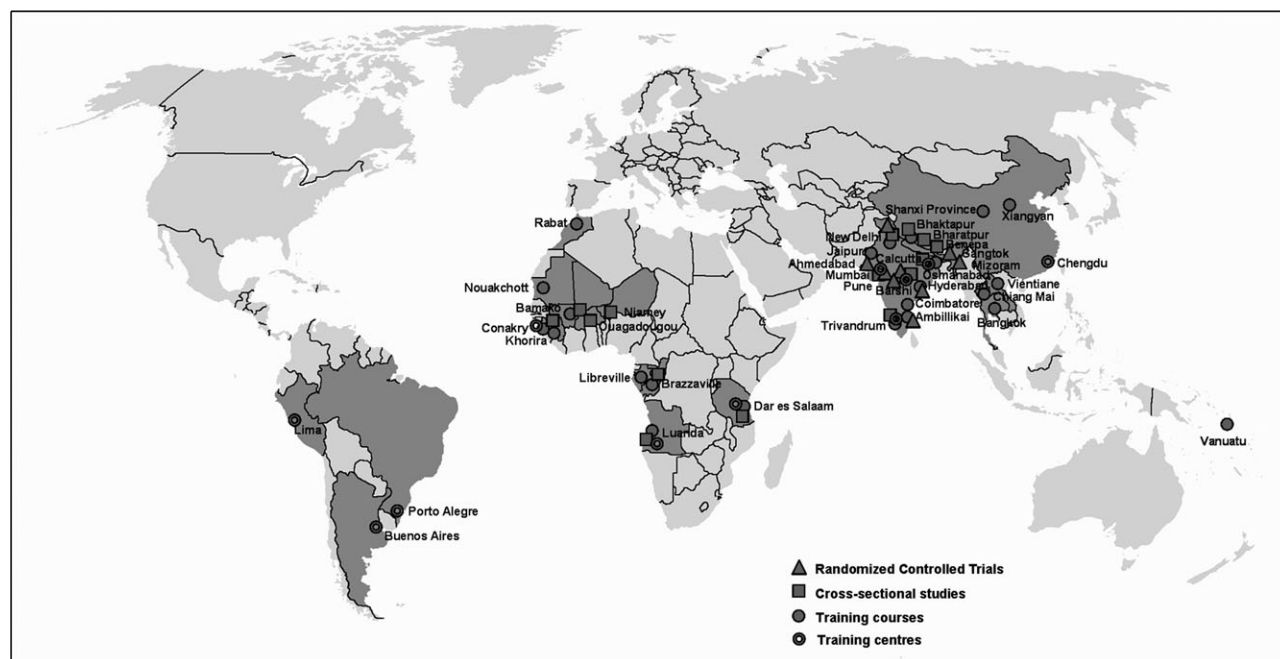


Figure 1. World-wide locations of IARC's screening initiatives in collaboration with national institutions for the prevention and early detection of cervical, oral and/or breast cancers

in China. There are large demonstration programmes using visual screening for cervical and oral cancers in two districts in Maharashtra, based on the IARC supported research studies in collaboration with Indian investigators. Founded on the findings from the cross-sectional studies in Kerala and the randomized clinical trial in Dindigul district, Tamil Nadu, visual screening for cervical cancer has been widely practised in opportunistic settings in both states and has facilitated rapid declines in cervical cancer incidence in Dindigul district [53, 54].

Our studies and those by other colleagues in India and Sri Lanka in the domain of cervical, breast and oral cancer early detection and prevention [55–63] have provided valuable scientific evidence on the utility, efficacy, safety, and acceptability of the different interventions. Before these studies were implemented, there was no wide-spread practice of screening, diagnosing and treating cervical pre-cancerous lesions in local health services in the Indian sub-continent. Consequently, these findings have encouraged the authorities to take a policy using VIA and VILI as a screening approach for cervical neoplasia within India in the district cancer control programmes and state-wide cancer control programmes until the time when a more affordable HPV testing becomes available. Moreover, within state governments' budget lines, colposcopy services were established, more providers have been trained, and several early detection screening outlets have become available in certain states. In the districts where the screening programmes were already implemented, wider and larger programmes have now been made available. Indeed, this situation has greatly increased the availability of both master trainers and providers across the healthcare services.

