The costs, affordability and feasibility of an essential package of cancer control interventions in low- and middle-income countries

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Word Count

Summary: 436

Text (without panels): 4804

5 Tables, 2 Figures, 3 Panels

Date: September 8, 2015

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Abstract

Investments in cancer control—prevention, detection, diagnosis, surgery, other treatment, and palliative care—are increasingly needed in low- and, particularly, middle-income countries, where most of the world's cancer deaths occur without treatment or palliation. To help countries expand locally appropriate services, *Cancer*, a volume in the *Disease Control Priorities, 3rd edition* series, developed an essential package of potentially cost-effective measures for countries to consider and adapt. Included in the package are: preventing tobacco-related cancer and virus-related liver and cervical cancer; diagnosis and treatment of early breast cancer and cervical cancer and selected childhood cancers; and widespread availability of palliative care, including opioids. These interventions would cost an additional \$20 billion per year worldwide, adding 3% to total public spending on health in LMICs. Implementing an appropriately tailored package, most countries could reduce suffering and premature death from cancer substantially before 2030, with even greater improvements in later decades.

Summary

Investments in cancer control—prevention, detection, diagnosis, surgery, other treatment, and palliative care—are increasingly needed in low- and, particularly, middle-income countries, where most of the world's cancer deaths occur. Of 8 million cancer deaths in 2012, 5 million occurred in middle-income countries (population 5 billion), and half a million in low-income countries (population 0.8 billion). Many of these individuals received no effective anti-cancer treatment, and no option of opioid drugs to control severe cancer pain. The number of cases of cancer in low- and middle-income countries (LMICs) will rise substantially over the coming decades, due mainly to adult population growth. Currently, many of those with cancer forego effective treatment, and many families become impoverished paying for treatment. In LMICs, public financing is essential for wide access to cost-effective cancer treatments, and global initiatives could help lower the costs of treatment inputs and expand capacity to deliver cancer services.

To help countries expand locally appropriate strategies, *Cancer*, a volume in the *Disease Control Priorities, 3rd edition* series, reviewed worldwide evidence on cancer interventions and developed an essential package of potentially cost-effective measures for countries to consider making available to substantial proportions of their populations. Most middle-income countries could achieve wide coverage within a few years. Some of the interventions can also be put in place by low-income countries in the near term, and others in the longer term. These measures address the preventable and the treatable cancer burden, and should stimulate country-specific analysis of what is locally relevant, cost-effective and affordable. The package includes prevention of tobacco-related cancer and virus-related liver and cervical cancer; diagnosis and treatment of early breast cancer and cervical cancer and selected childhood cancers; and widespread availability and use of palliative care, including opioids. These interventions, some of which require better access to cancer surgery and radiotherapy, improved pathology and diagnosis, and hence expanded physical and human resources and other system strengthening would cost an additional \$20 billion per year worldwide,

adding 3% to total public spending on health in LMICs: 2·6% in upper-middle-income countries, 5% in lower-middle-income countries, but 13% in low-income countries (respectively, \$5·7, \$1·7 and \$1·7 annually per capita).

Cancer control is a long-term strategy that is increasing in importance as populations age. Some interventions, in particular higher tobacco taxes and widespread pain palliation, can be extended relatively rapidly in many countries, while the expansion of anti-cancer treatment may require many years to achieve, particularly in low-income countries. Practicable, planned steps, starting soon, could in most countries reduce suffering and premature death from cancer substantially before 2030, with even greater improvements in later decades.

Introduction

At the 2012 WHO World Health Assembly, member states agreed to a goal of reducing rates of premature death from non-communicable diseases (NCDs) by 25% by 2025, starting from a 2008 baseline.^{1 2} The UN Sustainable Development Goals for 2030 that will be announced in September 2015 also include reducing premature death from NCDs, of which cancer is a substantial part. This paper summarizes the analyses and recommendations of the forthcoming *Disease Control Priorities, third edition (DCP3)* volume on cancer (one of nine planned volumes)³, analysing a set of interventions that could be effective, cost-effective, affordable and feasible in substantial parts of many low- and middle-income countries (LMICs), and which could help those countries meet the stated goals: Panel 1.

The intent is to help governments of LMICs commit to locally appropriate national cancer control strategies that will include a range of cost-effective interventions, customised to local epidemiological patterns and available funding, and to convey this commitment widely to their populations. Where affordable treatment can be provided, conveying this information to the public can motivate people to seek treatment when their cancer is at an earlier, much more curable stage. The full costs of cancer treatment are unaffordable for most individual patients in LMICs, so most cancer services considered appropriate in national packages should be included in any plans to expand universal health coverage.⁴

The *DCP3* package includes some prevention strategies, but many cancers cannot be prevented to any great extent by currently available methods. Some can be treated cost-effectively with curative intent (eg, early breast cancer, other resectable cancers, various childhood cancers), however, and the availability of effective treatment bolsters public confidence in the overall program.⁵⁻⁷ Cancer control programs can mobilize broad political support, as happened in Mexico with addition of breast and childhood cancer treatment into the expansion of national health insurance.⁸

In high-income countries, most who develop cancer survive, although survival depends strongly on the type of cancer (Table 1). In LMICs, less than one-third survive, and in some populations the proportion is much smaller.⁹ The differences in survival are due partly to differences in the patterns of cancer incidence; some types of cancer that are common in many LMICs, such as lung, oesophagus, stomach and liver cancer, have a poor prognosis even in high-income countries.¹⁰ The other major contributor to poor outcomes is that many fewer people come for treatment when the cancer is at an early, curable stage than in high-income countries, partly because effective treatment is not affordably available.^{9 11}

The aim of *DCP3* is to identify potentially cost-effective, feasible and affordable interventions that address significant disease burdens in LMICs (Panel 2). Accordingly, we have examined:

1. the avoidable burden of premature death (defined as before age 70, which approximates current global life expectancy) from cancer in LMICs (Table 1);
2. the main cost-effective interventions for the prevention, early detection, treatment and palliation of cancer; and
3. the costs and feasibility of developing, over an appropriate timescale, health system infrastructures that could deliver progressively wider coverage of a set of cost-effective cancer services.

