Research on cancer prevention, detection and management in low- and medium-income countries

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Received 7 October 2009; revised 21 January 2010; accepted 22 January 2010

The burden of cancer in low- and medium-income countries (LMIC) is expected to increase in the next decades. The application of current knowledge and results of research in key areas would contribute to limit the impact of this phenomenon. Opportunities for research on cancer prevention in LMIC include investigating specific circumstances of exposure to known carcinogens and to agents which are not prevalent in other regions, as well as interactions among carcinogens and between genetic and environmental factors. Early detection both by screening and early clinical diagnosis represents an important component of cancer control in LMIC. Research has been carried out to identify effective and sustainable approaches for early detection of cervical cancer through human papillomavirus testing and visual tests and of oral cancer through visual inspection. For other important neoplasms such as breast cancer, on the other hand, no effective low-cost screening methods are currently available. Downstaging represents a potentially important approach for cancer control and a priority area for future research. Studies addressing the efficacy of treatment protocols, country-specific cost-effectiveness of various interventions and the clinical utility and cost-effectiveness of innovative health care and communication technologies represent the priority for clinical cancer research.

Key words: cancer control, cancer research, clinical research, early detection, primary prevention, screening

introduction

Cancer control aims at reducing the burden and suffering from cancer by preventing exposure to risk factors, early detection, effective treatment and relief of symptoms and pain from incurable advanced cancers. A combination of different approaches involving education, awareness, advocacy, legislation, vaccination, screening, early diagnosis and treatment is used to prevent the occurrence of and suffering and death from cancer. There is considerable variation in the extent of implementation and impact of these measures across different countries in the world, particularly between the low- and medium-income countries (LMIC) and high-income countries (HIC), which is related to both the national commitment and the availability of resources. The national commitment to develop cancer control services is the single most critical factor for cancer control and for appropriate allocation of limited resources available in LMIC that results in a discernible impact on cancer burden. Developing and implementing a planned time-bound National Cancer Control Programme as advocated by the World Health Organization (WHO) offers the best opportunity to implement and improve cancer control in LMIC [1].

We aim at reviewing opportunities and challenges for cancer prevention, early diagnosis and management in LMIC; the key measures are summarized in Table 1.

cancer prevention

During the last decades, several causes of cancer which are of particular relevance to LMIC have been identified through epidemiological and clinical studies. Examples include aflatoxins and hepatitis B virus (HBV) for liver cancer [2, 3], Schistosoma haematobium infection for bladder cancer [4], and liver flukes for cholangiocarcinoma [5]. In addition, the etiological role of human papillomavirus (HPV) in cervical and other cancers and that of Helicobacter pylori in stomach cancer are of particular importance in LMIC because of the high incidence of these cancers and the high prevalence of the infections. These discoveries have resulted in major opportunities for primary prevention, including vaccination against HBV and HPV, treatment of H. pylori infection and improvement in food storage aimed at reducing aflatoxin contamination [6–8].