Although India has a reasonable healthcare infrastructure, ours as well as other studies have certainly contributed to its improvement in the context of screening. This is seen particularly by the increasing number of providers and widening establishment and dissemination of colposcopy, cryotherapy, cold coagulation and LEEP services, and of facilities for triple diagnosis triage for the early detection of breast cancer and increased facilities for early oral cancer detection in health services of various states. The studies on oral cancer screening have facilitated wide-spread in-service training of doctors and health workers in Kerala and adjoining states.

The findings from the Indian and studies elsewhere encouraged the Bangladesh Ministry of Health to develop national guidelines on cervical screening and to organize a nation-wide VIA screening programme supported by the United National Population Fund (UNFPA), which has resulted in the organization of screening and colposcopy services in 44 districts through 145 VIA screening centres since 2005 [64, 65]. This programme has more than 500 trained VIA providers and 50 gynaecologists offering colposcopy services and more personnel are currently being trained.

In Nepal, once the cross-sectional study was completed, the study centres became service outlets on a day-to-day basis where women come to seek visual screening, diagnosis and management of pre-cancerous lesions. The centres, particularly in Banepa, have taken the formal role of training centres for more than 2000 nurses and doctors throughout Nepal, and have generated human resources in each district.

IARC provided technical assistance in organizing a pilot cervical cytology screening programme during 1999–2003 in Nakhon Phanom province in Thailand, to inform and guide the development of a national cytology screening programme [66].

This project covered 45% of the target women aged 35–59 years with a single screen and showed the feasibility of integrating cervical cancer screening and treatment services in the existing health care infrastructure. Another important development in cervical cancer prevention in Thailand was the initiative by the Royal Thai College of Obstetrics and Gynecology (RTOG) in collaboration with JHPIEGO to introduce a screen and treat demonstration programme with VIA and cryotherapy in four districts of Roi-et province [67]. The findings from the above studies, as well as other experiences in Thailand and elsewhere in countries such as India, prompted a government policy that the provinces may provide population-based screening with either VIA screen and treat approach, with cervical cytology approach or with both. This led to the initiation of the first and second phases of an organized cytology screening project in 75 provinces by the National Health Security Office (NHSO) and the Ministry of Public Health (MOPH) in 2005 as a 5-year programme targeting around 12 million women aged 35–60 years for 5-yearly screening and the expansion of VIA screen and treat programme targeting women aged 30–45 years to 29 provinces in 2006.

The descriptive and analytical evaluation of the national oral cancer screening programme in collaboration with the Cuban National Cancer Institute has led to the reorganization of the programme with defined target population for screening, increasing the screening interval to 3 years and development improved referral systems and improved coverage of screen-positive persons with diagnosis and treatment [68, 69].

IARC's cervical cancer screening training courses and regional training facilities

Between 1999 and 2009, IARC organized 45 courses on cervical cancer screening in 15 countries (Tables 2 and 3). We trained 653 doctors and gynaecologists in visual screening techniques, colposcopy and treatment with cryotherapy, cold coagulation and LEEP and some in radical surgical procedures. We trained 210 nurses, midwives and health workers in visual screening and cryotherapy and some in providing colposcopy and LEEP. Most have evolved as master trainers in their countries thanks to experience gained through the training and re-training opportunities and the considerable hands-on experience gained. Eleven regional training centres have been set up supported by local institutions and governments (Figure 1). The faculties are provided by local and international institutions; and the training facilities are entirely financially supported by the local resources. IARC does continue to provide assistance to facilitate exchange of master trainers from different countries in the regions. The training facilities have contributed to the training of master trainers from Nepal, Bangladesh, China, Thailand, Cambodia, Laos, Vanuatu, Guatemala, El Salvador, Paraguay, Equator, Guinea Bissau, Cape Verde, Comoros islands among others apart from the host countries. The training courses organized by the Cancer Institute of the Chinese Academy of Medical Sciences in collaboration with IARC during 2003–2007 have resulted in training more than 120 master trainers in colposcopy and LEEP