Using these inputs, we define an 'essential package' of cost-effective interventions for cancer and discuss their affordability and feasibility, which differs markedly between low, lower-middle and upper-middle-income countries. Even within the same income category, countries may differ widely in epidemiological patterns and health systems (eg, Brazil and China are both upper-middle-income), resulting in different country-specific essential packages. Hence, this review is not intended to lead to a common cancer plan for all LMICs, but to spur dialogue within countries about rational cancer control planning and implementation, resulting in national cancer plans that are tailored to local conditions but retain the characteristics of effectiveness, cost-effectiveness, feasibility and affordability. Finally, we review some ways in which global initiatives, particularly on supplies, training and professional development strategies, that could help LMICs to lower the costs of expanded cancer control for their populations.

The evolving cancer burden

The WHO's International Agency for Research on Cancer (IARC) estimates that in 2012 there were 14 million new cases of cancer and 8 million deaths from cancer, more than half before age 70 (Table 1).⁹ Of the 4.4 million cancer deaths before age 70, 3.4 million were in LMICs (0.3 low income, 1.2 lower middle-income, 1.9 upper middle-income). Two-thirds of the cancer deaths before age 70 years in LMICs involved cancers of the lung, mouth or oesophagus (0.9 million, many caused by tobacco), liver (0.4 million, many caused by vaccine-preventable hepatitis B infection), stomach (0.3 million), breast (0.3 million), cervix (0.2 million, many caused by vaccine-preventable HPV infection) and colon or rectum (0.2 million) (Table 1, Figure 1).^{9 10 12}

Worldwide, cancer death rates among people of a given age are slowly decreasing (Table 2). Between 2000 and 2010, age-standardized cancer death rates before age 70 years fell by about 1% per year, bolstered by worldwide declines in cervical cancer and stomach cancer (for reasons that are not fully understood). Male lung cancer rates decreased in some countries, but in lower-middle-income countries the death rates from tobacco-associated cancers rose slightly.

Absolute numbers of cancer deaths and cancer as a proportion of all deaths will, however, continue to rise because of three factors: world population is increasing, particularly in later middle age and old age, mortality from diseases other than cancer is decreasing, and in some major populations the effects of tobacco are increasing.¹³

Cancer impact on household economies

Counter to common perceptions, cancer death rates are often higher in the poor than in the rich. In India, for example, the age-standardised death rate from cancer in middle age was twice as great in illiterate as in educated populations.¹⁴ Moreover, cancer, like other NCDs, can be an important cause of catastrophic health expenditures that push households into poverty¹⁵⁻¹⁸, as in many LMICs cancer surgery, radiotherapy and chemotherapy are paid for largely out of pocket. In Bangladesh¹⁵ and Cameroon,¹⁷ for example, high user fees increase the likelihood that patients will not return for cancer surgery. Conversely, however, in India some standard types of cancer surgery (eg, mastectomy) are supposed to be provided at low, affordable cost in public hospitals; likewise, in China the national health insurance scheme now offers standard types of cancer surgery at prices most people can afford. Nevertheless, even in China and India cancer can still impose a major financial burden on families, especially in the lowest income groups, and in the case of India, access remains limited to certain large cities.¹⁹

Essential packages of interventions

DCP3 seeks to develop essential packages of cost-effective interventions to be considered and modified as appropriate by countries for all of the health conditions addressed in its nine volumes. Both the specific interventions and the criteria used to choose them (effectiveness, cost-effectiveness, feasibility, affordability) are intended to help LMICs decide what to support and what not to.³ For middle-income countries that already have many cancer treatment centres and clinics, the *DCP3* approach could be used to help evaluate additional interventions, now or in the future, or to re-assess some current activities, and in all LMICs it could help ensure due consideration of how interventions that are considered locally appropriate can achieve high population coverage.

The WHO has already formulated its own list of NCD best buys for LMICs, which had to be considered feasible *without* hospital facilities. Those most relevant to cancer are three preventive measures: tobacco control interventions, hepatitis B vaccination to prevent liver cancer, and some form of screening and treatment for precancerous cervical lesions.¹ The *DCP3 Cancer* essential package (Table 3) adds HPV vaccination to prevent cervical cancer. It also adds treatment of early stage cervical cancer (and, by implication, other resectable cancers); diagnosis and treatment for early breast cancer;²⁰ diagnosis and treatment for selected highly curable childhood cancers;²¹ and palliative care²², including, at a minimum, opioid drugs for severe pain control. The package is organized according to delivery platforms, classified as national level policy; regulation or community information; primary health clinic or mobile outreach; first-level hospital; or specialized cancer centre.

Assessment of the feasibility of the interventions follows the model of resource-level appropriate interventions developed for breast cancer by the Breast Health Global Initiative.²³ This classification recognizes that several generations of effective breast cancer treatments are available with different resource costs and infrastructure requirements.

