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WOMEN'S CANCER IN LOW- AND MIDDLE-INCOME COUNTRIES

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THE BIG PICTURE

According to present trends, the global cancer burden will double over the next 20 years, with approximately 26.4 million new cancer cases and 17 million annual cancer deaths projected to occur worldwide by 2030[1]. The global cancer epidemic is not only growing, however – it is also changing. Once considered a disease of wealthy, industrialized societies, cancer is now increasingly a health burden for less-developed regions of the world. More than half of the 12.4 million estimated new cases of cancer in 2008, and two-thirds of the estimated 7.6 million cancer deaths, occurred in low- and middle-income countries[2], where cancer kills more people each year than AIDS, TB and malaria.

Once diagnosed, the chances of dying of cancer are typically three times higher for a person in the poorer regions of the world than for residents of wealthy countries[3].

Together, breast and cervical cancer account for more than one quarter of all female cancer deaths worldwide[4]. In the developing world, more than a quarter of a million (255,576) women died from breast cancer in 2007[5]. Cervical cancer takes an even bigger toll, with 272,238 women in developing countries dying of the disease in 2007[6]. Women in the world's poorer regions die of cervical cancer in highly disproportionate numbers: more than 85% of all deaths from cervical cancer occur in developing countries[7].

Despite the large and rapidly growing health burden and incalculable human suffering related to cancer in developing countries, the disease remains a low priority for low-and middle income country health spending, as well as for donor nations. Only 5% of global resources for cancer are spent in the developing world[8], and cancer control is conspicuously absent from the Millennium Development Goals. The WHO Model List of Essential Medicines, which is extremely influential in determining what therapies are available in developing countries, contains only one cancer drug -- Tamoxifen/Nolvadex. The WHO complementary list contains other cancer drugs, but these drugs require specialist medical care and facilities of which there are little in developing countries. In sum, the issue is simply not on the global health agenda.

In the poorer regions of the world, the paucity of cancer education, cancer registries to direct awareness-building and policy-making, or cancer prevention, diagnosis or treatment programs means women generally do not approach the health system until their disease is advanced, making treatment more costly and less effective for those who receive it. Moreover, the few properly equipped and staffed health facilities capable of cancer diagnosis and treatment that do exist are most often located in urban centers and are inaccessible to poor, rural populations. Health workers in low- and middle-income countries, including physicians, nurses and other health workers, are generally insufficiently trained in cancer prevention, diagnosis and treatment. Large majorities of women with cancer in poor countries, therefore, receive little or no medical attention at all throughout the course of their diseases.

"...If you can't travel overseas for treatment, you just sit and wait for your death..."

- Mary Onyango, Kenya, diagnosed with breast cancer aged 40 years [9]

While all cancers require much greater attention in low-resource settings, breast and cervical cancer warrant particular focus. Each is amenable to prevention and/or effective treatment options that can be provided in low-resource settings, but that

have not been widely available to women in need.[10, 11] A small number of highly effective programs demonstrate that much can be done to reduce risk and increase sustainable access to diagnosis and treatment for these high-mortality cancers -- including treatment of late-stage cancers and the provision of humane palliative care for individuals with untreatable disease – in a sustainable fashion in low-resource settings.

This paper outlines some of the realities of the overlooked global cancer epidemic, argues for expanding public and private sector support for cancer prevention, detection and care in resource-poor settings, and calls for a focus on women's cancers as an effective strategy to build capacity to treat a broader range of cancers and chronic diseases in such settings.

Eastern Europe and Central Asia

Discussions of issues affecting the poorer regions of the world often overlook the countries of Eastern Europe and Central Asia. However, the countries in this region are defined as low- and middle-income and share many of the same social and healthcare challenges as other countries thus defined. Some facts:

* Many countries in the region experienced a steep economic decline following the collapse of communism in 1989 and the subsequent war and civil turmoil that affected the region throughout the 1990s. Economic recovery in the region has been slow, and GDP in most counties has still not returned to 1989 levels.[12]

* In the region as a whole, GDP declined by 1.7% per year between 1990 and 2001[13]

* The proportion of the population currently estimated to be living in poverty is 29% in Romania, 25% in Albania, 20% in Bosnia, Herzegovina and Macedonia, and 10% in Croatia.[14]

* The proportion of ODA allocated to health is lower in this region than anywhere else in the world -- averaging 1.7%, compared with 16.5% in South America, 16.8% in South Asia, 8.6% in sub-Saharan Africa, and 9% globally.[15]

* The health gap between the countries of Eastern Europe and the EU-15 (the countries of the European Union prior to enlargement in May 2004) is wider today than in the early 1990s.[16]

* The migration of health professionals from the region in search of better pay and conditions elsewhere, and the unequal distribution of medical staff within countries are both major obstacles to quality health care. In the Republic of Moldova, it was estimated in 2002 that around 15% of rural areas were not covered by doctors. In Albania, many remote communities have no doctors at all.[17]

* Epidemiological and surveillance data on which to base health policy and funding in the region are extremely scarce and of variable quality, largely due to social disruption and large-scale movement of people in the 1990s.[18]

* Although health systems are being reformed across the region, the legacy of the Soviet-style centralized system remains strong. In many countries health services are inappropriate to current health needs and do not represent the most cost-effective use of scarce funds. For example, in 2000 the Republic of Moldova was trying to maintain three times as many hospitals as the UK on only 0.5% of the funds.[19]

Behind the Global Cancer Epidemic

Changing lifestyles, increasing lifespans and chronic infection lie at the root of the global growth in cancer. As more and more countries urbanize, changes in diet, insufficient exercise, smoking, drinking and obesity combine to increase cancer risk.

