

COMMENTARY

Women's Cancers in Developing Countries: From Research to an Integrated Health Systems Approach

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Abstract

The article focuses on two women's cancers, breast and cervical cancer, that are much more deadly in developing countries than in developed countries. Early detection can make a significant difference for the treatment outcome of these two cancers and there are now cost-effective tools for prevention and screening. The authors propose a new public health approach to these two cancers in developing countries where resources for effective cancer control are very limited and offer a framework for putting women's cancers in developing countries on the global public health agenda. The key areas are: 1. Proposals for a new, integrated public health approach to women's cancers (breast and cervical) in resource poor settings; 2. Reviews of the evidence for cost-effective screening and early detection of breast and cervical cancer, and discussion of some of the lessons learned from HIV/AIDS on an integrated health systems approach; 3. Outlines of ways to make a priority of women's cancers in developing countries on the political agenda of international agencies.

Key Words: Women's cancers - global public health- developing countries - cancer control- healthcare systems

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Background

In this article we wish to focus on two women's cancers, breast and cervical cancer, that are much more deadly in developing countries than in developed countries. Early detection can make a significant difference for the treatment outcome of these two cancers and there are now cost-effective tools for prevention and screening. We propose a new public health approach to these two cancers in developing countries where resources for effective cancer control are very limited and where health planners have had other pressing health priorities related to infectious diseases and high birth rates. Developing countries are now in rapid social-economic change and the incidence of cancer is rising every year without being matched by a proportional increase in resources.

We review the research evidence on cost-effective screening and prevention interventions for breast and cervical cancers for developing countries and propose a new public health approach for reducing the disease burden from these cancers in developing countries. We draw parallels to the lessons learned from another devastating chronic disease, HIV/AIDS, and we propose a framework for putting women's cancers in developing countries on the global public health agenda.

Global Trends in Women's Cancers

The incidence of breast cancer is rising globally but

mortality is declining in high income countries due to earlier detection and more effective therapy (Smith RA et al, 2006). In developing countries incidence is rising due to urbanization, population aging and lifestyle changes. Cervical cancer kills an estimated 274,000 women per year with 85% of deaths in developing countries (Alliance for Cervical Cancer Prevention, 2004). Incidence rates are estimated to be 30 per 100,000 women compared to only 10 per 100,000 in North America and Europe where effective screening programs have been in effect for years. In developing countries, the incidence of cervical cancer ranges from 69 per 100,000 in Tanzania to 55 per 100,000 in Bolivia. In India there are 132,000 new cases every year (ibid).

Breast Cancer

Awareness and Early Detection

The Breast Health Global Initiative (Cited in Yip et al, 2008, p2247) has defined what countries with different levels of resources could aim for in terms of breast cancer detection (Please see Table 1). Early detection of breast cancer has strong beneficial effects on effective treatment and survival (Smith et al., 2006). In Africa and Asia the treatment of breast cancer in stages I, II or III costs less than US\$ 390 per Disability Adjusted Life Years (DALY) averted. If the cancer progresses to stage IV treatment will cost more than 3,500US\$ per DALY averted (Groot et al., 2006) There is less agreement on the cost-effectiveness

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Table 1. Early Breast Cancer Detection Resource Allocation and Process Metrics (as adapted from Yip et al, 2008, Figure 1)