The cost of the essential package is for the entire population, not just age under 70. We estimated the global and per capita costs of each intervention in the package separately for low-, lower middle-income, and upper middle-income countries. Most LMICs should be able to implement a locally customized essential package that covers most of their population by 2030, given anticipated increases in public spending on health.⁴ The schedule of implementation will vary, however, as some interventions, in particular higher tobacco taxes and widespread pain palliation, can begin now in many countries.^{7 24} By contrast, affordable availability of treatments that require considerable infrastructure development may take many years to achieve fully after a start is made in particular locations.

Prevention

Most countries (183 worldwide) vaccinate infants against hepatitis B, with global coverage at 81% in 2013. This will prevent many liver cancers some decades hence, but a birth dose, important in countries with high mother-to-child transmission, reached only 26% of newborns in 2011.²⁵

75 countries (including high-income countries) have begun national HPV vaccination programs and others are developing experience with the vaccine.²⁶ In addition, Gavi, the Vaccine Alliance, is supporting pilot programs in several low-income countries in sub-Saharan Africa. The delivery cost of reaching adolescent girls for 3 doses is the major barrier, as Gavi-subsidized vaccine costs only \$0.60-1.20 for the recommended 3 doses, while program costs range between \$4-13 per fully immunized girl.^{26 27} Hepatitis B and HPV vaccinations will have their main effect on mortality during the second half of the century, when the cohorts of immunized children reach middle age.

Tobacco control comprises higher taxes, counter-advertising, warning labels and other packaging requirements; bans on advertising, bans on smoking in public places, cessation support for smokers, and anti-smuggling technologies.²⁸ Tobacco control can achieve relatively quick health gains: people who quit smoking before age 40 avoid more than 90% of the risk they would have incurred had they continued to smoke.²⁸ This means a substantial saving of lives starting within 5-10 years after tobacco control measures, most notably higher taxes and bans in smoking in public places, are put in place, and increasing gains thereafter as more comprehensive tobacco control measures are implemented. The most effective tobacco control intervention is higher taxes, which increase adult cessation and discourage youth initiation, which will prevent many deaths in the second half of the century. However, unlike in many high-income countries, cessation remains uncommon in most LMICs, with adults quitting only after developing cancer (or some other major disease), and not quitting while healthy to avoid disease.

Only 28 countries are undertaking comprehensive tobacco control programs with high taxes as a major strategy.²⁹ There are already some notable successes: France and South Africa used large tax increases in the 1990s to triple the price of cigarettes; by 2005 consumption had halved, but real

government revenues from tobacco had doubled.³⁰ Brazil has also reduced smoking prevalence considerably.³¹ Despite severe industry opposition, Mexico, and very recently, the Philippines and India, increased cigarette taxes significantly (above the rate of income growth so as to reduce affordability), and Mexican cigarette sales have already started to decline.^{29 32} The WHO's Framework Convention on Tobacco Control, adopted by more than 180 countries, is an important enabler of country action for comprehensive tobacco control measures.³³

Screening

The emphasis on diagnosing and treating cancers while they are still at an early stage (or, for cervical screening, in a pre-cancerous stage) might suggest the appropriateness of numerous cancer screening programs³⁴, but population screening is expensive and requires considerable infrastructure. Only opportunistic cervical screening (with or without some added outreach) meets the *DCP3* criteria and is, therefore, suggested for consideration in the essential package. Cervical screening using visual inspection (with acetic acid to stain abnormalities) can detect pre-cancerous changes that can be cured inexpensively, often during the same visit.^{27 35} When convenient rapid diagnostic tests for the main carcinogenic types of HPV infection become affordable they could make cervical screening even more effective and reliable.³⁶ 2-3 such screenings every 5-10 years from age 30-35, should halve lifetime cervical cancer risk.³⁷

The essential package does not include any type of screening for prostate or breast cancer. Both have attracted significant controversy in high-income countries, albeit for different reasons. The most widespread means of prostate cancer screening is through a blood test for prostate-specific antigen (PSA, a protein from cancerous prostate cells), with or without physical examination. Although simple, PSA testing can lead to overdiagnosis and overtreatment, with many more harmed by side-effects than saved from cancer. The US Preventive Services Task Force discourages PSA testing.³⁸ By contrast, screening mammography for breast cancer is supported by most high-income countries as an expensive but moderately effective measure, although the optimal age range for screening and screening frequency are still debated. Clinical breast examination might be a viable option in LMICs, but its effectiveness is uncertain.²⁰ Other common cancers with detectable precancerous stages are colorectal cancer (precancerous polyps)³⁹ and oral cancer (visible lesions).⁴⁰ Eventually, cancer screening may be widened, but a greater priority in LMICS now is appropriate treatment for the cancers already being found.

Diagnosis and treatment

Accurate diagnosis is often needed for cancer treatment, but trained pathologists and other laboratory technologists and a lack of facilities and supplies critically limit diagnostic capacity in many LMICs.⁴¹ In addition to an initial diagnosis of cancer (perhaps based on biopsy specimens) that can help assess the likely success of surgery, diagnostic services can help determine treatment strategies after surgery. Simple "TNM" (tumour, nodes, metastases) staging has long been clinically useful, and other tests on the tumour itself can determine post-surgical management. In particular,

breast cancer surgical specimens should be tested reliably for estrogen receptor (ER) positivity; only if they are ER+ will endocrine treatment substantially reduce recurrence and death (panel 3).