Individual risk of cancer also increases dramatically with age, and populations are aging more rapidly in low- and middle-income countries than in the richer world. It took more than a century for the proportion of people over age 65 in France to double, from 7% to 14%, in 1980. In Singapore, this same phenomenon is expected to take just 19 years, with people over 65 representing 14% of the population by 2019. And in China the proportion of people over 65 is projected to triple from 8% in 2006 to 24% in 2050. [20] In parts of Eastern Europe, too, the aging of the population is dramatic, with the proportion of people over 65 in Poland projected to rise from 13% in 2005 to 21% in 2025, and in Slovenia from 16% to 24% in the same period.[21]

Around one in four cancers in developing countries, as opposed to only one in ten in the developed world, are linked to infection[22]. These infections can be caused by viruses (e.g., hepatitis B for liver cancer, and human papillomavirus (HPV) for cervical cancer), bacteria (Helicobacter pylori for stomach cancer), or parasites (schistosomiasis for bladder cancer).[23]

Because so many human cancer cases are lifestyle-, behavior- or infection-related, however, they are also potentially preventable[24]. Estimates suggest that about half of new cancer cases and cancer deaths could be prevented.[25]

The knowledge and tools to make a major impact on these diseases exist today. Making the commitment to reduce significantly breast and cervical cancer in low- and middle-income countries will, however, require important changes in the way health services are managed and delivered. This will make them not only better able to address growing cancer rates in low- resource settings, but also better equipped to respond to a broad range of chronic diseases, including diabetes and cardio-vascular problems, that are an ever increasing burden on the poorer countries of the world .

Tackling myths and prejudices

In many countries women's cancers, and cancer in general, are surrounded by powerful myths, misconceptions and prejudices. In India, for example, women with cancer are sometimes prevented from using the same crockery and cutlery as the rest of the family and from preparing food because of unfounded fears that their disease is contagious[26]. Women with breast cancer in Ethiopia cite mystical forces, including the "evil eye," as possible causes of their illness[27]. And in Ukraine, women have reported that they were not told they had breast cancer, even when undergoing a mastectomy, because cultural taboos and official policy encourage doctors not to reveal a diagnosis of cancer to patients, to spare the sick person distress. [28]

An important first step in controlling breast cancer is education of the public at large to reduce stigma and misinformation, and of women to promote changes in behavior to minimize risk and to encourage timely treatment for any symptoms. Evidence from the UK indicates that good awareness among women and the general public can be more significant than a national breast cancer screening program in saving women's lives[29].

Evidence from HIV/AIDS programs shows that stigma is a major barrier to universal access to disease prevention, care and support. Stigma leads to a lower uptake of preventive and diagnostic services and to postponement or rejection of treatment, care and support. Stigma also disproportionately affects girls, women and socially vulnerable groups.[30]

Successful stigma reduction approaches target the problem at different levels, addressing the perceptions of individuals, communities, health service providers and policy makers. Successful stigma-reduction activities on an individual and community level include empowering people living with the disease; participatory education programs; and activities that foster interaction between people living with the disease and others. Successful initiatives at a health delivery level include providing education and training in specialized healthcare, such as the prevention, diagnosis and treatment of cancer, to health facility staff at all levels, while at the policy level, promising approaches include efforts to challenge stigma and discrimination in institutional settings, and to build human rights capacity..[31]

There is evidence, too, that access to treatment – at least for infectious diseases – encourages people living with the disease to disclose their status to their families, which also helps to reduce stigma. [32], [33]

Key points

- Cancer kills more people each year in low- and middle-income countries than AIDS, TB and malaria.
- More than half of all new cancer cases and almost two-thirds of cancer deaths in 2008 occurred in the poorer regions of the world.
- In 2008 there were 12.4 million new cases of cancer, 7.6 million cancer deaths and 28 million people living with cancer worldwide.
- By 2030 there will be an estimated 26.4 million new cancer cases per year and 17 million deaths worldwide.
- Cervical cancer kills more women in developing countries than any other form of the disease; 85% of global deaths from cervical cancer occur in the developing world.
- Modern lifestyles, coupled with rapidly aging of populations and, in poorer countries the high impact of cancer-causing infections are major driving forces behind the global cancer epidemic.
- An estimated half of the cancers diagnosed each year are potentially preventable.
- Stigma is a major obstacle to cancer diagnosis and treatment that can be overcome in part through education and access to treatment.

BREAST CANCER

Breast cancer is the single most prevalent cancer worldwide[34]. In 2007, an estimated 1.3 million new cases[35] brought the global total of people living with breast cancer to 4.4 million[36].

Today, a woman's lifetime chance of developing breast cancer before age 65 is still more than two and a half times greater if she lives in a developed country as opposed to in the developing world[37]. That gap is closing quickly, however. Whereas breast cancer incidence has been increasing globally at the rate of about 0.5% per year since 1990, it is rising as much as ten times faster – at up to 5% per year -- in low- and middle-income countries[38]. In the Czech Republic, for instance, breast cancer incidence increased by 4% per annum across the 1990s, to reach 93 per 100,000 women in 2001, compared with an increase of 0.6% per annum in the USA during the same period.[39] And cancer registries in China are reporting annual increases in incidence of 3-4%. [40] In 2007, more than half of all breast cancer deaths (255,576) occurred in the developing world[41].

Beyond the personal pain of losing a loved one, the death of a woman to cancer can have a profound impact on her family and on the wider community. In many instances, a woman with breast cancer is also the principal or even sole provider of family income or of care for children and elderly people. When a mother becomes ill or dies, daughters are often left to assume her responsibilities, forcing many girls to drop out of school.

The World Bank has attempted to quantify the loss to the family and national economies from breast cancer in different regions of the world for 2001, using Disability Adjusted Life Years, or DALYs (*see Table 1*) [42]. DALYs are a measure of the productive years of life that could have been expected and that are lost to premature death or disability.

Table 1: Number of cancer deaths and DALYs lost to cancer, by World Bank Region 2001

	East Asia and the Pacific	Latin America and the Caribbean	South Asia	Sub-Saharan Africa	(Eastern) Europe and Central Asia	High income countries
Cancer site	(Deaths) DALYs Lost	(Deaths) DALYs Lost	(Deaths) DALYs Lost	(Deaths) DALYs Lost	(Deaths) DALYs Lost	(Deaths) DALYs Lost
Breast cancer	(93,000) 1,730,000	(37,000) 642,000	(76,000) 1,246,000	(34,000) 574,000	(63,000) 1,058,000	(155,000) 2,509,000
Cervical cancer	(47,000) 805,000	(26,000) 494,000	(83,000) 1,423,000	(38,000) 627,000	(19,000) 356,000	(17,000) 319,000

Causes and risk factors

The hormones estrogen and progesterone play a major role in breast cancer. Risk of the disease begins at menarche, about the age of 15 years, and rises across a woman's reproductive life span to level off after the menopause. Women who start childbearing at a young age, have many children and breast feed for prolonged periods are at lesser risk[43], while the use of hormone replacement therapy is associated with increased risk[44], as are obesity, alcohol use and low levels of exercise. Alcohol is likely to be especially prominent as a cancer risk factor in south-eastern Europe, where rates of chronic liver disease and cirrhosis among women, mainly attributed to alcohol, are 70% higher than in the countries of the European Union prior to enlargement in 2004. Universally, women who have a family history of breast cancer are 2-3 times as likely to develop the disease as those without such an inherited risk[45].