Level of Resources	Basic	Limited	Enhanced	Maximal
Public Education and Awareness	Development of culturally sensitive, linguistically appropriate local education programs for target populations to teach breast cancer risk factors, breast health awareness (education and self examination), and value of early detection	Culturally and linguistically appropriate targeted outreach/education encouraging CBE for age groups at higher risk administered at district/provincial level using healthcare providers in the field	Regional awareness program regarding breast health linked to general health and women health programs	National awareness campaigns regarding breast health using media
Detection Methods	Clinical history and CBE	Diagnostic breast US + diagnostic mammography in women with positive CBE Mammographic screening of target group	Mammographic screening every 2 years of women ages 50 -69 Consider mammography screening every 12 -18 months for women ages 40-49	Consider annual mammographic screening in women ages 40 and older Other imaging technologies as appropriate for high -risk groups
Evaluation Goal	Breast health awareness regarding value of early detection in improving breast cancer outcome	Downsizing of symptomatic disease	Downsizing and/or downstaging of asymptomatic disease in women in highest yield target groups	Downsizing and/or downstaging of asymptomatic disease in women in all risk groups
Process Metrics	# patients with documented H&P/# patients evaluated Ratio of number of patients who have a recorded history and physical examination within the target group for a center or program providing organized breast healthcare.	% of Patients with CBE - detected abnormalities who undergo breast imaging for work -up	% of Patients age 50 -69 who had screening mammogram within the past 24 months	Maximal category process metrics determined based upon standards of care in high -income countries

of the various screening methods. The increase in US survival rates from breast cancer is attributed to early detection through mammography and increased awareness in women and doctors. However, research from the United Kingdom found that the rate of advanced cancer fell dramatically already before the national screening program had begun and concludes that greater awareness was the real cause of increased survival (Stockton et al., 1997).

In developing countries the lack of public knowledge of breast cancer means that patients go to traditional healers or ignore their symptoms until very late in the disease (Vorobiof et al., 2001). An estimated 80% of all patients with cancer in developing countries present with an advanced stage of cancer at the first consultation (Anderson et al., and Groot MT et al, 2006). In a study of breast cancer in 212 patients in a Nigerian hospital, the majority of patients were young premenopausal women presenting with advanced stages of cancer. Most were either dead or lost to follow up within a year of diagnosis (Adesunkanmi et al., 2006).

Raising awareness is not a simple exercise. A trial of clinical breast examination in the Philippines lost almost 65% of women after the first screening (Pisani et al., 2006). Research on immigrant and minority women in Israel

underscored the importance of understanding women's perceptions of cancer and treatment options (Remennick, 2006). There is a need for research on health beliefs before any awareness or screening programs are introduced.

There are very few examples of public education on cancer in developing countries. One is Sudan where authorities initiated a public awareness campaign to address misconceptions about cancer and promote early detection and referral. The radio was chosen as the best medium for reaching illiterate rural and nomadic people. Posters were put in public places and a simple booklet promoting breast self examination (BSE) was distributed widely. Health professionals were educated on smoking, healthy diet and the importance of screening and early detection (Hamad HMA, 2006).

Breast Self Examination

It has not been proven that training in breast self examination (BSE) reduces mortality from breast cancer (Thomas et al., 2002; Austoker, 2003) and some researchers feel that it may do more harm than good. A study in St Petersburg did not find any significant difference in tumor stage between the group trained in BSE and the control group or any difference in death rates (Semiglazov et al., 1999). A study of female workers in

Shanghai found that intensive instruction in BSE did not reduce mortality from breast cancer but that more benign lesions were diagnosed in the instruction group than in the control group (ibid). Similarly, a Canadian review of studies published from 1966 to 2000 argued that BSE gives women a false sense of security while increasing the number of physician visits for benign breast lesions and higher rates of benign biopsy results (Baxter, 2001). However, some have argued that the Shanghai trial was not actually a study of BSE but a trial of BSE instruction. The women were not observed when they did BSE so study results were linked to the effect of BSE instruction, not the BSE itself. Also, half of the tumors in the control population were stage 1 or less which indicates that the population already had very good awareness of breast cancer. This means that impact of BSE would be less than if the population had no awareness (Smith et al., 2006). In short, there are mixed opinions about the cost-effectiveness of BSE and research on this issue is difficult to do in a controlled way.