Treatment for early breast cancer and cervical cancer includes some or all of surgery, radiotherapy, chemotherapy and targeted (eg, endocrine) therapy, ie, all the basic components of cancer care.^{6 23}

For early cervical cancer, surgery is the primary treatment and radiotherapy an adjunct. For whatever is considered complete treatment in a given country context, all components of care should be accessible by patients once treatment is started. Incomplete treatment can cause side effects with little clinical benefit.

Childhood cancer is rare (1% of cancer deaths in high-income countries), representing the smallest burden of the cancers targeted by the essential package. While they cannot generally be prevented, certain childhood cancers have a high cure rate in high-income countries, making them feasible targets elsewhere.⁴² Cure rates in most LMICs are far lower, but reasonably good outcomes have been achieved in specialized childhood cancer centres and through national referral plans, particularly for acute lymphoid leukaemia, Burkitt lymphoma, and Wilms' tumour.⁴³

Palliative care

Many incurable cancers cause intractable pain. Opioid medications can generally relieve this pain, greatly improving the quality of the last few weeks or months of life for both patients and families. The simplest and least expensive preparation, oral morphine, works for an estimated 90% of patients with severe terminal cancer pain.²⁴ It is also used by patients with HIV/AIDS and some other chronic conditions. At present, reasonably good palliative care is widely available only in high-income countries, but it could be made available in LMICs quite rapidly, even before other types of treatment. Palliative care includes more than pain control and is relevant throughout the course of illness, but pain control is the core.

With appropriate organization and cooperation from government and healthcare sectors, opioids can be provided even in rural areas, at home, at low cost. The current reality is, however, that few people have access to effective pain medicines because of unnecessary restrictions at the country level. In 2006, 66% of the world's population lived in countries that had virtually no consumption of prescribed opioids, 13% in countries with low consumption, and 4% in countries with moderate consumption.⁴⁴

Local priority conditions

Any essential package should be customized and augmented with locally appropriate and feasible interventions. Examples include storage of grain and other foods to avoid fungal contamination causing liver cancer in parts of Africa and Asia;^{45 46} opportunistic screening (especially of high-risk tobacco users) and treatment for pre-cancerous lesions and early-stage oral cancer in India and other countries with high oral cancer burdens;^{14 40} screening and treatment for colorectal cancer in Argentina and Uruguay;^{35 39} elimination of liver flukes (by 1 day of generic praziquantel) to prevent

bile duct cancer in the limited areas where flukes are common, or treatment of schistosomiasis to prevent bladder or intestinal cancer in parts of Africa, the Middle East and Asia.⁴⁷

Finally, occupational and environmental cancer hazards (eg, use of power tools on asbestos roofing or insulation, heavy smoke pollution in houses, heavy fungal contamination of stored carbohydrate foodstuff) should be monitored and mitigated where appropriate.⁴⁸

Cost-effectiveness of interventions

For most types of cancer, the cost-effectiveness literature for LMICs is slim⁴⁹: 9 studies were identified for breast cancer, 2 (plus 4 from high-income Asian countries) for colorectal cancer, 1 for liver cancer prevention, and none for paediatric cancer. Seventeen studies were sourced from an expert search for cervical cancer, and a recent systematic review for vaccines⁵⁰ identified three studies for hepatitis B vaccination. A useful benchmark was to exclude from the essential package those interventions that are not clearly cost-effective in high-income countries. Most new drug treatments for advanced cancer fall into this category, such as bevacizumab (a monoclonal antibody) for metastatic breast cancer, which, at current prices, does not meet cost-effectiveness criteria even in high-income countries^{51,52 53}. Similarly, cetuximab (a monoclonal antibody for metastatic colon and lung cancers) plus irinotecan (a new treatment for colon cancer) are not considered cost-effective in the UK.⁵⁴ Radiotherapy is one of the interventions included in curative treatments for early cervical and breast cancer, and where it is available, also is considered cost-effective.⁵⁵

Excise taxes on tobacco, opportunistic cervical cancer screening and treatment of precancerous lesions and hepatitis B vaccination are, however, cost-effective in LMICs; HPV vaccination cost-effectiveness depends on vaccine price and programme costs; and some aspects of the treatment for early breast cancer are cost-effective wherever breast cancer surgery is performed. The perspective of tobacco control is of health gains compared to the minimal costs of the interventions. Various reviews of the broader welfare perspective on taxation have reached similar conclusions about the desirability of higher tobacco taxes.^{18, 28, 32} In China, for example, higher tobacco taxes provide substantial financial protection to the poor.⁵⁶

Costs of national packages

To illustrate per-capita cost estimates for an essential package, we combined information on costs and demography structures from three large, diverse countries (Nigeria, India and Brazil; although Nigeria is lower-middle-income, we use its demographic structure and lack of facilities and human resources to represent low-income countries, mainly in sub-Saharan Africa). To account for training, pathology services and other system costs, we used a multiplier, equal to 50% of the intervention-based costs, drawn from similar costing studies for nutrition⁵⁷ and for health systems.⁵⁸ We do not however, include the one-time investment costs for building hospitals, clinics and other infrastructure that would eventually be needed to support cancer and other clinical services.^{7 41}

The *DCP3* essential package of cancer control interventions would cost roughly an additional \$1.7, \$1.8 and \$5.7 per capita (table 4) in low-income, lower middle-income and upper middle-income countries, respectively, corresponding to total costs of about US\$1.4 billion, \$4.4 billion and \$13.8 billion. There are obvious uncertainties about current and future costs. Importantly, drug costs can fall substantially as drugs go off patent, and global initiatives could further reduce prices of key generics.