Prevention, screening and diagnosis

Early detection is critical to improving breast cancer survival. In the USA, for example, 98% of women whose breast cancer is diagnosed and treated early are still alive 5 years later, compared with 84% of women whose disease has spread to the lymph nodes before treatment starts, and 28% of those whose cancer has spread to distant organs[46]. Early detection is particularly relevant in limited resource settings, where the costs of proper treatment for advanced stage disease are largely or completely unaffordable.

Early detection can be particularly difficult to achieve in less-developed regions of the world, where many people with disease symptoms consult a traditional healer before seeking trained medical help. Fear, stigma and misinformation also keep many women from seeking diagnosis and treatment for breast cancer. As a result, around 80% of cancer patients in developing countries are not seen by the health services until their disease is advanced, difficult and costly to treat[47] -- up to nine times more costly than treating early disease.[48] In India, for instance, 50-70% of the 75,000 or more women newly diagnosed with breast cancer each year present with disease that has spread, compared with 38% and 30% in Europe and the US respectively[49].

A central pillar in early detection of breast cancer is the routine screening of women in the relevant age group. Mass screening with mammography is not feasible in the poorer regions of the world, but evidence suggests that clinical examination of the breasts by a nurse, combined with public education about the value of early breast cancer diagnosis, can be equally effective, especially in countries where patients typically present with locally advanced or metastatic disease. Clinical examination has the added advantage of being applicable even in remote clinics and health centers[50]. Currently, however, the proportion of women covered by breast screening programs of any kind in the poorer regions of the world remains extremely low.

Case studies of less-developed countries that are making important progress in cancer control show that resource constraints and other cultural and logistical challenge can be overcome. The Sudan, for example, has launched a comprehensive cancer control program that focuses on the country's three major cancer killers: breast, cervical and oral cancer. Public education is the cornerstone of the Sudan's effort. Since 80% of the country's 41 million people live in rural areas or are nomadic and illiteracy is widespread, radio, backed up by posters, TV and discussion in public places have been chosen as the principal communication tools

for the Sudanese program. Though the Sudan's efforts have yet to be fully evaluated, there is evidence that patients there are seeking cancer treatment earlier and reducing some risk behaviors, such as alcohol and tobacco consumption[51].

Treatment

Radiotherapy is a key component of comprehensive cancer care, and access to radiotherapy should be a high priority for the cancer programs in low- and middle-income countries[52]. More than 50% of all cancer patients will require radiotherapy at some point in their illness, though the proportion is higher among those whose disease is advanced. There is, however, an acute shortage of radiotherapy services in the poorer regions of the world. In Africa, only 20% of patients in need have access to radiotherapy. The Asia-Pacific region has less than one third of the machines required for a cancer burden of 3 million new cases a year. And more than 30 countries in Africa and Asia have no radiotherapy services at all[53].

In 2002, Eastern Europe as a whole had about half the number of radiotherapy machines required to meet estimated cancer treatment needs. Access to radiotherapy in the region varies widely by country, however. In the same year, Albania had just one of the 8 machines it needed; Bosnia and Herzegovina had three of the 16 machines required to meet their population's needs, while Uzbekistan had 21 of the estimated 26 machines required and the Czech Republic had 54 of the 61 machines needed. [54]

Again, the gap between demand and supply, though large, is not insurmountable. Recognizing the scale of unmet need, the International Atomic Energy Agency (IAEA) has provided over US$200 million worth of technology and training to help developing countries establish radiotherapy services since 1981[55]. In 2004, the IAEA established the Program of Action for Cancer Treatment (PACT) to expand these activities to cover all aspects of cancer control, treatment and care, in partnership with organizations such as the World Health Organization (WHO)[56]. Six pilot projects, known as the PACT Model Demonstration Sites, are currently working to establish comprehensive cancer control programs in Albania, Nicaragua, Sri Lanka, United Republic of Tanzania, Viet Nam and Yemen [57]. Many more countries, however, need this type of support to increase access to basic care with radiotherapy.

A global initiative for breast care

In 2002, The Breast Health Global Initiative (BHGI) -- an alliance of national and international health organizations, government agencies, non-governmental organizations, corporations and individuals dedicated to improving breast health and cancer treatment for women in the poorer regions of the world – was founded by the US-based Fred Hutchinson Cancer Research Center and Susan G. Komen for the Cure. One of BHGI's first activities was to develop and publish Guidelines for International Breast Health and Cancer Control aimed at low- and middle-income countries. These guidelines describe the essential requirements for early detection, diagnosis and treatment for breast cancer, and outline a range of options for providing these services in different socio-economic settings[58].

In a 2008 supplement to the journal *Cancer*, BHGI proposed the development of "learning laboratories" [59] to review and refine these guidelines, with the ultimate goal of expanding their applicability and use. These Laboratories will bring together experts from a variety of socio-economic settings to share their skills and personal experiences of delivering health care in very different environments, so the guidelines could best reflect the "real world" challenges of creating service models and delivering services in resource-poor settings.

The first of these laboratories was established in Kumasi, Ghana in October 2008[60], in collaboration with the Ghana Breast Cancer Alliance. The laboratory's initial task is to develop a curriculum for the ongoing training of Ghanaian health personnel in breast cancer care and management that takes into account the resource limitations that exist in Ghana and other developing countries. A second learning laboratory has also been established in Bogota, Colombia in collaboration with the Colombian Instituto Nacional de Cancerologia (National Cancer Institute).