Clinical Breast Examination and Mammography

Clinical breast examination (CBE) is generally accepted to be cost-effective. In high income countries it is combined with an offer of mammography once a year or biannually. The cost-effectiveness of CBE has not been questioned. However, there has been criticism of routine mammography as screening method. A trial of mammography in Sweden concluded that the number of women who would have to be screened for one breast cancer death to be prevented or postponed were 68,000. It concludes that this is a very small potential benefit and that the public has not been informed of the risks associated with mammography (false positive diagnoses and unnecessary surgical operations) (Skrabaneck, 1989).

A comparison of mammography with CBE concluded that the latter seemed as effective as mammography in reducing mortality from breast cancer (Mitra I et al, 2000). The authors argue that results from NHS breast screening program for women aged 50 to 64 years showed that only 22% of the invasive cancers of less than one centimeter detected by mammography would be missed by a clinical breast examination and that these advantages are clinically unimportant. Another study showed that after 13 years of follow up mortality was not lower in women who had done mammography screening than those receiving CBE. Clinical examinations performed by nurses were as good (Baines et al, 1989), or better, than those performed by surgeons. These results are important for developing countries that cannot afford large scale mammography screening, have few doctors and where CBE with nurses is a far more viable option.

Treatment

There are few examples of breast cancer treatment projects in developing countries. One such example is the breast cancer project in Tikur Anbessa Hospital in Addis Ababa, Ethiopia. The project is a comprehensive approach to breast cancer diagnosis and treatment and it has, for a relatively modest sum of money, 300-500,000 US\$ per year, improved the quality of breast cancer diagnosis and

treatment at the hospital. However, in spite of the project's support for public education through the Ethiopian Cancer association, most women with breast cancer still present very late, and treatment outcomes are often not optimal (Reeler et al, 2008). These problems are similar to situations in other countries. In India 50-70% patients present with locally advanced breast cancer, in peripheral facilities invariably resulting in radical mastectomy and in South America significant proportion of the patients are diagnosed at clinical stages II and III (Chopra and Schwartzmann, 2001).

Cervical Cancer

Prevention

The Human Papilloma Virus (HPV) vaccine holds great promise for protecting effectively against HPV 16 and 18 which cause up to 70% of cervical cancer cases, as well as genital warts. Gardasil by Merck is now on the market and Merck has donated 3 million doses to developing countries. GlaxoSmithKline's vaccine, Cervarix, has also become available this year. The vaccine needs to be administered in three doses to adolescent girls before onset of sexual activity. Health planners need to decide on how to administer this vaccine to the target group in the most cost-effective way, i.e. through the health system, in school based vaccination programs or through community outreach programs. An effective vaccine program would have a very positive impact on the cervical cancer incidence although the impact of such a program is not likely to be measurable for the next 20 years.

Early Detection

Challenges in developing countries include: limited access to health services and labs, no screening programs, limited or non-existent awareness among populations and health workers, limited or no access to diagnostics and laboratories, poor referral and follow up etc. Analysis of population-based surveys indicates that coverage of cervical cancer screening in developing countries is on average 19%, compared to 63% in developed countries (Gakidou et al, 2008). Most women present with advanced stages of cervical cancer with poor prognosis.

Screening Strategies

Pilot programs carried out by the Alliance for Cervical Cancer Prevention (ACCP) have tested the feasibility of cervical cancer screening in developing countries where most women have access to only primary health care facilities staffed with nurses and health workers rather than doctors.

Evidence from the pilot programs have shown that cervical cancer screening can be carried out in a cost-effective way in low resource settings. Programs in Africa, Asia and Latin America have demonstrated that cervical cancer screening is possible in primary health care settings if there is sufficient awareness in the population (men and women), good training of health workers, efficient management, and good monitoring and evaluation systems with feedback of results to managers.

The key principle in cost-effective cervical cancer

screening in developing countries is to cover a large number of women in the right age group who have not previously been screened. Research has shown that screening a large number of women at the age of 35 years who have never screened before reduced the life time risk of cancer by 25-36% and cost less than \$500 per year of life saved. Relative risk declines an additional 40% with two screenings at 35 and 40 years (Goldie et al, 2006).