Affordability and domestic financing of essential cancer services

The total estimated annual cost of the essential package of cancer interventions for all LMICs is about US\$20 billion (2013 USD) (table 5). As a proportion of current total public spending on health, this is 2.6% in upper-middle-income and 5% in lower-middle-income, but 13% in low-income countries.⁵⁹ As a broad benchmark, high-income countries devote 3-7% of total health spending to cancer control.⁶⁰ Most LMICs currently allocate far less; cancer accounts for about 1% of health spending (public and private) in Brazil and India, and 2% in China and Mexico.^{6 35 61}

Financing for cancer control will have to come mainly from national healthcare budgets, particularly in middle-income countries, where rising incomes are enabling expansion of public financing for health.^{4 62} South Africa, for example, has assessed which interventions it might include in an expanded national health insurance package⁶³ and similar work is underway in India.^{58 64} In low-income countries, it would be inappropriate for governments to shift to spending 13% of their healthcare dollars on cancer. External assistance will be needed in those countries to establish an expansion path for cancer control. A clear principle to adopt is the eventual goal of coverage for every person (even if coverage expands gradually), but not coverage of everything,⁶⁵ since poorly conceived plans may provide expensive, non-ineffective treatments for a few, while missing the opportunity to expand cost-effective population coverage. Public finance is not necessarily synonymous with public delivery,⁶⁶ however. Properly regulated private hospitals, facilities and providers can be contracted to deliver cancer control interventions. For both public and private hospitals, aligning payment incentives to good quality and good outcomes is essential.⁶⁴

Several Latin American countries are already expanding their health insurance systems from coverage limited to occupational groups or selected vulnerable groups, to more comprehensive coverage (utilizing general taxation).³⁵ However, for some lower-middle income countries and most low-income countries, substantial increases in public finance for health, paired with economic growth or external assistance, would be needed to adopt a full package of interventions.⁴ Even those countries, however, could benefit from considering the future cancer burden, costs and financing to project a future cancer control plan. Higher tobacco taxes are the most important single cancer prevention intervention at a practical level, and a tripling of the excise tax on tobacco (thereby approximately doubling prices) could mobilize an extra \$100 billion worldwide in annual revenue.²⁸

For all LMICs, the epidemiologic dividend that accrues from a decreased burden of infectious disease should generate revenue that can be spent on NCD control.⁶⁷

Implementation challenges for an essential package

Within the essential package, some aspects of interventions may be implemented reasonably quickly, notably tobacco control measures that involve taxation and regulation,³² and policy changes to increase access to narcotics (although establishing nationwide programs and training a full cadre of providers may take years).²² Some interventions can be scaled to reasonably high coverage quickly with existing infrastructure, such as school-based HPV vaccination among adolescent girls, or hepatitis B vaccination in newborns. By contrast, other interventions will need expanded clinical access, most notably surgical treatment of early stage breast cancer and cervical cancer.⁶⁸ Increasing surgical capacity is relatively expensive but feasible from an organizational perspective, especially if existing district hospitals can be strengthened^{69 70} (paired with central cancer clinical expertise), whereas expanding chemotherapy treatment requires an extensive network of laboratories and follow-up, which in low and lower-middle income countries is currently feasible only in urban areas. Scaling up radiotherapy requires large capital expenditures, and substantial attention to guidelines, treatment protocols and monitoring of safety precautions.^{71 72}

Particularly for low-income countries where minimal cancer services currently exist in the public sector, the needed expertise and resources for cancer treatment will require years of steady investment in physical and human infrastructure. Elements missing or in short supply in LMICs^{14 41 73} include: trained professionals in oncology and relevant disciplines; appropriately-equipped facilities for surgery, radiotherapy, pathology and other laboratory testing services (eg, breast cancer ER testing: panel 3); supplies (including chemotherapy drugs); geographic access to facilities with affordable cancer services, including surgery; public awareness of the availability and effectiveness of cancer control interventions; and cancer incidence and cause-of-death data.

As more people are successfully treated and live for many years, survivorship services (eg, rehabilitation, remedies for physical deficits caused by treatment, limiting the social stigma of having had cancer, follow-up for recurrence) will increase in importance, but costs for survivorship programs are not included.⁷⁴

The package emphasizes treatment for *early stage* cervical and breast cancers (and similarly for other cancers included in specific country plans) because cure rates are substantially higher than in more advanced cancers. Locally appropriate opportunistic cervix screening is included, but organised population-wide screening programs are not. Even without screening, however, LMICs might be able to achieve a somewhat earlier stage of presentation of common cancers by making affordable treatment available, and communicating this to people. Historical evidence from high-income countries (eg, stage-shifting cervix cancer in Sweden before organized screening began around 1960) supports this approach.⁷⁵

Cancer treatment can be organized through existing medical facilities (particularly district hospitals) or through specialized centres, but good links between facilities, with a centralised locus of monitoring and guidance, are needed.^{7,41} For example, all children with cancer in Honduras (population 8 million) are treated in 2 centres that collaborate and communicate closely.⁷⁶ In contrast, children with cancer in Colombia (population 48 million) are treated in over 150 healthcare institutions of varying size, with little communication between centres.²¹ This adversely affects patient outcomes and costs. India, population 1.3 billion, is building a National Cancer Grid,⁷⁷ linking non-specialist hospitals to specialist cancer centres and standardising treatment protocols.

Building and improving cancer control capacity requires attention to the quality of services, from pathology and diagnosis to surgery, chemotherapy, radiotherapy and palliative care.⁴¹ It also requires upgrading hospitals to provide basic cancer surgical services⁶⁹, developing cancer referral networks, tracking service performance, integrating the delivery of different types of services and ensuring that financial flows accompany services.