Table 3. Training resources on early detection and treatment of cervical, breast and oral cancers

Cervical cancer	<ul style="list-style-type: none"> A practical manual on visual screening for cervical neoplasia A Training Course in Colposcopy A Training Course in Loop Electrosurgical Excision Procedure (LEEP) – practical A Training Course in Loop Electrosurgical Excision Procedure (LEEP) – theory A Training Course in Visual Inspection using 4% Acetic Acid (VIA) – theory and practice (movie) A Training Course in Visual Inspection using Lugol's iodine solution (VILI) – theory and practice Colposcopy and treatment of cervical intraepithelial neoplasia: a beginner's manual. Course in visual methods for cervical cancer screening: Visual inspection with acetic acid and Lugol's iodine Cytopathology of the uterine cervix - digital atlas Digital learning series – A training course in Cryotherapy Digital learning series – A training course in Loop electrosurgical excision procedure (LEEP) Digital learning series – A training course in Visual Inspection with 5% Acetic Acid (VIA) Digital learning series – A training course in Visual Inspection with Lugol's Iodine solution (VILI) Histopathology of the uterine cervix – digital atlas Quick Clinical Reference Chart for Visual Inspection with Acetic Acid (VIA) Quick Clinical Reference Chart for Visual Inspection with Lugol's iodine (VILI)
Breast cancer	<ul style="list-style-type: none"> Digital training resource for clinical breast examination and breast awareness Quick reference chart for clinical breast examination
Oral cancer	<ul style="list-style-type: none"> A digital manual for the early diagnosis of oral neoplasia Detecting Oral Cancer – A guide for health care professionals Quick Clinical Reference Chart for Visual Inspection of the Oral Cavity to Detect Precancerous Lesions and Invasive Cancers

Available at <http://screening.iarc.fr/>

in China. They in turn have trained a large number of providers in the past 5 years, resulting in the establishment of several new colposcopy and LEEP services and opportunistic VIA screening services within China and in the region.

conclusions

A widely held perception is that the standards and rigor of health research in developing countries vary considerably.

Consequently, the findings are viewed with some scepticism and their reliability and validity are sometimes questioned and are seldom considered while evolving international consensus and practice guidelines. In spite of the robust evidence from the Indian randomized trial indicating the effectiveness of oral visual screening in reducing oral cancer mortality significantly by 34% among the high-risk group of users of tobacco or alcohol or both, an international NGO review concluded that there was insufficient evidence to recommend inclusion or exclusion of oral visual screening and the US National Cancer Institute's PDQ cancer information summary on oral cancer screening did not even make a reference to the above randomized trial evidence and states that there is inadequate evidence to establish that screening would result in a decrease in mortality from oral cancer [70–73]. Such perceptions underscore the importance of particular care and standards that should be applied while conducting health research in developing countries. It is important to point out that there are disadvantaged populations within developed countries that would benefit from the findings of studies from developing countries.

Right from the planning stages, one major emphasis in IARC research studies has been to organize them with quality assurance of different inputs and in such a way that the infrastructure, trained human resources and quality assurance practices, in-built as part of the research programme, contributes to improving the capacity of the local health systems for early detection and treatment of cancers and in providing related preventive services. The studies provided priority to offer diagnosis and treatment to subjects detected with lesions, in addition to answering the research questions and contributing to the evidence base to evolve sound public health policies. The studies were implemented with scientific rigor, after obtaining ethical clearances, in appropriate platforms within the health services of the host countries so that they have a reasonable chance to sustain and continue to provide services and expand their outreach and contribute to augmenting human resources and early detection services. IARC studies have had mixed success in fulfilling these overall objectives. A major deciding factor in the context of success has been the demand and acceptability of services from the local community, enthusiasm on the part of participants to seek and utilize screening services, commitment of the national institutions and collaborating colleagues and their ability to mobilise local resources and obtain government support and expand activities. Our initiatives in Angola, Mali, Guinea, and Tanzania in Africa, in India, Thailand and China in Asia, as well as the overall training initiatives through the regional training centres, have been particularly successful in mobilizing national resources and contributing to improved health services in host countries and in the region during and after the course of the studies.

