Cancer in low and middle income countries

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In 2010, cancer overtook ischaemic heart disease as the leading cause of death in the world. While different grouping of diseases (e.g., combining all cardiovascular disease or dividing cancer into many different types) would produce a different rank order, the point should not be missed that cancer can no longer be ignored by global health policy-makers as a major cause of disability or death as well as economic loss.

In 2008, global economic loss resulting from disability or death from cancer, and not counting the costs of cancer control (the reduction of morbidity and mortality from cancer), was estimated to be US$895 billion for the 17 types of cancer examined – higher than the cost of heart disease and sufficiently large that it can no longer be ignored by governments.

Yet cancer is a complex set of diseases requiring both public health experts and clinical care providers and the participation of a broad range of institutions, ranging from government to academia and civil society, for its effective control. New approaches to creating concerted actions and developing the necessary finances need to be found. As such, the development of effective cancer control programmes at a global level provides both an enormous challenge, but also a unique opportunity to reshape the structure of health services in low and middle income countries (LMIC) as they grow and develop (see article by Richard Sullivan).

Unfortunately, the cancer burden in the LMIC, which has been growing steadily, has been largely neglected, by the governments of these countries, by international organizations and even by civil society. In contrast, considerable attention (appropriately) has been paid to HIV/AIDS, tuberculosis and malaria (the Global Fund to Fight AIDS, Tuberculosis and Malaria, for example, has committed, to date, US$19 billion in 144 countries since its creation in 2002). No similar fund exists for cancer or even all non-communicable diseases combined, which are responsible for 60% of global deaths, although much could be accomplished with similar funding directed at non-communicable diseases in general and cancer in particular, the latter being the only potentially curable NCD.

Only in the last few years have a number of positive steps been taken to address the problem of cancer in developing countries: the International Network for Cancer Treatment and Research, dedicated to cancer in developing countries was established in 1998 to deal exclusively with this problem and has been supported by the National Cancer Institute, USA for the last 10 years; the International Atomic Energy Agency has for long been providing radiotherapy units and training of the necessary health professionals in developing countries, but only in 2004, after recognition that radiation therapy alone is not enough, did it establish a broader Program for Action in Cancer Therapy.

Similarly, more than 50 years after the definitive recognition of the health risks engendered by tobacco, the Framework Convention on Tobacco Control, the first treaty negotiated by the World Health Organization (WHO) and adopted by the World Health Assembly (WHA) in 2003, entered into force (2005). That same year, the WHA passed a resolution (WHA58.22) recommending that all countries develop
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FIGURE 1: AGE STANDARDIZED INCIDENCE AND MORTALITY RATES IN VARIOUS WORLD REGIONS FOR ALL CANCERS EXCEPT NON-MELANOMA SKIN CANCERS; BOTH SEXES, ALL AGES

Development Goals, Heads of State and Governments committed themselves to “a coordinated response to NCDs at national, regional and global levels.” This will be further discussed at the High-Level Meeting at the UN General Assembly in 2011.

This article addresses some of the reasons that cancer – along with other NCDs – has become an important health priority in LMIC and why it does not command the attention that its contribution to disability and mortality rates (which are now similar across the world when corrected for the differing age structures of populations) demands (Figure 1). It provides basic information about the nature of cancer and its clinical features in order to inform the humanitarian argument for avoiding suffering from advanced cancer through prevention or early detection followed by efficient care (including palliation). It also discusses the need for international cooperation in creating the human and other resources needed to design and implement feasible cost-effective actions directed towards cancer control and to assist in the expansion and improvement of existing treatment facilities, thereby ensuring more rapid access to care.

Without such actions, which should be strongly promoted and supported by the G20, mortality rates from cancer in the LMIC will reach catastrophic proportions with a resulting devastating effect on their economies. For success to be achieved, it is essential to dispel the notion that cancer in LMIC is an insoluble
problem, and to encourage cancer control efforts in a systematic way as part of a global health initiative based on health priorities, not expediency. Present distortions and inadequacies in the health systems of the LMIC result in millions of cancer patients dying a sometimes slow and frequently painful, undignified death, scarring and negatively influencing the well being of their families for life, and increasing the burden of suffering already predominantly carried by the 85% of people who live in the LMIC.