Screening Methods

A recent article used computer-based models to assess the cost-effectiveness of different cervical cancer screening strategies in India, Kenya, Peru, South Africa and Thailand. The most cost-effective strategies were those that required the fewest visits as these resulted in improved follow up testing and treatment. The research concluded that visual inspection using acetic acid or DNA testing for HPV in one or two visits are cost-effective alternatives to cytology based screening programs with three clinical visits (ibid). However, HPV testing is far more expensive (an HPV test is US\$ 35-45) than visual inspection with acetic acid (vinegar) or visual inspection with Lugol Iodine (VILI) (Sankaranarayanan et al., 2005). Acetic acid has the same sensitivity as a pap smear but less specificity. Visual screening using acetic acid is relevant for developing countries because it is simple, low cost and requires little equipment. Results are immediate which enables treatment in the same visit thereby minimizing loss to follow up.

Treatment

It is important to be able to offer treatment to women who show signs of precancerous cells. In fact, there is no point in screening women if treatment cannot be offered to those who need it. Cryotherapy seems the most promising procedure for removing precancerous tissue from the cervix. Cryotherapy is simple, inexpensive, does not require electricity, has few side-effects and is up to 95% effective in treating severe abnormalities (Alliance for Cervical Cancer Prevention, 2004). It can be transported and administered by lower level health personnel in outreach facilities (Jacob et al., 2005). Nurses can be effectively trained in 5-10 days on visual inspection with acetic acid (VIA) and cryotherapy, especially if they get frequent, on-the-job, quality assurance visits from a trainer and the combination of VIA and cryotherapy is highly effective (Blumenthal et al., 2005). Clients showed a high degree of satisfaction with more than 95% of women reporting to be totally satisfied (Jacob et al., 2005).

The Loop Electrosurgical Excision Procedure (LEEP) which uses a thin electric wire to remove the lesions requires surgical tables, sterilization equipment and a smoke evacuator. There also seems to be more side-effects. While LEEP is less adapted to primary health care settings, it has the advantage of allowing tissue samples to be collected and send to the laboratory for further analysis.

Women's Cancers: A Public Health Approach

With the rising incidence of breast and cervical cancers in developing countries health planners are now faced with

the challenges of how to provide prevention, early detection, diagnosis, treatment and care for growing numbers of women every year. Few developing countries will be able to afford the mammography screening that high income countries are paying for. The good news is that there are a number of validated tools that are highly cost-effective and feasible in developing countries and that could significantly reduce mortality from breast and cervical cancers. Clinical breast examination, visual screening with acetic acid and cryotherapy have been shown to be effective in early detection and treatment and the new HPV vaccines will prevent many deaths.

The question is how interventions can be delivered in a cost-effective way that reaches large numbers of women. We propose a new approach that focuses on how screening and early detection for cervical and breast cancer can be offered by primary health care services which are more accessible to women than higher level services. Most approaches so far, including the pilot programs of ACCP, have looked at how cervical cancer screening and treatment can be integrated in existing services and/or how mobile clinics can help reach women who are otherwise not reached. None, as far as we know, have piloted how to combine the screening for breast and cervical cancer at lower levels of the health system. We propose a holistic approach of simultaneous screening for both cervical and breast cancer using existing stationary or mobile health services with nurses and health workers. Rather than setting up parallel services we should focus on an integrated, holistic approach to women's cancers.

Lessons from HIV/AIDS

Lessons learned from the HIV/AIDS epidemic in developing countries have demonstrated that the only way we can reach high service coverage is through integrating programs in existing health care services. Testing and treatment for HIV/AIDS started in most countries started as stand alone services. But it was eventually realized that there was no way of reaching, screening and treating large numbers of HIV positive people unless the service became integrated in the general health care services. The HIV testing was more cost-effectively done in health care settings than in stand alone centers (Axios International program data, n.d.) and the specialized centers for HIV/AIDS treatment quickly became overwhelmed with patients. The specialized HIV/AIDS centers have now become centers for initial diagnosis and complications while all follow up is done in the general health services. This has made it possible to reach many more infected people with effective treatment.