Global Initiatives for Cancer Control

Only 1% of the \$30 billion development assistance for health in 2010 was for NCDs, little of which was for cancer.⁷⁸ NCD funding will increase with increasing global recognition of their importance, but it is unlikely that significant global funds will be allocated to national health systems to deal with cancer. As additional funding becomes available, we suggest three priorities for international support.

1. *Lower the costs to countries of key inputs for the essential package and other cost-effective interventions, such as HPV and other vaccines, cancer drugs (including generics), pathology tests, radiotherapy machines, and other relevant goods.* The Global Fund for AIDS, TB and Malaria, Gavi, the Clinton Health Access Initiative and other international partnerships developed mechanisms to reduce prices of infectious disease control commodities, utilizing economies of scale. Similar efforts for cancer are possible, with subsidies for reputable and affordable medicines, advanced market commitments, and bulk purchases of drugs or radiotherapy machines.^{71,78}

2. *Expand technical assistance in cancer control.* International and regional networks exist for many aspects of cancer care (treatment guidelines, networks on cervical screening, childhood cancer treatment and research, palliative care, etc). Other support modalities (eg, twinning institutions) typically involved institutions in high- and low-income countries (North-South collaborations), but opportunities should grow to add South-South collaborations. Within countries, peer-based professional standards of cancer care and reporting of outcome and performance for various facilities can improve quality of care.^{79,80}

3. *Support for research* may be the best use of limited overseas developmental assistance. Research could include tracking national cancer burdens, clinical trials, implementation science (including research on delivery systems and economics, notably, local economic analyses to define appropriate essential packages of services), cancer epidemiology and biology, development of widely practicable, low-cost technologies.⁸¹

Benefits of expanded cancer control

Despite substantial challenges in most LMICs, appreciable reductions in the cancer burden might well be possible by 2030 (with even greater reductions by 2050 and beyond⁸²), particularly through treating common cancers that are detected early, tobacco control that encourages widespread adult smoking cessation, and vaccination against hepatitis B and HPV. Age-standardised cancer death rates at ages 0-69 years were declining globally at 10%/decade in 2000-10. If this continues, then from 2010-2030 the rates will fall by about 20%. WHO's recently proposed⁷⁹ one-third decrease by 2030 requires faster progress, particularly in smoking cessation. WHO estimates that tobacco control, HPV and hepatitis B vaccination and opportunistic cervical cancer screening could avoid about 6% of cancer deaths by 2030 (about 200,000 deaths annually before age 70), and the *DCP3* essential package could achieve greater reductions. If, as expected, the availability of treatment shifts diagnoses for common treatable cancers to earlier stages, further lives could be saved. The benefits of pain relief are not measured in lives saved, but are important to patients and those around them. Providing cancer services may also help shrink the health gap between rich and poor, as many of the cancers and risk factors suggested for targeting are more prevalent among those at the lower end of the economic ladder. Cancer control is often approached with pessimism, but practicable, deliberate, cost-effective steps can enable many countries to reduce substantially by 2030 the suffering and premature death from cancer, with much greater improvements by 2050.

Panel 1: Key messages

Cancer is already a major cause of death in LMICs, particularly in middle-income countries, and will increase as a percentage of deaths in all LMICs, driven by population aging and faster declines in age-standardised mortality from other causes than from cancer.

In most populations, helping current tobacco users to quit and young people not to start smoking are the most urgent priorities in preventing cancer (and other NCDs), along with vaccination against the cancer-causing hepatitis B and human papilloma virus (HPV). Higher tobacco taxes will reduce cancer incidence and generate substantial extra revenues for governments.

Other than tobacco- and virus-related cancers (helped, where appropriate, by control of certain occupational hazards), most of the increase in cancer numbers is not currently preventable, but many cases can be effectively treated. Breast and colorectal cancer are common, and moderately curable if treated early. In addition, for the next several decades, until the protective effects of HPV vaccination are widespread, cervical pre-cancerous changes and early cancers are eminently treatable. The interventions supported by these *DCP3* analyses go somewhat beyond WHO best buys, which are limited to interventions deliverable without hospital facilities.

The *DCP3* essential package of cost-effective and feasible interventions would, if fully implemented, cost an additional \$20 billion per year, or 3% of total public spending on health in LMICs: 2-6% in

upper-middle-income and 5% in lower-middle income countries, but 13% in low-income countries. In per capita terms, this would cost \$5.7, \$1.7 and \$1.7 annually in upper-middle-income, lower-middle-income, and low-income countries, respectively. Such increases are potentially feasible in all but the low-income countries, which would require external support.

Some cancer services should be considered for inclusion in strategies for universal health coverage, focusing on ensuring that cancer interventions considered appropriate for a national cancer strategy should be available and affordable.

Global initiatives for cancer control in LMICs are needed: (i) to lower the costs of key inputs for the essential package, including large-scale commodity purchases; (ii) to expand technical assistance and dissemination of skills; and (iii) to promote cancer research.

Panel 2: Methods

The 79 authors of the 18 *DCP3 Cancer* chapters surveyed the published and grey literature to identify cost-effective interventions for the cancers studied. Cancer-specific incidence and mortality data are from IARC's GLOBOCAN.⁹ Mortality data are from WHO's Global Health Estimates¹² and demographic estimates are from the UN.⁸³

Analyses were stratified by World Bank country-income classifications (Figure 2), as defined by 2013 per capita Gross National Income (GNI): 34 low-income countries (<\$1045), 50 lower middle-income countries (\$1046 to \$4125) and 55 upper middle-income countries (\$4126 to \$12,745).⁸⁴

Cost-effectiveness estimates were compiled for each cancer and each intervention. Systematic searches were conducted via PubMed for all interventions covered in the volume, for studies in or including LMICs, published 2003-13.⁴⁹ For colorectal cancer, studies from high-income Asian economies were also sought. A recent review of cost-effectiveness of cancer interventions for high-income countries was also useful.⁸⁵ The studies identified used various outcome measures: life-years saved, quality-adjusted life-years (QALYs) gained, and disability-adjusted life-years averted.