In addition to risk factors which are specific to LMIC, the transfer of recognized cancer hazards from HIC to LMIC represents a major challenge for cancer prevention research and intervention. Control of tobacco smoking represents the main
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<th>Cancer site</th>
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<th>Treatment</th>
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<tr>
<td>Head and neck</td>
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<td>+++; surgery; radiotherapy</td>
<td>Implementation and evaluation of tobacco and alcohol control measures and population-based visual screening for oral cancer; evaluation of clinical downstaging; formulation of locally feasible cost-effective management protocols and evaluating their adherence and effectiveness</td>
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<td>Esophagus</td>
<td>+++; tobacco control; reduced alcohol use; healthy diet</td>
<td>+</td>
<td>+</td>
<td>Evaluation of the effectiveness of tobacco/alcohol control measures and promotion of healthy eating practices; evaluation of chemoprevention</td>
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<tr>
<td>Stomach</td>
<td>+++; prevention and eradication of H. pylori infection; healthy diet; tobacco control; improved living conditions</td>
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<td>+++; surgery</td>
<td>Evaluation of the efficacy and cost-effectiveness of screening individuals for infection with <em>Helicobacter pylori</em> and then eradicating H. pylori with antibiotic therapy; vaccination to prevent H. pylori infection</td>
</tr>
<tr>
<td>Colon, rectum</td>
<td>+++; control of overweight/obesity; promotion of healthy diet and physical activity</td>
<td>+++; awareness; early clinical diagnosis; screening by fecal occult blood test; endoscopy</td>
<td>+++; surgery; chemotherapy</td>
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</tr>
<tr>
<td>Liver</td>
<td>+++; HBV vaccination in infancy; prevention of exposure to liver flukes; reduced fungal contamination of stored grains; blood supply and injection safety measures to prevent exposure to HCV; reduced alcohol use; tobacco control</td>
<td>+</td>
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<td>Evaluation of long-term protection from HBV vaccination, need for booster doses; evaluation of methods to cure chronic HBV and HCV infection</td>
</tr>
<tr>
<td>Lung</td>
<td>+++; tobacco control; regulation of occupational exposures; ventilation and improved low-technology heating and cooking</td>
<td>+</td>
<td>+</td>
<td>Implementation and evaluation of primary prevention measures, in particular tobacco control</td>
</tr>
<tr>
<td>Breast</td>
<td>+++; control of obesity; promotion of physical activity; reduced alcohol use</td>
<td>+++; breast awareness; early clinical diagnosis</td>
<td>+++; surgery; chemotherapy; hormone therapy; radiotherapy</td>
<td>Evaluation of chemoprevention; evaluation of breast awareness and physical examination; evaluation of clinical downstaging; formulation of locally feasible cost-effective management protocols and evaluating their adherence and effectiveness</td>
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priority for cancer control in LMIC, as the number of smokers is projected to increase in these countries during the next future [9]. While abundant data exist on the carcinogenicity of tobacco smoking in LMIC [10], several important questions remain to be answered, including the effect of local products, the interaction with diet, infections and other risk factors and the pattern of risk after cessation of smoking. Use of smokeless tobacco products is prevalent in many LMIC; adequate data is available only for the most common products used in India and neighboring countries [11], while little research has been conducted in regions such as West and Central Asia and Latin America. Although the number of cancers attributable to alcohol drinking in LMIC is relatively low [12], alcohol consumption is increasing in many developing regions of the world, in particular in Asia. In addition, research should be established to evaluate the effectiveness of tobacco and alcohol control interventions, including restriction of smoking in workplaces and public settings and fiscal policies, in order to avoid misuse of very limited resources, e.g. in ineffective public education campaigns.

Many LMIC are experiencing a rapid transition from a traditional lifestyle to a society characterized by urban or suburban residence, sedentary jobs and high caloric intake. This transition results in increasing prevalence of overweight and obesity, increasing incidence of cardiovascular and metabolic diseases and other nutritional and behavioral changes (e.g. reduction in physical activity) which are likely to affect cancer risk. Furthermore, these nutritional changes are closely linked to the modification of other risk factors, such as reproductive patterns in women. Therefore, if the incidence of female breast cancer is increasing in many LMIC, the relative contribution of known risk factors such as delayed age at first pregnancy, shorter breast-feeding history, smaller number of pregnancies, increased prevalence of overweight and obesity, low physical activity and higher alcohol intake is unclear, as is the possible role of suspected risk factors such as environmental pollutants potentially acting on hormonal pathways. The investigation of the determinants of trends in risk of major cancers in LMIC would not only represent an important contribution to cancer control in these countries but would also contribute to the understanding of the causes of mechanisms of cancer in general. From this point of view, longitudinal epidemiological studies of populations in rapid transition, while challenging, would offer a unique opportunity to etiological research on human cancer.