The nature of cancer
Cancer or neoplastic disease, (“new” growths or malignant tumors) result from the development of multiple genetic changes that, with occasional exceptions, occur after birth and are not heritable. These genetic abnormalities occur in a stepwise process in a single cell of almost any tissue or organ in the body and modify the behaviour of the cell (and its progeny), creating precancerous lesions, some of which take on a “cancer phenotype,” which consists primarily of deregulated cell growth. Cancer cells proliferate inappropriately, forming masses or sheets of cells (they may also circulate in the bloodstream) that become progressively more able to invade adjacent tissues. At a variable point in its evolution, cancer disseminates, through a process known as metastasis, via lymphatic vessels to regional lymph nodes and via the bloodstream to more distant bodily sites.

Leukemias and lymphomas are neoplastic “clones” of cells that occur in the bone marrow, spleen or lymph nodes. They can be generally considered to have spread widely throughout the body via the lymphatic system or blood stream, but can often be controlled for long periods, or even cured, by anti-cancer drugs.

In LMIC the incidence of cancer tends to be higher in urban regions, presumably a consequence of differences in lifestyle and/or environmental exposures. Cancer has a higher incidence in older individuals (above the age of 65 years), in part due to more prolonged exposure to environmental risk factors and in part, to biological reasons, such as the accumulation of genetic changes. However, cancer can occur at any age, and in LMIC accounts for a higher proportion of cancer because of the lower average age of the population. For both reasons of population age structure, differences in lifestyles and environmental exposures, and, to a degree, ethnicity (i.e., different genetic make-up), the distribution of cancer subtypes varies quite markedly in different regions and countries (Figure 2).

In high income countries, tobacco, overeating and a sedentary lifestyle are the major causes of cancer. In LMIC, chronic infections account for a higher, sometimes much higher, proportion of cancer. However, LMIC countries are faced with a low, but increasing burden of obesity, while still grappling, in the poorest of their people, with malnutrition.
There is much that can be done to control cancer, different cancers being more or less preventable or treatable (particularly in their early stages). Patients with incurable cancers should have access to palliative care.

Prevention and early detection
Cancer prevention of course, can only be accomplished if there is knowledge of the causal factors or predisposing causes for different types of cancer and the risk factors are such that environmental or behavioural changes designed to reduce risk can be promoted via legislation, the media, or via direct group or individual interventions in the context of the health system (including education and screening of the public), all of which require education and sometimes training of the appropriate sector of the community. This is not the case for all cancers, but it is important to note that some of those amenable to prevention (e.g., tobacco related cancers), are often quite refractory to treatment. Unfortunately, although legislation relevant to tobacco control, (the single most important approach to cancer prevention at a global level), has been passed in many countries, it is not always adhered to, or falls short of FTCT recommendations... Smoking rates are increasing in developing countries by 3-4% per year and women and adolescents are increasingly targeted. Approximately a billion of the world’s estimated 1.4 billion smokers in 2010 live in developing countries, as do 70% of the 5.4 million who die each year from tobacco-related diseases. Much work needs to be done at the “grass roots” level to encourage smoking cessation, even though this will require a decade or two before it translates into a lowered incidence of smoking-related cancers. Discouraging the smoking habit entirely may be more readily accomplished, given sufficient effort, in those countries or regions that still have relatively low proportions of smokers, since popular opposition to smoking bans will be less.

Cancers that occur in the context of chronic infections can also be prevented if vaccines or effective therapy exist for the infection. Vaccination against hepatitis B has been shown to reduce the incidence of hepatocellular carcinoma (liver cancer), and there is much hope that the new vaccines against some types of Human Papilloma Virus (HPV) will reduce the incidence of carcinoma of the cervix, 80% of which occurs in LMIC.