Although our studies have contributed to improvements in local health systems and development of point of care and opportunistic services, we would like to see their impact in terms of development of large scale, organized national programmes in many developing countries. It takes several years to assess the outcome of screening studies and, perhaps it is too early to expect concrete, large scale impact from our and

other studies on a global dimension, given the fact that these were organized over the last 10–15 years and long-term results have been obtained only in the recent past. We are hopeful that the large evidence base, resulting from ours and other studies will, in due course, lead to scaling up screening and treatment services through organized programmes.

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disclosures

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references

1. Viviani S, Carrieri P, Bah E et al. 20 years into the Gambia Hepatitis Intervention Study: assessment of initial hypotheses and prospects for evaluation of protective effectiveness against liver cancer. *Cancer Epidemiol Biomarkers Prev* 2008; 17: 3216–3223.
2. Sankaranarayanan R, Basu P, Wesley RS et al. Accuracy of visual screening for cervical neoplasia: Results from an IARC multicentre study in India and Africa. *Int J Cancer* 2004; 110: 907–913.
3. Sankaranarayanan R, Ramadas K, Thomas G et al. Effect of screening on oral cancer mortality in Kerala, India: a cluster-randomised controlled trial. *Lancet* 2005; 365: 1927–1933.
4. Sankaranarayanan R, Esmey PO, Rajkumar R et al. Effect of visual screening on cervical cancer incidence and mortality in Tamil Nadu, India: a cluster-randomised trial. *Lancet* 2007; 370: 398–406.
5. Sankaranarayanan R, Nene BM, Shastri SS et al. HPV screening for cervical cancer in rural India. *N Engl J Med* 2009; 360: 1385–1394.
6. Muwonge R, Mbalawa CG, Keita N et al. Performance of colposcopy in five sub-Saharan African countries. *BJOG* 2009; 116: 829–837.
7. Muwonge R, Manuel MG, Filipe AP et al. Visual screening for early detection of cervical neoplasia in Angola. *Int J Gynaecol Obstet* 2010; 111: 68–72.
8. Screening Group. International Agency for Research on Cancer. Available at: <http://screening.iarc.fr/>.
9. Ferlay J, Shin HR, Bray F et al. GLOBOCAN 2008, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer. 2010. Available from: <http://globocan.iarc.fr>.
10. Ngoma T, Muwonge R, Mwaiselage J et al. Evaluation of cervical visual inspection screening in Dar es Salaam, Tanzania. *Int J Gynaecol Obstet* 2010; 109: 100–104.
11. Kuhn L, Wang C, Tsai WY et al. Efficacy of human papillomavirus-based screen-and-treat for cervical cancer prevention among HIV-infected women. *AIDS* 2010; 24: 2553–2561.
12. Batra P, Kuhn L, Denny L. Utilisation and outcomes of cervical cancer prevention services among HIV-infected women in Cape Town. *S Afr Med J* 2010; 100: 39–44.