The other lesson learned from HIV/AIDS is the importance of the right strategies for public awareness and using community mechanisms to help in the fight against a disease. In HIV/AIDS the first messages that went to people in developing countries were that AIDS kills ("so you better not get it" and "there is no hope if I am infected"). Many people thought that there was no hope and they therefore did not want to test. People only started to test when there was access to effective treatment and people realized that one could lead a healthy life in spite of being infected. In an Axios managed program in

Tanzania the education and use of trusted community sources such as traditional birth attendants proved highly effective in bringing pregnant women forward for testing (ibid).

Strengthening Health Care Systems

We need to learn from the HIV/AIDS experience and make sure that we from the start integrate women's cancer programs as much as possible in the existing health care services. This will require much effort to strengthen health care systems in developing countries which are currently set up to deal mainly with infectious diseases. HIV/AIDS was the first large scale chronic disease that developing countries had to face and the first 10 years of this epidemic have shown how much effort is needed to enable health systems in developing countries to detect, diagnose and treat chronic diseases. These health systems have to change their focus from recording disease episodes to having individual patient files and records that allow chronic disease management. The whole "back office" (Dare and Reeler, 2005) of the health system including access to appropriate diagnostics, management systems, training of human resources, referral and patient education need profound strengthening. Health centers will have to have proper patient records so that individualized treatment and patient follow up can be ensured (fortunately, the last ten years of HIV/AIDS have already contributed to bringing about this change in patient management). High cost cancer vaccines and drugs need to be available in developing countries at affordable prices and health care workers need to be trained in how to monitor and adjust cancer treatment. The frequent absence of morphine for palliative care in developing countries should be addressed at international and national levels as soon as possible.

Cancer service delivery needs to be innovative and make the best use of scarce resources in developing countries. The effectiveness of cancer initiatives depend to a large extent on effective collaboration between the health system and the communities. The lower levels of the health systems need to have the capacity to do prevention, screening and early detection and the commitment of the community is needed for ensuring that these offers reach the right target group at the right time. Community engagement and support is needed to help patients overcome fear and comply with long duration treatment. Fortunately there are already examples of such innovative collaboration between health systems and communities in the area of cervical cancer prevention.

Under the Gardasil Access Program, Merck and Co., Inc., the pharmaceutical company, has pledged to make available at least 3 million doses of Gardasil® (Human Papilloma Virus Quadrivalent (types 6, 11, 16 and 18) Vaccine, Recombinant) for use in projects in eligible low income countries. The first round of applications was in September 2008 and a number of applications proposed innovative approaches for reaching girls in the targeted age group. Institutions in eight developing countries from Africa, Asia and Latin America applied for donations of Gardasil vaccines and applicants included a Ministry of Health, private and public hospitals and non-governmental

organizations with health care services. Applicants proposed innovative program approaches for vaccine delivery, including:

1. Mobile health units for hard to reach populations
2. Vaccinations at dispensaries and health centers
3. School based vaccination programs
4. Mother-daughter combinations where the mother gets screened for cervical cancer while the daughter gets vaccinated against HPV
5. Primary health care teams that collaborate with school teachers and traditional birth attendants to reach communities

All of the above programs had to address two key features of chronic treatment: communication to women, families and communities and how to ensure follow up. These follow up measures proposed a range of methods to ensure that families are reminded to complete the three doses of vaccine including use of village elders, traditional birth attendants, health workers, religious leaders and school teachers. Experience and evaluations will show the effectiveness of these follow up methods but the basic principle is that follow up systems for health interventions, whether multiple injections or chronic treatments, require a collaboration between informed communities and health systems.