In the meantime, the screening of appropriately aged women for “in-situ” carcinoma of the cervix, which is easily treated with minimally toxic and very inexpensive therapy, has successfully reduced the incidence of invasive cancer at this site in technologically advanced countries, and with sufficient upscaling and methodological changes, could reduce the incidence of this numerically most important disease in poor women in LMIC countries.

The visual detection of leukoplakia has been shown capable of reducing the mortality from oral cancer in India, but again, major upscaling will be required to have an impact at a population level. Simple screening methods requiring very little training, particularly if...
objective, are worthy of consideration in cancer control, but the consumption of skilled human resources in screening methods, e.g., for breast cancer, in LMIC countries is best avoided in the absence of good evidence of their utility and cost effectiveness. What little funding is available might best be spent on improving the education of primary care health workers and the public on the early signs of cancer, but early detection in the absence of facilities where patients can be diagnosed and treated effectively is an exercise in futility.

**Diagnosis and treatment**

The first critical step in the management of cancer is to establish the diagnosis, which, with rare exceptions, is made after removing a piece of the tumor (or sometimes the entire tumor) and subjecting it to pathological examination. In the poorer countries or regions, and in circumstances where the patient must pay for diagnostic tests, modern and precise diagnostic methods may not be used, such that many patients are misdiagnosed and treated inappropriately.

Because of late diagnosis, however, a consequence of poor access to care for a variety of reasons addressed below, most patients have advanced disease in such settings. Although figures of 60-80% advanced staged disease are often quoted for patients in LMIC, this will vary according to regionally available resources and other factors, and most figures are likely to be an underestimate because of inadequate staging (i.e., assessing the extent of disease).

Cancer is treated by one or more treatment modalities, i.e., surgery, radiation therapy or systemic therapy (chemotherapy, hormonal therapy or monoclonal antibody therapy). Systemic therapy has been available only since the late 1940s.

The wider use of radiation and and systemic therapy in cancer treatment has permitted the abandonment of most types of mutilating surgery (performed in an attempt to remove all cancer cells, including those that may have invaded adjacent tissue) although in many world regions, where radiation and systemic therapy is not accessible, or where follow up is poor, mutilating surgery is often still performed on the grounds that it gives the poorest patients, who cannot afford additional treatment, or may not return for follow-up therapy, the best chance for survival.

The greatest problem with radiation and systemic therapy is balancing the destruction of tumor cells with damage to normal cells. This is much more readily achieved with very early tumors – i.e., small tumors with no evidence of either significant regional involvement or distant spread when both cost and side effects are much less (although there is considerable inter-country variability).

Unfortunately, such localized tumors represent the minority of cancers in LMIC, in contrast to the situation in HIC. Moreover, patient compliance, whether due to cost issues, the difficulty of staying away from home for long periods (travel to a specialized facility may be lengthy when few specialized facilities exist), social stigmata or a host of other issues is often poor.

All of these factors contribute to the higher mortality rates in cancer in LMIC compared to those in HIC countries, but it must also be remembered that documentation of all aspects of care, and particularly outcome (because many patients are not adequately followed after treatment has been completed), also means that the quality of available information is often poor and published mortality rates probably give an overly optimistic view in LMIC.

**Palliative care**

A particularly sad aspect of cancer treatment in
developing countries is the very limited access to palliative care. Of course, it is better to prevent or cure, but it will be many years before the necessary steps can be taken to accomplish this. Meanwhile, symptom control is imperative to avoid suffering – throughout the patient’s clinical course, but especially when there are no curative options. Unfortunately, there is a paucity of information about the extent or quality of palliative care in the developing countries, although it is estimated that two thirds of patients with cancer suffer from moderate to severe pain and few have access to pain relief. Palliative care is appropriately considered a human right; Human Rights Watch has equated the failure to provide physical and mental comfort to dying patients with cruel and degrading treatment – essentially, torture. Oral morphine is inexpensive but grossly underused at a global level to treat pain, while psychosocial support is generally provided by the family, whose emotional suffering and lack of knowledge mean that not only are they poorly equipped for this task, especially in the absence of effective pain control but they themselves are in need of support.