13. Denny L, Kuhn L, De SM et al. Screen-and-treat approaches for cervical cancer prevention in low-resource settings: a randomized controlled trial. *JAMA* 2005; 294: 2173–2181.
14. Denny L, Kuhn L, Pollack A, Wright TC Jr.. Direct visual inspection for cervical cancer screening: an analysis of factors influencing test performance. *Cancer* 2002; 94: 1699–1707.
15. Denny L, Kuhn L, Pollack A et al. Evaluation of alternative methods of cervical cancer screening for resource-poor settings. *Cancer* 2000; 89: 826–833.
16. Denny L, Kuhn L, Risi L et al. Two-stage cervical cancer screening: an alternative for resource-poor settings. *Am J Obstet Gynecol* 2000; 183: 383–388.
17. Kuhn L, Denny L, Pollack A et al. Human papillomavirus DNA testing for cervical cancer screening in low-resource settings. *J Natl Cancer Inst* 2000; 92: 818–825.
18. Wright TC Jr., Kuhn L, Denny L. Human papillomavirus detection to screen for cervical cancer. *JAMA* 2000; 284: 39–40.
19. Megevand E, Denny L, Dehaeck K et al. Acetic acid visualization of the cervix: an alternative to cytologic screening. *Obstet Gynecol* 1996; 88: 383–386.
20. Gaffikin L, McGrath J, Arbyn M, Blumenthal PD. Avoiding verification bias in screening test evaluation in resource poor settings: a case study from Zimbabwe. *Clin Trials* 2008; 5: 496–503.
21. Gaffikin L, McGrath JA, Arbyn M, Blumenthal PD. Visual inspection with acetic acid as a cervical cancer test: accuracy validated using latent class analysis. *BMC Med Res Methodol* 2007; 7: 36.
22. Visual inspection with acetic acid for cervical-cancer screening: test qualities in a primary-care setting. University of Zimbabwe/JHPIEGO Cervical Cancer Project. *Lancet* 1999; 353: 869–873.
23. Blumenthal PD, Gaffikin L, Deganus S et al. Cervical cancer prevention: safety, acceptability, and feasibility of a single-visit approach in Accra, Ghana. *Am J Obstet Gynecol* 2007; 196: 407–408.
24. De Vuyst H, Claeys P, Njiru S et al. Comparison of pap smear, visual inspection with acetic acid, human papillomavirus DNA-PCR testing and cervicography. *Int J Gynaecol Obstet* 2005; 89: 120–126.
25. Sangwa-Lugoma G, Mahmud S, Nasr SH et al. Visual inspection as a cervical cancer screening method in a primary health care setting in Africa. *Int J Cancer* 2006; 119: 1389–1395.
26. Mwanahamuntu MH, Sahasrabudhe VV, Pfaendler KS et al. Implementation of 'see-and-treat' cervical cancer prevention services linked to HIV care in Zambia. *AIDS* 2009; 23: N1–N5.
27. Wesley R, Sankaranarayanan R, Mathew B et al. Evaluation of visual inspection as a screening test for cervical cancer. *Br J Cancer* 1997; 75: 436–440.
28. Sankaranarayanan R, Wesley R, Somanathan T et al. Visual inspection of the uterine cervix after the application of acetic acid in the detection of cervical carcinoma and its precursors. *Cancer* 1998; 83: 2150–2156.
29. Sankaranarayanan R, Shyamalakumary B, Wesley R et al. Visual inspection with acetic acid in the early detection of cervical cancer and precursors. *Int J Cancer* 1999; 80: 161–163.
30. Basu P, Sankaranarayanan R, Mandal R et al. Evaluation of downstaging in the detection of cervical neoplasia in Kolkata, India. *Int J Cancer* 2002; 100: 92–96.
31. Basu PS, Sankaranarayanan R, Mandal R et al. Visual inspection with acetic acid and cytology in the early detection of cervical neoplasia in Kolkata, India. *Int J Gynecol Cancer* 2003; 13: 626–632.
32. Sankaranarayanan R, Wesley R, Thara S et al. Test characteristics of visual inspection with 4% acetic acid (VIA) and Lugol's iodine (VIL) in cervical cancer screening in Kerala, India. *Int J Cancer* 2003; 106: 404–408.
33. Bhatla N, Gulati A, Mathur SR et al. Evaluation of cervical screening in rural North India. *Int J Gynaecol Obstet* 2009; 105: 145–149.
34. Pimple S, Muwonge R, Amin G et al. Cytology versus HPV testing for the detection of high-grade cervical lesions in women found positive on visual inspection in Mumbai, India. *Int J Gynaecol Obstet* 2010; 108: 236–239.
35. Shastri SS, Dinshaw K, Amin G et al. Concurrent evaluation of visual, cytological and HPV testing as screening methods for the early detection of cervical neoplasia in Mumbai, India. *Bull World Health Organ* 2005; 83: 186–194.
36. Sankaranarayanan R, Rajkumar R, Esmey PO et al. Effectiveness, safety and acceptability of 'see and treat' with cryotherapy by nurses in a cervical screening study in India. *Br J Cancer* 2007; 96: 738–743.