Laboratory-based pathology services are also a fundamental part of any successful cancer treatment program. Accurate diagnosis of breast cancer, determination of the stage of the disease and how best to treat it – i.e. through what combination of drugs, radiotherapy and surgery -- all require the services of a pathologist, a doctor who specializes in medical diagnosis. But such specialists are extremely scarce in the poorer regions of the world. Where pathology laboratories do exist, they often lack essential equipment, supplies and technicians as well as senior staff.

In 2005, a small group of pathologists at the University Hospital of North Norway (UNN) working in collaboration with the Breast Health Global Initiative (BHGI – *see box*) helped to re-establish pathology services at the Komfo Anokye Teaching Hospital (KATH) in Kumasi, Ghana that had been closed down for lack of resources[61]. In so doing they also provided a model of effective international collaboration for other resource-poor countries facing similar problems. Two laboratory technicians from KATH received three months' training in the preparation of tissue slide and specimens at the UNN. On their return to Ghana they began sending slides of breast cancer biopsies every week by courier to UNN for expert diagnosis, which was then communicated swiftly back to Kumasi by phone or email. At the same time, two young Ghanaian physicians joined the pathology training course at UNN with the aim of returning to Ghana as qualified pathologists in 2010, to re-establish a full pathology service and, importantly, to start training new pathologists within the country.

Ethiopia: A centre of excellence in breast cancer care

In 2005, Axios established a pilot project designed to build Ethiopia's capacity to manage all aspects of breast cancer, with the support of the drug company AstraZeneca and the close cooperation of the ministry of health[62]. When the project began there were no data on breast cancer patients, no mammography, no treatment or care guidelines, little drug treatment available and only one cancer specialist and one radiotherapy unit for a country of 72 million people. By late 2008, Tikur Anbessa Hospital in Addis Ababa had become a centre of excellence and referral for women with breast cancer. Guidelines for treatment and care had been developed, state-of-the-art equipment had been installed, procurement systems for drugs and lab supplies had been set up, staff had been trained to run the program, and drugs were made available through AstraZeneca donations. In parallel, an Ethiopian Cancer Association has been strengthened and is focused on raising public awareness and establishing a national cancer registry to gather data on the disease in Ethiopia. By end 2008, 3,634 patients had been screened, diagnosed, or treated at Tikur Anbessa, and were being followed up as necessary.

Key points

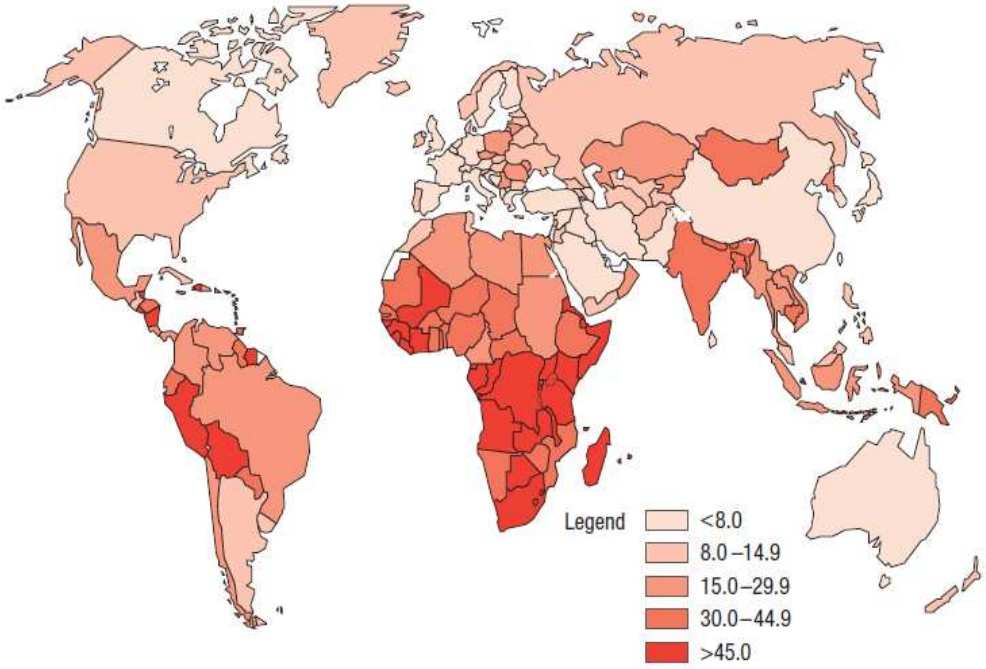
- Breast cancer is the single most prevalent cancer worldwide.
- In 2007 there were 1.3 million new cases of breast cancer worldwide, and 464,854 deaths. More than half of deaths (255,576) were in the developing world.
- The incidence of breast cancer has been increasing globally by 0.5% per year since 1990. But in the poorer regions of the world it has been rising up to ten times as fast.
- A woman's childbearing history, lifestyle (diet/exercise) and family history are all associated with her breast cancer risk.
- Early detection is the single most important factor in surviving breast cancer. Yet, around 80% of cancer patients in developing countries are not seen by the health services until their disease is advanced. Late stage breast cancer is up to nine times more costly to treat than early disease, and outcomes are much poorer.
- More than half of all cancer patients -- and a higher proportion of those with advanced disease -- require radiotherapy at some point in their illness.
- In Africa only 20% of patients in need have access to radiotherapy, and 30 countries in Africa and Asia have no radiotherapy services at all.

CERVICAL CANCER

Incidence of cervical cancer varies widely between different countries. Generally speaking, the lowest rates – below 7/100,000 women per year– are found in West Asian countries and China, and the highest rates – typically above 25/100,000 women per year -- in sub-Saharan Africa, Latin America and the Caribbean, and South and East Asia[63]. Cervical cancer affects 10/100,000 women per year in North America and Western Europe. The rates in Haiti, Tanzania and Bolivia, which are

the highest in their regions, are 87/100,000, 69/100,000 and 55/100,000 women per year respectively[64].