Evidence from studies in LMICs would have been preferred, but was rarely available. Cost-effectiveness evidence from high-income countries was therefore reviewed, with evidence from high-income Asian economies preferred. We adopted the scale used by the Commission on Macroeconomics and Health (2001) to define very cost-effective, cost-effective and cost-ineffective as costing <1, 1-3 or >3 times per capita income per QALY (or other measure).⁸⁶

The essential package includes interventions rated as very cost-effective and cost-effective and considered potentially affordable and feasible in resource-constrained middle-income countries. Costs were expressed as USD2012, requiring inflation of costs from earlier studies. Costs were also expressed as a percentage of national public spending on health, as estimated by the World Bank.⁵⁹

More detail on the methodology of the cost-effectiveness analysis and the costing exercise; and citations for the studies included in the systematic review, are available on the DCP3 website at <http://dcp-3.org/resources/methodology-and-results-systematic-search-cost-and-cost-effectiveness-analysis-cancer>.

Panel 3: Possible strategies for treating early breast cancer in LMICs

By definition, in early breast cancer (stage I/II/IIIA) all detectable disease can be removed surgically, but micrometastases may remain that, perhaps years later, cause recurrence and death, and adjuvant treatments may be given after surgery to reduce this risk. In high-income countries most women receiving appropriate treatment for early breast cancer survive their disease.⁸⁷ The success rate of breast-conserving surgery (lumpectomy) plus radiotherapy to the conserved breast is about the same as for mastectomy (removal of the entire breast, plus perhaps some local lymph nodes) and either can be offered, if safe radiotherapy is available. The most basic surgical procedure for early breast cancer is some form of mastectomy.²⁰ For women in LMICs with early breast cancer, the first requirement is good quality, safe surgery. In low-income countries, in particular, timely access to safe surgery is a major barrier. In middle-income countries, where there is generally better population access to surgical services, *quality* cancer surgery is the major surgical concern, particularly adequate resection of the tumour.⁶⁸ After technically successful surgery, treatments can be based on oestrogen-receptor (ER) status, estimated recurrence risk, and general health.²⁰

ER status of surgically removed breast cancers can be determined (for about US\$10, in India). If, but only if, the cancer is ER-positive, about 5 years of endocrine drug therapy substantially reduces the 15-year recurrence risk and is relatively non-toxic. Endocrine drugs such as tamoxifen or, for post-menopausal women, an aromatase inhibitor (AI)⁸⁸ can be dispensed safely to outpatients and are available as relatively low-cost generics (although even generic tamoxifen costs about \$15/year in India, and generic AIs currently cost about \$50/year). Chemotherapy also reduces recurrence, but is more toxic and requires more careful medical supervision to ensure safety and efficacy. New drugs (eg, trastuzumab) that target other breast cancer receptors are not at present cost-effective in LMICs.

Relatively simple regimens of generic cytotoxic drugs (eg, 4 cycles of daunorubicin and cyclophosphamide with drug costs of about \$200 in India) should be practicable wherever surgery is practicable,²⁰ and could be offered to women who are otherwise in good health but whose disease has already spread from the breast to the local lymph nodes.⁸⁷ More effective cytotoxic regimens (eg, with taxanes) would increase toxicity, drug costs, and supervision costs.

Finally, global initiatives might well help to lower cost of cancer drugs and other commodities, and develop and disseminate standardised resource-appropriate treatment protocols, such as those developed by the Breast Health Global Initiative. The successful global initiatives to aid in the diagnosis and treatment of HIV/AIDS provides a model.⁸⁹

Contributors

HG and PJ generated the plan for this study. HG prepared the first draft with input and revisions from all authors. SH and PJ developed the costs of the essential package. All authors approved the final draft. HG and PJ had responsibility for submitting for publication.

Acknowledgements

We thank George Alleyne for helpful comments on an earlier draft. Funding: Bill and Melinda Gates Foundation, US National Cancer Institute, Canadian Institutes of Health Research (grant 126347), and Centre for Global Health Research.

DCP3 cancer group

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Figure 1: Incidence and mortality of selected cancers before age 70 years, low-and middle-income countries, 2012

Source: Ferlay et al. 2013⁹

Figure 2. Countries by World Bank income groupings and population in 2013

Source: World Bank⁸²

Table 1: Worldwide cancer deaths in 2012 at ages 0-69 years by cancer site and country income grouping, and 5-year survival rates in LMICs and high-income countries