37. Nene BM, Hiremath PS, Kane S et al. Effectiveness, safety, and acceptability of cryotherapy by midwives for cervical intraepithelial neoplasia in Maharashtra, India. *Int J Gynaecol Obstet* 2008; 103: 232–236.
38. Rema P, Suchetha S, Thara S et al. Effectiveness and safety of loop electrosurgical excision procedure in a low-resource setting. *Int J Gynaecol Obstet* 2008; 103: 105–110.
39. Sankaranarayanan R, Keshkar V, Kothari A et al. Effectiveness and safety of loop electrosurgical excision procedure for cervical neoplasia in rural India. *Int J Gynaecol Obstet* 2009; 104: 95–99.
40. Sankaranarayanan R, Shastri SS, Basu P et al. The role of low-level magnification in visual inspection with acetic acid for the early detection of cervical neoplasia. *Cancer Detect Prev* 2004; 28: 345–351.
41. Sankaranarayanan R, Thara S, Sharma A et al. Accuracy of conventional cytology: results from a multicentre screening study in India. *J Med Screen* 2004; 11: 77–84.
42. Sankaranarayanan R, Rajkumar R, Theresa R et al. Initial results from a randomized trial of cervical visual screening in rural south India. *Int J Cancer* 2004; 109: 461–467.
43. Sankaranarayanan R, Nene BM, Dinshaw KA et al. A cluster randomized controlled trial of visual, cytology and human papillomavirus screening for cancer of the cervix in rural India. *Int J Cancer* 2005; 116: 617–623.
44. Nene B, Jayant K, Arrossi S et al. Determinants of women's participation in cervical cancer screening trial, Maharashtra, India. *Bull World Health Organ* 2007; 85: 264–272.
45. Sankaranarayanan R, Rajkumar R, Arrossi S et al. Determinants of participation of women in a cervical cancer visual screening trial in rural south India. *Cancer Detect Prev* 2003; 27: 457–465.
46. Ramadas K, Sankaranarayanan R, Jacob BJ et al. Interim results from a cluster randomized controlled oral cancer screening trial in Kerala, India. *Oral Oncol* 2003; 39: 580–588.
47. Sankaranarayanan R, Mathew B, Jacob BJ et al. Early findings from a community-based, cluster-randomized, controlled oral cancer screening trial in Kerala, India. The Trivandrum Oral Cancer Screening Study Group. *Cancer* 2000; 88: 664–673.
48. Mathew B, Sankaranarayanan R, Sunilkumar KB et al. Reproducibility and validity of oral visual inspection by trained health workers in the detection of oral precancer and cancer. *Br J Cancer* 1997; 76: 390–394.
49. Pandey M, Thomas G, Somanathan T et al. Evaluation of surgical excision of non-homogeneous oral leukoplakia in a screening intervention trial, Kerala, India. *Oral Oncol* 2001; 37: 103–109.
50. Subramanian S, Sankaranarayanan R, Bapat B et al. Cost-effectiveness of oral cancer screening: results from a cluster randomized controlled trial in India. *Bull World Health Organ* 2009; 87: 200–206.
51. Ramadas K, Arrossi S, Thara S et al. Which socio-demographic factors are associated with participation in oral cancer screening in the developing world? Results from a population-based screening project in India. *Cancer Detect Prev* 2008; 32: 109–115.
52. Sankaranarayanan R, Ramadas K, Thara S et al. Clinical breast examination: preliminary results from a cluster randomized controlled trial in India. *J Natl Cancer Inst* 2011; 103(19): 1476–1480.
53. Swaminathan R, Selvakumaran R, Esmey PO et al. Cancer pattern and survival in a rural district in South India. *Cancer Epidemiol* 2009; 33: 325–331.
54. Swaminathan R, Selvakumaran R, Vinodha J et al. Education and cancer incidence in a rural population in south India. *Cancer Epidemiol* 2009; 33: 89–93.
55. Singh V, Sehgal A, Parashari A et al. Early detection of cervical cancer through acetic acid application—an aided visual inspection. *Singapore Med J* 2001; 42: 351–354.
56. Parashari A, Singh V, Sehgal A et al. Low-cost technology for screening uterine cervical cancer. *Bull World Health Organ* 2000; 78: 964–967.
57. Singh V, Sehgal A, Luthra UK. Screening for cervical cancer by direct inspection. *BMJ* 1992; 304: 534–535.
58. Sehgal A, Singh V, Bhambhani S, Luthra UK. Screening for cervical cancer by direct inspection. *Lancet* 1991; 338: 282.
59. Mehta FS, Gupta PC, Bhonsle RB et al. Detection of oral cancer using basic health workers in an area of high oral cancer incidence in India. *Cancer Detect Prev* 1986; 9: 219–225.