Figure 1: Worldwide Incidence of cervical cancer per 100 000 females (all ages), age-standardized to the WHO standard population, 2005. Reproduced with permission from WHO.[65]



A woman's chances of surviving cervical cancer are equally variable. Mortality from the disease is considerably higher in Eastern Europe than in the EU, for example, with the death rate in Romania alone being 15.4 per 100,000 women compared with the EU-15 level of 2.4 per 100,000.[66] Studies also show that fewer than one in four women with the disease in Uganda and Zimbabwe are still alive five years after diagnosis, compared with 30-50% in Cuba, India and the Philippines, 50-60% in Thailand and China, and 60-75% in the developed world as a whole[67]. Again, the World Bank has attempted to quantify, in terms of DALYs, the loss to each region of so many women in their most productive years *(see Table 1)*. Early detection of cervical cancer is key to survival.

Causes and risk factors

The principal cause of cervical cancer is infection with the human papillomavirus (HPV), an extremely common sexually transmitted organism that destroys the regulatory machinery within the cells of the cervix. In most cases, HPV infection clears up spontaneously within a few years, and only a small percentage progresses to cancer. Of the 40 or so types of HPV known to infect the genital tract, 15 have been found to put women at significant risk for cervical cancer -- with just two types, HPV 16 and 18, responsible for more than 60% of cases[68].

However, a number of other risk factors also contribute to the development of cervical cancer in someone infected with HPV. Co-infection with HIV and some other sexually transmitted organisms, such as chlamydia and herpes simplex viruses, appear to heighten the risk, as does tobacco smoking, long-term use of oral contraceptives and a poor diet. Moreover, some women have a genetic susceptibility to cervical cancer[69].

Prevention, screening and diagnosis

The single most important measure in preventing cervical cancer is avoiding infection with HPV. Vaccines that protect against two or four of the types classified as "high-risk" for cervical cancer -- types 16 and 18 or 6, 11, 16 and 18 respectively -- have recently become available[70]. The cost of the vaccines, however -- currently around US$100 per dose in countries where they have been licensed -- is a formidable barrier to access[71]. One manufacturer, Merck, has pledged at least three million doses of its HPV vaccine, Gardasil, to eligible countries through a donation program managed by Axios. Under the first round of donations agreed in September 2008, 190,000 doses of the vaccine are being shipped to eight countries in Africa, Asia and Latin America[72].

Cost is not the only challenge to developing effective HPV vaccine programs in resource-poor countries, however. In order to achieve protection of 90% or above, HPV vaccines must be administered in three doses to adolescent girls before they become sexually active. Most adolescent girls are not in routine contact with health services in the same way that mothers and babies may be, meaning an HPV vaccination program must include in its design effective mechanisms to reach adolescent girls with information and vaccination services, and to ensure that they return for all three vaccine doses.

A number of strategies have been proposed and are being tested to increase the accessibility of HPV vaccines. PATH-supported demonstration projects in India, Peru, Uganda and Viet Nam, in cooperation with the national Ministries of Health, are exploring and developing strategies to reach adolescent girls more effectively through school-based programs[73], health-centers[74] and government-sponsored child care centers[75]. Applications to the GARDASIL® Access Program have included proposals for vaccine delivery through mobile health units or local dispensaries.[76]

Whatever methods are employed to reach adolescent girls, however, the support of families and communities is essential to any child-focused health initiative. In the case of HPV, this means addressing a variety of issues related to moral, religious and cultural resistance to ideas of girls' sexual activity, knowledge, independence and decision-making. Studies in countries as diverse as Malaysia, South Africa and the UK suggest, for example, that a common concern among parents and guardians is that HPV vaccination programs might encourage promiscuity, and/or stigmatize young women[77, 78,79, 80]. However, initial experiences from the GARDASIL® Access Program and other HPV vaccine programs do not indicate that these perceptions have affected vaccine uptake in program sites.

Even if vaccination against HPV infection is widely adopted, the decline in cervical cancer incidence rates will not become apparent for another 20 years, due to the time-lag between infection with HPV and development of cervical cancer. Moreover, women who are vaccinated remain at some risk, though modest, from at least four other types of HPV not covered by existing vaccines. Therefore, early detection and treatment must remain a principal focus of cervical cancer control programs and cervical cancer screening should be included in HPV vaccination programs whenever possible. The benefits of such efforts are great: research shows that screening a woman only once between the ages of 35 and 40 reduces her lifetime risk of cervical cancer by 25-35% [81]. Currently, however, coverage of cervical

screening in developing countries is on average 19%, compared to 63% in developed countries, though coverage varies widely, from 1% in Bangladesh to 73% in Brazil[82].

Screening programs in the developed world use mainly Pap smear technology, which involves microscopic examination of cells taken from the cervix. Where the necessary laboratory facilities and expertise are not available, however, screening can be carried out effectively and at much lower cost by visual inspection of the cervix, using staining with acetic acid (vinegar) or Lugol iodine to identify abnormal cells. Such screening can be performed by nurses trained in the procedure, even in the most basic primary health care settings.

Other methods to identify women at risk for cervical cancer are also in use and development. Researchers in India recently reported the results of a large-scale, seven-year study of a new HPV test in rural women. The new test proved significantly more effective than Pap smears or visual inspection, but is more time-consuming, requires sophisticated laboratory services, and costs US$20-30 per test.[83] Following the release of the study, the test's manufacturer, Qiagen, announced that it will donate one million of the new tests for use in resource-poor countries. The company also expects to launch a second generation product designed specifically for resource-poor countries, called *care*HPV test [84] in the near future, following promising results in a study on 2530 women in Shanxi province, China[85].

These case studies and research results demonstrate that cost, equipment, technical needs and lack of trained personnel are significant but not insurmountable challenges in cervical cancer detection. Extremely poor detection rates of cervical cancer in its early or precancerous stages in low- and middle-income countries can be reversed through concerted action.

A school for cervical cancer training in Latin America

In 2004, a Latin American School for Cervical Cancer was established in Peru by the Instituto Nacional de Enfermedades Neoplasicas (INEN) in collaboration with the International Agency for Cancer Research (IARC)[86]. The School was established to address delays in efforts to expand cervical screening throughout Latin America caused by shortages of properly trained program administrators. Today, the School offers courses tailored to the needs of the different professionals involved in cervical cancer management, from gynecologists and screening providers to policy-makers and non-medical staff such as cancer registry and record-keepers. The school's objective is to train people who are able to train others in order rapidly to increase capacity region-wide. Reaching out to remote rural areas where women are particularly deprived of services is a particular focus of the school's efforts.