The growth of populations and the cancer burden

In recent history, the industrial revolution led eventually to increased living standards of ordinary people. Between 1800 and 2000, it is estimated that the world’s income increased ten-fold and the population over six fold. As a result of this demographic transition (Figures 3 and 4), the global population reached one, two, four and six billion in 1825, 1930, 1975 and 1999 respectively. It is projected to reach 7 billion by late 2011 or 2012.

The demographic transition, resulting in larger and, on average, older populations in less developed countries has markedly influenced both the burden and distribution of various cancers (and many other diseases) in various countries and regions. In fact, it has resulted in an epidemiological transition in which the major disease burden moves from communicable to non-communicable diseases. Unfortunately, as they make the transition, countries face high burdens of both, while their health systems remain adapted to dealing (however inadequately) with their prior health problems. An understanding of ongoing demographic changes permits predictions to be made with respect to the cancer burden in less developed countries based on demographic changes alone (Figure 5), or demographic changes plus an estimate of the additional numbers of cases that will be caused by other consequences of the industrial revolution, namely, increased exposure to risk factors, such as smoking, obesity and a sedentary lifestyle (potentially offset by reductions in cancer related to chronic infections).

It should not be assumed that the burden of cancer will be confined to older people, whose risk of cancer is greater, but whose death or disability has a lesser impact. According to the IARC, the actual number of cancer cases in less developed world regions in individuals aged less than 65 years will increase by 3.3 million cases per year, compared to 3.9 million in patients of 65 or over between 2008 and 2020. This has significant economic implications, for even without considering the cost of treatment (and in low income countries particularly, many patients may never receive therapy), the amount of disability and death will have a significant negative economic impact on all countries.

Resource deficiencies

The negative aspects of population growth must be offset by the technological benefits of the industrial
revolution. Advances in healthcare that occurred resulted from research in an extraordinarily wide range of topics, but the spread of technical advances across the world has been both varied and slow. Even today, according to the IAEA, some 20 countries lack radiation therapy entirely and many have a grossly insufficient number of machines (half of all radiotherapy machines are located in 15% of countries in the world!). Many radiotherapy machines are non-functional for lack of maintenance or require lengthy treatment durations because of an aged radiation source (cobalt machines). There are often shortages of radiation oncologists, technicians and radiation physicists – as well as severe deficiencies in a broad range of health professionals required to provide efficient care to cancer patients. Cancer drugs, even those on the WHO’s essential drug list, may be available only intermittently, and even if inexpensive by western standards, complete treatment courses may be beyond the means of many families.

The dramatic differences in resources for disease control, whether relating to prevention or treatment, between the LMIC, and HI, or OECD countries, cannot be emphasized enough. Those world regions with the smallest work forces of health workers and lowest expenditure on health (Africa and SE Asia) have the greatest disease burdens. Africa, for example, according to WHO, has 17% of the world’s population, 2–3% of the global health work force, less than 1% of global health expenditure but approximately 25% of the global disease burden. Figures for the density of doctors and nurses (which vary by 7-8 fold) are available for most countries (Table 1) but information on numbers of specialists is largely lacking. In the poorer populations in the poorer countries there is essentially no access to even primary medical care, although traditional healers are likely to be available. Per capita government and total annual expenditure on health (US$ at average exchange rate) approximately doubled between 2000 and 2007, but has an enormous span (several hundred fold) among countries grouped by income (Table 2). Moreover, there is gross maldistribution between urban and rural regions (Cote-d’Ivoire, an extreme example, had 2055 physicians in urban regions and none in rural regions in 2004). Insurance schemes are largely lacking in the poorer countries, where the bulk of health expenditure is private, out-of-pocket (Table 3).

Poor professional circumstances and the needs of high income countries, coupled to higher salaries, encourage emigration (it has been estimated that 40% of African doctors are working abroad) as well as entry into the private, for-profit sector which, as countries develop socio-economically, evolves more rapidly than the public sector. This has meant that the growth of resources to control cancer at a global level has been much slower than the increase in the cancer burden, leading to an ever-worsening plight of the cancer patient. The limitations in advanced human and physical resources are a combination of limitations in the economies of countries which ultimately stem from poverty, ill-health and inadequate educational systems – a triad of interacting problems that have implications at all levels of society. Without completion of primary education, for example, there can be no secondary or higher education.