60. Amarasinghe HK, Johnson NW, Laloo R et al. Derivation and validation of a risk-factor model for detection of oral potentially malignant disorders in populations with high prevalence. *Br J Cancer* 2010; 103: 303–309.
61. Warnakulasuriya KA, Nanayakkara BG. Reproducibility of an oral cancer and precancer detection program using a primary health care model in Sri Lanka. *Cancer Detect Prev* 1991; 15: 331–334.
62. Warnakulasuriya KA, Ekanayake AN, Sivayoham S et al. Utilization of primary health care workers for early detection of oral cancer and precancer cases in Sri Lanka. *Bull World Health Organ* 1984; 62: 243–250.
63. Mitra I, Mishra GA, Singh S et al. A cluster randomized, controlled trial of breast and cervix cancer screening in Mumbai, India: methodology and interim results after three rounds of screening. *Int J Cancer* 2010; 126: 976–984.
64. Basu P, Nessa A, Majid M et al. Evaluation of the National Cervical Cancer Screening Programme of Bangladesh and the formulation of quality assurance guidelines. *J Fam Plann Reprod Health Care* 2010; 36: 131–134.
65. Nessa A, Hussain MA, Rahman JN et al. Screening for cervical neoplasia in Bangladesh using visual inspection with acetic acid. *Int J Gynaecol Obstet* 2010; 111: 115–118.
66. Deerasamee S, Srivatanakul P, Sriplung H et al. Monitoring and evaluation of a model demonstration project for the control of cervical cancer in Nakhon Phanom province. Thailand. *Asian Pac J Cancer Prev* 2007; 8: 547–556.
67. Gaffikin L, Blumenthal PD, Emerson M, Limpaphayom K. Safety, acceptability, and feasibility of a single-visit approach to cervical-cancer prevention in rural Thailand: a demonstration project. *Lancet* 2003; 361: 814–820.
68. Fernandez GL, Sankaranarayanan R, Lence Anta JJ et al. An evaluation of the oral cancer control program in Cuba. *Epidemiology* 1995; 6: 428–431.
69. Sankaranarayanan R, Fernandez GL, Lence AJ et al. Visual inspection in oral cancer screening in Cuba: a case-control study. *Oral Oncol* 2002; 38: 131–136.
70. Kujan O, Glenny AM, Oliver RJ et al. Screening programmes for the early detection and prevention of oral cancer. *Cochrane Database Syst Rev* 2006; 3: CD004150.
71. Kujan O, Glenny AM, Sloan P. Screening for oral cancer. *Lancet* 2005; 366: 1265–1266.
72. Ramadas K, Arrossi S, Thara S, Sankaranarayanan R. Keynote comment: importance of recognising scientific evidence. *Lancet Oncol* 2006; 7: 962–963.
73. Oral cancer Screening. National Cancer Institute: U.S. National Institutes of Health. Available at: <http://www.cancer.gov/cancertopics/pdq/screening/oral/healthprofessional> (29August 2011, date last accessed).