The major role of chronic infections in human cancer, in particular in LMIC, is increasingly recognized. It has been estimated that 26% of cancers in LMIC are attributable to infection [13]. The development of vaccines against HBV and HPV represents a great success in terms of prevention of major cancers; the implementation of these vaccination programs in LMIC, however, poses a major economic challenge. A national HBV vaccination program launched in Taiwan in 1984 is the world’s first successful implementation of universal HBV program for infants. Following this program, the surface antigen of HBV carrier prevalence decreased from 15%–20% to

Table 1. (Continued)

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<tr>
<td>Uterine cervix</td>
<td>++; HPV vaccination;</td>
<td>+++; awareness; early clinical</td>
<td>+++; surgery;</td>
<td>Implementation and evaluation of HPV vaccination and alternative methods of</td>
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<td></td>
<td>tobacco control</td>
<td>diagnosis; screening with</td>
<td>radiotherapy;</td>
<td>screening; integration of HPV vaccine and screening programs; effectiveness of</td>
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<td></td>
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<td>cytology, VIA or HPV testing</td>
<td>chemotherapy</td>
<td>screening with fast HPV testing followed by VIA triage and treatment in preventing</td>
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<tr>
<td>Lymphohematopoietic (lymphoma,</td>
<td>+</td>
<td>+</td>
<td>+++; chemotherapy;</td>
<td>Evaluation of affordable forms of chemotherapy regimens in low-resource settings;</td>
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<td>multiple myeloma, leukemia)</td>
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<td>radiotherapy</td>
<td>formulation of locally feasible cost-effective management protocols and evaluating</td>
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<td>their adherence and effectiveness</td>
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LMIC, low- and medium-income countries; HBV, hepatitis B virus; HCV, hepatitis C virus; HPV, human papillomavirus; VIA, visual inspection with acetic acid; +, limited role; ++, moderate role; ++++, substantial role.
<1% and most importantly, the annual incidence of childhood liver cancer decreased from 0.67 to 0.19 per 100 000 children [14, 15]. This program proves that universal HBV vaccination provides long-term protection up to 20 years, and a universal booster is not indicated before adulthood. Research is needed to define the best strategy for vaccination (number of doses, age at vaccination) and to assess the effectiveness of the vaccine in different populations. Findings from trials evaluating bivalent (HPV16 and HPV18) and quadrivalent (HPV6, HPV11, HPV16 and HPV18) vaccines indicate that a regimen of three intramuscular injections is well tolerated and safe and offers HPV-naive women >90% protection from infection and CIN associated with the HPV types included in the vaccine [16, 17]. Translating the vast potential of HPV vaccination into public health practice is currently limited by high costs, uncertain long-term protection and cross-protection against other HPV types, acceptability issues, information needs, health system capacity and delivery logistics to vaccinate preadolescents and adolescents [18]. Development of vaccines against other carcinogenic viruses and bacteria, including strains of HPV not covered by the available products, remains a major priority in cancer control in LMIC. Control of HIV/AIDS in sub-Saharan Africa through avoidance of infection and therapy would also have an important impact on cancer since HIV-associated Kaposi sarcoma represents the main cancer in several countries in that region [19].

Prevention of occupational cancer has been implemented with relative success in HIC during the second half of the 20th century. About 30 occupational exposures have been recognized to cause cancer in exposed workers [20]; very limited information is available from LMIC on patterns of exposure to occupational carcinogens and cancers that can be attributed to workplace carcinogenic exposures [21]. Priority for future research should be given to the main occupational carcinogens, including asbestos, mixtures of polycyclic aromatic hydrocarbons and benzene. Furthermore, the contribution of social development to cancer risk should be better characterized.