**Cancer as a 21st century global health problem**

Cancer has been progressively increasing in importance as a health problem since the industrial revolution, and particularly in the latter part of the 20th century, according to calculations based on available figures for the age standardized incidence rates of cancer for various countries in the world in 1974-5 and in 2008 (Table 4). Mortality rates, based on either cancer registry data or death certificates confirm this progressive increase which has been remarkably rapid in many LMIC, although cancer incidence also increased in the HIC in the latter half of the 20th century, particularly as a consequence of the tobacco epidemic, a more sedentary lifestyle and increased calorie consumption. It is also true however, that due to education and the resultant earlier detection of cancer (in some cases, by screening e.g., for cancer of the cervix uteri), coupled to advances in treatment, there has been a progressive fall in cancer mortality. In the European Union countries (15), for example, between 1997 and 2004 mortality rates fell from 187.9 to 173.1 per 100 000 (standardized to a European population) (www.ec.europa.eu/health/indicators).
Mortality rates, however, are generally rising in less developed due to increasing incidence rates resulting from the progressive adoption of a western lifestyle and urbanization. Unless cancer control can be dramatically improved, this will lead to an increase in the already large number of deaths from cancer in LMIC – perhaps reaching a total of 60-65 million between now and 2020.

According to IARC’s Globocan, in 2008 there were 12.7 million incident cases of cancer and 7.6 million deaths, corresponding to age-standardized rates (adjusted to the structure of the world population) of 181.6 and 106.2 per 100 000 per year. It is predicted that in 2020, based on population growth alone (figures from the United Nations World Population Prospects, 2008 revision), the number of cancer cases in the world will have risen to 16.9 million and the number of deaths to 10.2 million. The less developed countries will account for 2.8 million of these additional cases and 2 million of the additional deaths respectively – approximately 66% and 76% of the global increases (Figure 5). Already approximately 50% of both new cancer cases and cancer deaths each year occur in Asia and an additional 13% in Africa and Latin America combined (Figure 6). These predictions may be high or low, but given current trends, there is no doubt that the cancer burden will increase in the next 10 years and that this increase will be both larger in the LMIC and result in an even higher fraction of cancer deaths occurring in these countries because of their resource limitations. These same countries are also the most vulnerable to pressures from the commercial world designed to prevent them from enacting and enforcing legislation designed to reduce unhealthy behaviour in their citizens, such as smoking an overconsumption.

An unknown number of patients in LMIC with overt cancer remain undiagnosed and untreated – for reasons ranging from wrong beliefs about the causes of cancer (e.g., evil spirits) and consequent stigma, especially with genital cancers, to fear of cities where treatment facilities are located, ignorance, poverty or wrong advice (e.g., from traditional healers or local health workers). Others are diagnosed only when their cancer is advanced such that curative therapy is no longer an option, or would be costly and of low efficacy but high toxicity. The twin but associated problems of limited resources and late presentation result in high mortality rates, doubtless frequently leading to the misapprehension that there is nothing that can be done for cancer.

Proposed approaches to global cancer control

It is clear that cancer is a neglected health problem in LMIC. At the same time, there is a great deal of information about what can be done to control risk factors (often overlapping with risk factor control for other NCDs), detect cancer earlier, improve diagnosis and treatment and provide palliative care, although not all of this information is directly applicable to the LMIC. This means that research into what works and what doesn’t in LMIC must be given a high priority; frequently, specific actions may be inexpensive and highly cost-beneficial but their utility may vary from one country to another. Research will also create a more effective workforce, improve documentation essential to cancer control planning, allow an approach based on relevant evidence and increase the pace of progress.