	Annual deaths (thousands) at ages 0-69 years, by World Bank income grouping of countries					5-year survival (%), cancer registry data	
	Low income †N=0.8	Lower middle †N=2.4	Upper middle †N=2.3	High income †N=1.2	World (total) †N=6.7	Low- or middle- income	High income
Cancer, by site (ICD-10 C00-99)							
Lung, mouth or oesophagus	70	260	560	300	1200	10	20
Liver	30	90	270	60	440	10	20
Breast	30	140	110	80	360	75	90
Stomach	20	80	210	50	360	20	40
Colon or rectum	20	80	120	100	310	50	60
Cervix	40	90	60	20	200	55	65
Ovary	8	30	30	30	100	25	40
Leukaemia, age 0-14 years	3	10	10	2	30	65	90
age 15-69 years	10	40	60	30	140	30	50
Prostate	4	10	20	20	60	70	90
Other/unknown site	110	330	470	310	1220	-	-
All cancers	350	1170	1920	1000	4400	-	-
(% of all causes)	(6%)	(9%)	(22%)	(37%)	(14%)		
All non-communicable diseases	1660	6300	5950	2200	16 070	-	-
Communicable/external causes	4100	7380	2650	500	14 660	-	-
All causes	5760	13 680	8600	2700	30 730	-	-

Notes: Population and mortality data from WHO Global Health Observatory¹² and UN Population Division⁸²
Numbers of deaths above 10,000 are rounded to the nearest 10,000 so totals may differ. †N is the 2012 population (in billions) at ages 0-69 years only, excluding older ages; including all ages, total world 2012 population was 7.0 billion. Estimated 5-year survival from Allemani et al. 2015¹¹ rounded to the nearest 5%.

Table 2: All cause and cancer deaths by country income group, % change in mortality rate over 10 years, 2000-2010, age 0-69

Cause and World Bank income group of countries	Change in % 2000-2010				
	Low-income	Lower-middle income	Upper-middle income	High-income	World
All cancers	-6	-2	-12	-13	-10
Lung, mouth, oesophagus (mainly tobacco-related)	-6	+1	-11	-12	-9
Cervix, liver, stomach (mainly infection related)	-13	-2	-18	-24	-15
All other cancers	-4	-3	-9	-12	-8
All causes	-21	-15	-23	-17	-19

Source: Authors, based on data from IARC GLOBOCAN⁹ and WHO Global Health Observatory data¹².

Table 3: Essential cancer intervention package

Cancer type No. of deaths age <70 years, 2012 (000s)	Interventions	Level of delivery
All cancers* 3230	Education on tobacco hazards, value of HPV and HBV vaccination and importance of seeking early treatment for common cancers	National policies, regulation or information
	Palliative care, including, at a minimum, opioids for pain relief	National policies, regulation or information
Tobacco-related cancers (oral, lung and oesophagus) 900	Taxation; warning labels or plain packaging; bans on public smoking, advertising and promotion; and monitoring	National policies, regulation or information
	Cessation advice and services (mostly without pharmacological therapies)	Primary health clinical or mobile outreach
Liver cancer 380	Hepatitis B vaccination (including birth dose)	Primary health clinical or mobile outreach
Breast cancer 280	Treat early-stage cancer [†]	Specialised cancer centre/unit [‡]
Colorectal cancer 210	Emergency surgery for obstruction	First-level hospital [§]
Cervical cancer 180	School-based HPV immunisation	National policies, regulation or information
	Opportunistic screening (visual inspection or HPV DNA testing); treat precancerous lesions	Primary health clinical or mobile outreach
	Treat pre-cancerous lesions	First-level hospital
	Treat early-stage cancer	Specialised cancer centre/unit
Childhood cancers 80[¶]	Treat selected cancers in paediatric cancer units/hospitals	Specialised cancer centre/unit

Notes: Cancer totals are rounded to nearest 10,000. * Education and basic palliative care are relevant for cancers at all ages. [†] Early-stage cancer generally refers to stages I and II. [‡] Some interventions may take place at first-level hospitals, by a specialized surgeon visiting once per month, for example. [§] First-level hospitals are referred to as district hospitals in some countries. ^{||} Opportunistic screening focuses on existing available populations, and differs from organized screening which is a well-defined process including formal invitations to participate, recalls, reminders, tracking results, ensuring follow-up, monitoring and reporting program performance results. It may include some outreach, however. [¶] Including some solid tumours.

Table 4: Approximate marginal costs of essential package for low-income, lower-middle income and upper-middle income countries, per capita in 2012 US dollars

Intervention	Low-income	Lower-middle Income	Upper-middle income
Comprehensive tobacco control measures	0.05	0.07	1.06
Palliative care and pain control	0.05	0.06	0.06
Hepatitis B virus vaccination	0.08	0.04	0.04
Promote early diagnosis and treat early stage breast cancer	0.43	0.43	1.29
HPV vaccination	0.23	0.23	0.40
Screen and treat precancerous lesions and early stage cervical cancer	0.26	0.29	0.87
Treat selected childhood cancers	0.03	0.03	0.09
Subtotal	1.13	1.15	3.81
Ancillary services (50% of subtotal)	0.57	0.58	1.91
TOTAL COSTS	1.70	1.73	5.72

Notes: Authors' calculations based on DCP3 Cancer, Horton and Gauvreau, 2015.⁴ Demographic and epidemiologic information from Nigeria, India and Brazil is used to model costs for low-income (primarily in sub-Saharan Africa), lower-middle income and upper-middle income countries, respectively. However, country-specific planning will require country-specific estimates.

Table 5: Resource requirements for essential cancer intervention package for LMICs

World Bank Income Category	Low-income	Lower-middle income	Upper-middle income	Total LMIC
Public spending on health as % GDP, 2013	2·0	1·8	3·1	3·0
Total public spending on health in US\$ 2013 (billions)	11	89	534	634
Required amount for cancer in US\$ 2013 (billions)	1·4	4·4	13·8	19·6
Cancer package as % of total public spending on health in 2013*	13·0	4·9	2·6	3·1

*Authors calculations; spending data from World Bank, 2014⁵⁷