In addition to the investigation of known causes of cancer, as outlined in the previous paragraphs, there are other opportunities for research on cancer prevention in LMIC. Patterns of exposure to lifestyle and environmental carcinogens may differ between LMIC and HIC. For example, intake of Chinese-style salted fish is an established risk factor of nasopharyngeal carcinoma [22], and the risk is highest when exposure starts in infancy. Very limited research has been conducted on risk in such susceptible groups of the population. Chemoprevention is an area of cancer prevention research which can be particularly promising in LMIC [23]. Furthermore, because of the specific patterns of exposure, the study of interactions between carcinogens in LMIC could provide unique information for cancer research. For example, the pattern of interaction between HBV infection on the one hand and tobacco smoking and alcohol drinking on the other hand in hepatocellular carcinogenesis would clarify the mechanism of action of these different factors [24]. Finally, there is still ample scope for original research on risk factors, which would have implications in terms of primary cancer prevention worldwide. One striking example is the high risk of esophageal squamous cell carcinoma experienced by many populations in Central Asia (the so-called ‘Central Asian esophageal cancer belt’), causes of which are not yet fully elucidated despite research efforts, mainly in China [25] and Iran [26]. Novel etiological hypotheses include dietary exposure to polycyclic aromatic hydrocarbons [27] and thermal injury from hot beverage drinking [28]; these hypotheses are best addressed through large-scale prospective studies including collection of biological samples [29]. Given the importance of squamous cell carcinoma of the esophagus in overall cancer burden among other populations, in particular in Eastern and Southern Africa and South America [30], findings of studies from Central Asia would have far-reaching implications in terms of cancer prevention.

**cancer detection**

Early detection both by screening and early clinical diagnosis is an important intervention to control cancer in LMIC. The main objective of cancer screening and early clinical diagnosis (through improved awareness and health services infrastructure and accessibility) is to detect cancer cases early enough to provide less toxic and less expensive curative treatment.

**cervical cancer**

LMIC account for four-fifths of the estimated 500 000 new cervical cancer cases and 300 000 deaths annually worldwide, yet there are no effective screening programs in most of these countries. While early detection by screening is an established control option, HPV vaccination is a promising new approach. Screening is the most feasible current approach to prevent invasive cervical cancer by detecting and treating women with high-grade cervical intraepithelial neoplasia (CIN 2 and 3 lesions). It is critical to complete the entire process of testing, diagnosis, treatment and follow-up care to ensure the success of screening. Currently, precancerous lesions are rarely diagnosed and treated and invasive cancers generally present at advanced stages with poor survival in most high-risk developing countries. There are several options such as cytology, HPV testing and visual tests for cervical screening and reducing the incidence of cervical cancer. Cytology screening in HIC has reduced the burden of cervical cancer, but this requires complex inputs in sample collection, processing, reading and reporting of smears and quality assurance inputs for assured success. The cytology screening projects in LMIC in South and Central America, over the last three decades, have achieved only limited success in preventing cervical cancer [31, 32]. For screening to be successful in LMIC, the screening test, diagnosis and treatment should be provided on-site, preferably all in one or two visits (to ensure wide coverage) and tests must be affordable.

The challenges and difficulties in implementing cytology screening in LMIC have stimulated the search for alternative methods of screening such as visual inspection with acetic acid (VIA) or with Lugol’s iodine and HPV testing [33, 34]. A range of personnel including doctors, nurses, midwives and paramedical health workers can be rapidly trained in providing visual screening in short training courses of 4–10 days [35]. A wide range of teaching materials is now available for training.
personnel in carrying out visual screening competently [34]. However, it is a subjective test that suffers from high false-positive rates and low to moderate specificity and reproducibility. Quality assurance procedures for visual screening are yet to be standardized and assuring consistent high performance can be challenging under field conditions and requires constant monitoring and frequent retraining of test providers. A 25% reduction in cervical cancer incidence and a 35% reduction in cervical cancer mortality were found following a single round of VIA screening provided by trained nurses in a randomized trial in India [36]. The greatest reduction in incidence and mortality rates were observed for the 30- to 39-year age group which is explained by the fact that the transformation zone, where cervical neoplasia occurs, is fully exposed on the ectocervix in young women, enabling VIA to detect the abnormalities.

HPV testing has clearly a higher sensitivity (pooled sensitivity 90%) but somewhat lower specificity (pooled specificity 88%) than cytology [37]. However, it is limited by its current costs, cumbersome procedure and equipment, and there are efforts to develop inexpensive, rapid yet accurate HPV test formats and tests on the basis of E6 and E7 viral oncoproteins to improve specificity and the need for repeat HPV DNA testing. In LMIC, HPV testing may provide an objective method of identifying and investing the limited resources on women at risk for disease. However, the currently available HPV tests are expensive and cumbersome and there is a need to develop simple, affordable, safe, accurate, reliable, rapid, portable and acceptable biochemical tests for use in low-resource settings. An important research question is to evaluate the accuracy of the fast HPV tests in routine screening settings. In a randomized trial in South Africa, cryotherapy for HPV test-positive women, triaged by VIA, resulted in a 77% and 74% decline in the prevalence of CIN 2–3 at 6 and 12 months, respectively, while VIA followed by cryotherapy resulted in a 37% and 46% lower prevalence, respectively, compared with a control group [38].