Cancer registration is essential if the size of the cancer problem and the major types of cancer in
Widespread participation in clinical studies should help to improve the quality of services, since the research will provide relevant evidence while creating a scientific approach on the part of those responsible for determining national guidelines or actually caring for cancer patients.

different countries and regions is to be identified, and trends documented – thus enabling interventions to be prioritized, or the population impact of measures already put in place evaluated.

In determining what should be done in a given context, it is also important to identify available resources, including facilities, equipment and human resources. Cancer control measures, for maximal effectiveness, will require the establishment of national and international networks to ensure the widest dissemination of expertise, whether in person or via telemedicine/e-learning of one kind or another. In addition to fully implementing the FCTC, decisions will need to be taken on the priority and resources required for the delivery of hepatitis B and HPV vaccines and the control of other chronic infections associated with cancer. Although still a relatively small problem in developing countries, the enactment of measures designed to minimize the obesity epidemic that has swept the high income countries, bringing with it serious health consequences, should also be given a high priority. Early detection should be integrated, wherever possible, with the early detection of other NCDs with similar risk factor profiles. This will require close collaboration among the various tiers of the health sector and begins in the community.

Approaches to improving access to care, include such diverse issues as strengthening health systems, adapting them to NCDs and improving patient navigation. Insurance schemes, possibly initially covering only chronic diseases, as well as relevant public and professional education must be planned and implemented. Continuing education of existing healthcare providers in a broad variety of professions should be undertaken, again, making maximal use of modern telecommunications as well as expertise from high income countries, or, where feasible, from centres of excellence in-country or from other LMIC. It will be important that each country has at least one (depending upon size) focal point for comprehensive cancer control – i.e., a cancer centre – which takes responsibility for the development and conduct of training programmes as well as the organization of cancer services in the context of the overall health service structure, including the implementation of early detection, cancer diagnosis, treatment and palliative care at a regional level. This will generally be a component of the national cancer control plan (NCCP).
necessary infrastructure for research. Widespread participation in clinical studies should help to improve the quality of care, since the research will provide relevant evidence while creating a scientific approach on the part of those responsible for determining national guidelines or actually caring for cancer patients.

Treatment approaches should be adapted to available resources, including drugs, and cost. Expensive equipment, reagents or drugs may sometimes be cost-beneficial when they improve diagnosis or staging, permits patient throughput to be increased, toxicity reduced and, consequently, higher cure rates achieved, although maintenance and staffing must be included in decision making. Rehabilitation programmes for cancer survivors will greatly speed up return to work and contribution to the national economy.
It is clear that a set of diseases as complex as cancer require a team approach and participation by a wide range of individuals with both public health and clinical expertise as well as an intersectoral approach on the part of government. While the complexities and cost that this entails may seem daunting to policymakers and international organizations, such that much less attention is paid to cancer than its increasing importance as a health problem warrants, failure to address it effectively will result in a the rising cancer burden continuing to outpace the growth of the resources required to address it and will have an increasingly negative impact on states’ economies – in fact, with the cost of interventions daily increasing, this applies even in HIC. Novel and effective solutions to the necessary restructuring of health services health insurance, the education and training of medical and paramedical staff, task shifting (e.g., the use of medical assistants and training nurses to a higher level), the establishment of strategically located specialized centres which act as regional coordination sites for cancer control and interact frequently and effectively with primary and secondary healthcare facilities must be identified within the briefest possible timeframe.

The identification of funds from national health budgets, international bodies, academic centres from high income countries that can act as partners, and civil society will be essential to the rapid and effective implementation of selected cancer control measures. We have recently witnessed a number of calls to action in the context of addressing the problem of cancer in LMICs. This is (as was the case with lung cancer and smoking), clearly due to the problem reaching a threshold level such that it has become difficult to ignore. It is imperative that cancer is recognized by policy makers as the high priority health problem it has become in LMIC. Cooperation between and among LMIC and HIC is essential to lessen its ever-increasing impact, and there are lessons to be learned by all. Necessary resources must be mobilized and joint efforts by governments, intergovernmental organizations, academic institutions and NGOs is essential. Discussing the problem is a beginning, but is not enough; immediate action is essential.

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