Women Friendly Health Services

Globally, there are now more new cancer cases reported every year than there are new cases of HIV/AIDS and we need to mainstream cancer prevention and care. There is still much fear and superstition surrounding cancer and in most developing countries a diagnosis of cancer is perceived to be a death sentence just as it was with HIV in the early years of the HIV/AIDS epidemic. There will be a need for much education and awareness to make women come forward for screening and once at the health center there may be a need for child minding. Being screened for cervical cancer is an intimate procedure and women will need to leave their children outside the consultation room. There is a need for targeted public education of women, husbands and religious leaders and hopefully some of the learnings from the Gardasil Access Program will help to define the right kind of messages.

For women who do develop cancer there should be an effective referral system and local support groups like we have seen it with the traditional birth attendants for HIV positive mothers in Tanzania and elsewhere. These local groups help sick women and their families with psychological support, food and care of children.

The technical cornerstones of a cancer integration strategy would include:

1. Research to understand local perceptions of women's cancer and the local opinion leaders and to bring them onboard as partners
2. Culturally appropriate messages on the fact that cancer does not have to be a death sentence but can be cured if detected early enough
3. Community awareness campaigns to make women request screening for women's cancers in health facilities

4. Training of health staff in clinical breast examination, visual inspection of the cervix and cryotherapy for dysplasia

5. Women's health days where health facilities are dedicated to screening for women's cancers and vaccinating young girls for HPV

6. Mobile clinics for women's cancers to target market days and distant villages

7. Good referral systems and guidelines for women detected with cancer

8. Good monitoring and evaluation systems (likely to be manual)

9. Women's health booklets for women where information is recorded on screening dates and results as well as HPV vaccine for young girls. These booklets should be kept by women themselves as people are increasingly mobile. The booklets do not replace clinic records

10. Effective management, human resource development and quality assurance

11. Supportive staff supervision from higher level facilities and client feedback

12. Effective drugs and supply chain management

13. Clear policies on screening, diagnosis and treatment for women's cancers

Getting Women's Cancers on the Political Agenda

The only way developing countries will be able to afford to address women's cancers is by integrating the screening into the general health care services. We have validated, cost-effective tools but we need political will and funding. The question is how we mobilize such political will. Scholars have convincingly argued that it is not just cost-effectiveness that determines the political health agenda. A review of the national response to breast and cervical cancer in Ghana illustrated how breast cancer became the political priority despite of cost-effectiveness analysis pointing towards cervical cancer as the logical priority. A similar analysis of why maternal mortality never became a priority on the international agenda (Reichenbach, 2002) stresses the importance of political factors rather than cost-effectiveness measures. The authors identify four factors that influence whether an issue makes it to the international political health agenda and the associated funding:

1. The power of the actors, organizations, individuals involved

2. The extent to which the policy community agrees on causes and solutions and the emotional appeal of the issue

3. The political context including global governance and favorable political moments/opportunities

4. The extent to which there are clear measures of the severity of the problem, how impact can be measured and effective interventions (Shiffman, 2007).

We conclude that we need a coalition of organizations in cancer that will focus on bringing women's cancers on

the international health agenda. The beginnings of such a coalition can already be seen with organizations such as American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), European Cancer Organisation (ECCO), International Agency for Research on Cancer (IARC), World Health Organisation (WHO) and the International Union Against Cancer (UICC), increasingly focusing on the cancer burden in developing countries. We have consensus on cost-effective solutions, in particular with regard to cervical cancer but also increasingly for breast cancer. At the international level we need the same mobilization and political momentum around cancer as there has been for HIV/AIDS and hopefully the same international funding mechanisms for prevention, screening, treatment and care. However, this time a Global Fund or a President's Emergency Fund for AIDS Relief (PEPFAR) initiative should not focus on just a few specific diseases, but on the strengthening of health care systems in developing countries to cope with the rising burden of chronic diseases, including cancer.

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