Treatment

Cancer screening is only effective and ethical if it is part of a well-organized system of follow-up and treatment. In low-resource settings, abnormal cervical cells that have not yet become cancerous can be treated at a primary health care facility using cryotherapy, a minimally invasive procedure that destroys tissue by freezing. Cryotherapy is simple, inexpensive, does not require electricity and is up to 95% effective for small lesions[87]. Nurses can be trained to use both the acetic acid screening technique and cryotherapy in 5-10 days, and both procedures can be performed at the same place and on the same day, reducing the need for repeat health centre visits.

Another procedure for treating early disease is loop electrosurgical excision (LEEP), which uses a thin wire heated with electricity to remove abnormal cells. LEEP has comparable effectiveness to cryotherapy, but provides an additional advantage in that a reliable histopathology sample can be obtained through the procedure, which makes it possible to assess if the disease has become invasive. LEEP requires more intensive training, a reliable power supply, surgical tables, sterilizing equipment and a smoke evacuator, and is therefore most suited to a secondary level facility such as a clinic or district hospital[88].

As already noted, early detection of cervical cancer is the key to survival, particularly in low-resource settings. Treatment options are based on the extent or “stage” of the disease at the time of diagnosis, as assessed by pathological criteria such as tumor size, and the extent of spread of disease in the pelvis and distant organs. Patients with advanced cervical cancer require referral to a specialist hospital for treatment that may involve surgery, radiotherapy, or chemotherapy, singly or in combination.

The prognosis for a woman with cervical cancer is influenced by factors such as the clinical stage of disease at presentation, her age, lymph node status, general health and degree of immunosuppression.[89] Even with optimal treatment, five-year survival ranges from 30% if the cancer involves only the vagina, to less than 5% if it has spread to distant organs[90]. In the poorer regions of the world, however, treatment for late stage cervical cancer is available to virtually no one – meaning that early detection and destruction of suspect cells in the pre-cancerous stage is key to improving survival for women in these regions.

Key Points

- The lowest incidence rates for cervical cancer are in China and West Asia, and the highest are in Africa, Latin America and the Caribbean, and South and East Asia.
- The principal cause of cervical cancer is infection with the human papillomavirus (HPV), with just two types, HPV 16 and 18, responsible for more than 60% of cases.
- Compounding risk factors for cervical cancer include tobacco smoking, long-term use of oral contraceptives, poor diet and co-infection with other sexually transmitted organisms.
- Screening a woman only once between the ages of 35 and 40 reduces her lifetime risk of cervical cancer by 25-35%.
- Coverage of cervical screening in developing countries as a whole average 19% compared with 63% in the developed world.

THE NEED FOR LATE-STAGE TREATMENT

Increasing early detection must remain a top priority. But it is unlikely that a significant reduction in the proportion of women presenting to health systems with late-stage disease will occur soon. A vital part of scaling up cancer services therefore must include developing treatment protocols for all stages of disease – early, mid and late-stage –, enabling access to radiotherapy and improving surgery skills where needed[91]. Finally, it is a ethical and medical must to improve the nearly non-existent palliative care options now available for women with untreatable cancer.

It is distressing to note that almost no literature exists on the question of late-stage cancer treatment in low-resource settings. The reality for women with advanced cancers in low- and middle-income countries is that most are sent home to die often excruciatingly painful deaths, with little or no treatment or care. This cannot be acceptable to policy-makers, funders, advocates or the private sector, and urgent work is required to develop cost-effective and sustainable approaches to late-stage and palliative care for women's and other cancers in the poorer regions of the world.

In wealthy countries, late-stage treatment for most cancers involves very expensive therapies that in many cases add only months of life. Exporting such approaches to very poor countries is clearly inappropriate and unsustainable. Appropriate options may include new cost-effective combinations of existing therapies, including some that have gone off-patent, that may extend and/or improve quality of life for women with late stage cancer.

Palliative Care

Palliative care is an essential element of cancer treatment that integrates clinical, psychological and spiritual aspects of care. Its purpose is to improve the quality of life of people with incurable disease, to give practical and emotional support to patients and their families in the final phase of life and to help patients with advanced disease die with dignity. A core function of palliative care is the prevention and control of distressing symptoms -- most notably the often-intense pain that accompanies late-stage cancer.

Palliative care services are especially important in the developing world, where 80% of cancer patients present with advanced disease. Yet, palliative care is often overlooked or barely mentioned in what national cancer control programs do exist in low- and middle-income countries. Access to morphine -- which is the mainstay of cancer pain control and a basic human right, according to the World Health Organization – is non-existent or almost non-existent in 150 of WHO's 193 member states, leaving an estimated 30 to 86 million people worldwide with no relief for moderate-to-severe pain[92].

The use of narcotics is controlled by a number of international conventions designed to prevent illicit production and trafficking of potentially addictive drugs, and in many countries tight restrictions and excessive paperwork deter doctors from prescribing them for patients in pain[93]. Intense, but ill-founded fears about addiction also inhibit their use. In very many cases, however, palliative care is simply not considered because doctors and nurses have received no training in the discipline and are not familiar with its principles.

At the same time a number of pioneering initiatives show what can be done to relieve cancer-related suffering, even in the poorest settings. The Nairobi Hospice, for example, one of the first palliative care programs on the sub-continent outside South Africa, recently produced a Palliative Care Toolkit[94] – a practical manual that draws on its two decades of experience to encourage and equip health workers in similar settings to provide palliative care to their patients.

In 1993, the Nairobi Hospice's first medical director, Dr. Anne Merriman, founded Hospice Uganda, which has worked with the Uganda Ministry of Health to make morphine – purchased in powder form at less than one tenth of one US cent per milligram and mixed on site -- available to health facilities across much of the country[95]. In its first nine years of operation, Hospice Uganda served 4,000 patients – an extraordinary number, yet only a minute proportion of those in need. In 2002, the organization began offering a distance learning diploma course in palliative care to raise awareness and increase capacity among health professionals within Uganda and across the sub-continent.

In Ethiopia the introduction of morphine followed the development of palliative care guidelines and much negotiation with the drug regulatory authorities[96].

In Eastern Europe the provision of palliative care varies enormously between countries. Uzbekistan and Tajikistan, for example, have no services, while Hungary had an estimated 57 services covering 13% of cancer patients in 2006 .[97]

Hungary: Hospice movement triumphs over ancient taboos

In Hungary – where death and dying were taboo subjects until the political and social changes that followed the collapse of communism – the palliative care movement began to emerge in the late 1980s. With tacit support from President Arpad Goncz and other political figures, the Hungarian Hospice Foundation, initiated by two groups working at the National Institute of Oncology, was formally established in April 1991. Its first tasks were to change public attitudes to death and dying, and to enlist support for palliative care among social organizations. The earliest services were provided by volunteers in patients' homes, but in 1994 more formal hospice teams began to develop with help from the US-based Soros Foundation.

After years of educating the public and health professionals in the philosophy and principles of palliative care, and lobbying government to turn tacit support into practical and legal action, palliative care became an integral component of the Hungarian national health service in 2004, with strict definition, standards and regulations. In 2005, Hungary established a National Cancer Control Program as part of the national development plan, and the following year palliative care was included in the program.

Today, all cancer patients have the right to free morphine and other opiates, even if some physicians still lack knowledge and experience in prescribing such drugs. Despite the fact that provision is patchy, with some Hungarian counties still having no services at all, it is estimated that approximately half those in need countrywide receive specialist palliative care.[98]

Key points

- Almost no literature exists on the issue of late-stage treatment for cancer in resource-poor settings.
- A core function of palliative care is the relief of pain, which afflicts the great majority of cancer patients
- Morphine, the mainstay of cancer pain control, is virtually unavailable in 150 of WHO's 193 member states, due largely to cultural prejudices and excessively restrictive narcotic control laws and policies
- Palliative care is an essential element of cancer treatment, yet in the poorer regions of the world it is either a very low priority or not considered at all in cancer programs.
- In many countries palliative care is completely missing from the curriculum of medical and nursing schools

THE CHALLENGES

The knowledge and tools exist today to cut dramatically the toll of lives lost to breast and cervical cancer in low- and middle-income countries, as an initial step toward addressing a broader range of cancers that are rapidly increasing in low-resource settings. Translating knowledge into effective action, however, raises many challenges – for program designers and implementers, policy-makers, funders, patients and advocates. These include:

* *Lack of awareness and knowledge about cancer among the general public*. Basic levels of education about cancer risk, prevention, detection and treatment are very low in many settings in which the cancer burden is growing rapidly. Women must be educated to seek screening if available as well as timely treatment for signs and symptoms. Families and entire societies must be part of the education process, in order to reduce stigma, overcome fear of cancer and increase support for early cancer diagnosis and treatment.

* *Lack of awareness and knowledge about cancer among health workers*. The healthcare community also needs increased education about cancer, as many health workers have little knowledge or experience of working with cancer or other chronic diseases.

* *Lack of surveillance and statistical data about cancer.* In 2000, less than 20% of the world population were covered by Cancer Registries, which means that health ministries in much of the world do not know the extent of the cancer problem in their countries and lack the basic data needed to plan for services or allocate resources[99].

* *Poor health infrastructure.* Hospitals and clinics in poor countries often lack essential equipment and supplies. Moreover, services tend to be concentrated in urban areas, leaving rural people with specially limited access to health care.

* *Shortages of skilled personnel.* Many low- and middle-income countries have fewer than 20 doctors and 100 nurses per 100,000 people, which is the minimum standard set by WHO. The shortages are most acute in Africa, which has 24% of the global burden of disease and only 3% of global health workers. By contrast the Americas, with 10% of the global disease burden, have 37% of the world's health workers[100]. Specialist skills are even more scarce. Ethiopia, for example, had only

one oncologist for a population of 72 million in 2005[101]. And Tanzania's Ocean Road Cancer Institute, the country's first and only cancer treatment centre, has only one part-time pathologist and one gynecologist[102]. Health worker shortages are exacerbated by the emigration of health professionals from developing countries to the wealthy world in search of better working conditions and pay. According to WHO, one in four doctors and one in twenty nurses trained in Africa was working in an Organization for Economic Cooperation and Development (OECD) country in 2006[103].

* *High cost of drugs and diagnostics.* The prices of cancer therapies often put them beyond the reach of public health systems in low- and middle-income countries. To date, there have been only very limited efforts to make lifesaving cancer therapies available through drug access initiatives, similar to those that have brought treatment to people living with HIV/AIDS in the poorer regions of the world.

* *Inadequate and inappropriate health care systems.* In many places, health services have been set up to deal with acute, time-limited infectious diseases. Dealing with chronic illness requires fundamental changes, from the training and reorientation of health staff to record keeping and the long-term management and follow-up of patients.

"Health systems in developing countries can usually cope with the intermittent emergencies caused by infectious diseases. The patient either survives or dies. In contrast, the demands of chronic care can push a fragile health system to the breaking point."

- Dr Margaret Chan, Director-General of WHO[104]

THE SOLUTIONS

The knowledge and experience exist today to guide profound and positive changes on the management of breast and cervical cancer in low- and middle-income countries. The challenge is to apply that knowledge through a public health framework, maximizing the benefits for as many women as possible while keeping costs at a manageable level for poorer countries and international donor agencies alike. This is not an easy task, as both diagnostics and treatment for women's cancer are expensive and difficult to obtain in resource-poor countries. Investing in improving facilities for diagnosis and late stage treatment for women's cancer, however, will likely produce multiple benefits by improving the diagnosis and treatment of other cancers as well. Provision of treatment will lead -- as it has with other diseases, notably with HIV/AIDS -- to increased awareness and increased numbers of people seeking early diagnosis. Earlier presentation will, in turn, lead to less costly treatment and better treatment outcomes.

Furthermore, resources invested in improving cancer diagnosis and treatment in the health systems of low- and middle-income countries will have benefits beyond cancer. The training of health care professionals and the development of new management and patient follow-up systems will strengthen care also for other chronic diseases such as diabetes and cardiovascular disease.

Successfully addressing women's cancers requires that services be "women friendly." To draw women at risk, health services must be sensitive to women's feelings about their bodies and fears about cancer; respectful of women's need for

privacy during consultations; available at convenient times and in convenient locations; and include supervision for accompanying children where possible. Mobile clinics that can target market days and reach remote communities, and special 'women's health days' are just two examples of what can be done to make health services woman friendly. Another is to provide one-stop services that, when appropriate, combine screening and treatment, or that screen for both breast and cervical cancer at the same time and same venue.

While there is an urgent need to provide services for the many thousands of women in poorer countries with little or no access to treatment and care for their cancer, countries should not overlook prevention, which is a vital element of a comprehensive cancer control program. Much can be done to minimize the burden of the disease by investing in measures to raise public awareness and to reduce the risk of cancer by, among other things, promoting and supporting healthy lifestyles that include good nutrition, adequate exercise, moderate consumption of alcohol, and avoidance of tobacco smoking. Breastfeeding, which has multiple benefits for babies and mothers, should also be promoted as a measure to protect against breast cancer. And vaccination of young girls against HPV should be considered as a preventative measure against cervical cancer.

In addition to these primary prevention measures, investment is needed in secondary prevention – screening services that can detect abnormal cells in their early or pre-cancerous state when they can be most easily and effectively treated.

A CALL TO ACTION ON WOMEN'S CANCERS

In 2005, the World Health Assembly issued a Resolution on Cancer Control (WHA58.22) calling for global collaboration in developing and reinforcing comprehensive cancer control programs through the systematic, stepwise and equitable implementation of evidence-based strategies for prevention, early detection, diagnosis, treatment, rehabilitation and palliative care. The resolution also emphasizes the need to tailor cancer control efforts to the socioeconomic context of each country. [105]

In 2008, the International Union Against Cancer (UICC), a leading international NGO dedicated to global cancer control, issued its World Cancer Declaration (WCD), which has been endorsed by governmental agencies, NGOs and international health organizations. The declaration is available at http://www.uicc.org and can be endorsed by organizations or individuals.

These declarations represent important steps toward recognizing and formulating an agenda to address the rising incidence and lack of diagnosis and treatment options for women's cancers in the poorer regions of the world. Despite these important initial efforts, however, cancer control programs in low- and middle-income countries remain largely undeveloped. The great majority of women who develop breast or cervical cancer in the poorer regions of the world today will never be diagnosed or treated for their disease – leading to an extremely painful disease progression and death that in many cases also destabilizes families and communities.

The following is a consensus call for action to address the pressing need for low- and middle-income countries to acknowledge and act to address and reverse the

crisis of rapidly growing, undiagnosed and untreated rates of women's cancers in developing countries:

1. Governments should take a public health approach that seeks to address the root causes and risk factors in the population of women at large, rather than focusing on disease in individual patients.

2. Ministries of health should take steps to establish cancer registries and other surveillance mechanisms to ascertain the extent and epidemiological pattern of breast and cervical cancer and provide insights into local knowledge, attitudes and practices regarding these diseases. Such information is essential for properly focused and effective planning.

3. Greatly increased health education, information and communication are needed as a matter of priority, to raise public and professional awareness of women's cancer and how best to protect against disease, as well as to encourage women to use those services that are available and to demand the additional services they need.

4. In addition to raising public awareness, other measures should be taken to help prevent cancer including the promotion and support of healthy lifestyles and behavior, and the provision of screening services.

5. The pharmaceutical industry, in partnership with governments, should look to the lessons of experience with other diseases – notably HIV and AIDS – and explore innovative ideas for improving access to medicines and diagnostics, including differential pricing strategies.

6. Services for breast and cervical cancer should not be stand-alone but should be integrated with general healthcare services, so that the system as a whole is strengthened by the new skills, facilities, equipment and other resources that a cancer program generates. Referral systems and the availability of late stage treatment should be strengthened.

7 Services that address women's cancers should be "women friendly" -- that is, sensitive to women's feelings and fears, respectful of their special needs, and tailored to fit in with busy lives as much as possible

8. Palliative care must take a central role in health worker training. Access to medications to relieve cancer pain, especially morphine, must be made available as medically appropriate in resource-poor settings in which prejudices, misinformation and excessively restrictive laws and policies mean most people with cancer die in extreme pain.

Much can be done to save women's lives, and everyone -- from governments, donors, and the national and international health community, to healthcare advocates and ordinary citizens -- has a role to play. What is required now is political will to act, strong leadership and greatly increased spending. Already the majority of new cancer cases and two thirds of cancer deaths occur in developing countries, yet they attract only 5% of global funds for cancer[106]. There are signs that chronic non-communicable diseases are beginning to find a place on the health agendas of resource-poor countries. But for real progress to be made, these

countries' commitment to tackle their cancer epidemics must be matched by equal commitment from the international community to support their efforts and to award them a much fairer share of the world's resources.

ENDS

The Informal Working Group on Cancer Treatment in Developing Countries (CanTreat International) comprises experts from leading global cancer organizations working in an individual capacity to develop new models for the delivery of treatment and palliative care for cancer, in particular women's cancers, in developing countries.

CanTreat International members include*:*

1. Ben Anderson (Breast Health Global Initiative)
2. Michel Ballieu (Chief Executive Officer, ECCO – the European CanCer Organisation)
3. Colm Bradley (ELN Foundation)
4. Ahmed Elzawawy (International Campaign for the Establishment and Development of Oncology Centres)
5. Joe Harford, (Director, International Affairs, National Institutes of Health)
6. David Kerr (AFROX, Professor, Oxford University)
7. Len Mafrica (Publisher, Oncology Nursing Society)
8. Ian Magrath (International Network for Cancer Treatment and Research)
9. Doug Pyle (Director International Affairs, American Society of Clinical Oncology)
10. Anne Reeler (Chief Technical Officer, Axios International)
11. Lewis Rowett (European Society for Medical Oncology)
12. Joseph Saba (Chief Executive Officer, Axios International)

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