In recent years, new paradigms have been proposed to maximize participation of women in screening and treatment and to improve cost-effectiveness and efficiency. These include aiming for a single or twice in a life-time screening, targeting women aged 30–49 or 30–59 years, using HPV testing as a primary screening test followed by cytology triage or VIA triage (in low-resource settings) and the use of ‘single-visit approach’ [39] that entails treatment of VIA- or HPV-positive women, with no evidence of invasive cancer, by cryotherapy in the same screening session, without diagnostic procedures such as colposcopy and biopsy or colposcopy, directed biopsies and treatment with cryotherapy or loop electrosurgical excision procedure provided in the same sitting following a positive screen [40]. The cost-effectiveness of this approach has been confirmed using computer-based models of a variety of cervical cancer screening strategies in India, Kenya, Peru, South Africa and Thailand, with an estimated reduction in the lifetime risk of cancer by ~25%–36% and a cost of <$500/year of life saved [41]. The evidence, on the basis of terms of safety, acceptability and effectiveness of the new screening algorithms implemented by midlevel providers in LMIC settings, thus justifies and encourages such innovative approaches in routine practice, thereby contributing to cervical cancer prevention.

The large body of research findings and managerial guidelines, as well as further information from ongoing studies on the cost-effectiveness of different screening approaches in preventing cervical cancer, should be taken into account while reorganizing existing inefficient screening programs and when considering new initiatives in LMIC [42–44]. While HPV vaccination provides the hope for the future, screening provides the current means of cervical prevention.

breast cancer

Breast cancer incidence is increasing in almost all LMIC and effective control measures are urgently required to reduce mortality. There are no safe and effective preventive measures available now to reduce the burden of breast cancer. Currently, more than two-thirds of breast cancer cases are detected in advanced stages in LMIC. Methods for early detection of breast cancer include screening by mammography, clinical breast examination (CBE) and breast self-examination (BSE). There is uncertainty about the magnitude of benefit of organized BSE screening due to inconsistent findings. A randomized controlled trial of CBE screening for breast cancer began in Manila in 1995, but the intervention was discontinued after the first round because compliance with referral among women who were found to have a breast lump was extremely low (21%) and attempts to improve compliance failed [45]. Recent controlled studies of BSE screening indicate that this approach is not effective in reducing breast cancer mortality [46].

Mammography screening is expensive, involves substantial financial and manpower resources and thus is not feasible in most LMIC. Many breast cancers are found by women themselves, even in countries that have a mammographic screening program. Most of these changes are discovered by chance, when women are dressing or taking bath. It is therefore important that women are able to recognize early signs and symptoms and seek medical advice as soon as possible. Breast awareness seems to be a clinically useful strategy in which women are made aware of what is normal for them, what changes to look and feel for and what changes to report without delay to their family doctor and seek prompt referral for appropriate care through public education through mass media, targeted educational material in health centers and advice by health professionals. In the absence of evidence that routine systematic BSE reduces deaths from breast cancer, a number of international health organizations now recommend that women look and feel for changes in their breasts as part of general body awareness and health care. Along with creating breast awareness, sufficient capacity should be developed in health services for diagnosis and treatment of detected cases. A nonresponsive and inefficient health service with poor infrastructure and accessibility in the light of increasing demand due to awareness counteracts the potential benefit of a program of early clinical diagnosis.

oral cancer

Oral cavity is an easily accessible site for screening by doctors, nurses and health workers or for self-examination and visual screening has been shown to detect early oral neoplasia, when provided as part of routine medical care and by health workers.
Early oral cancer cases have a better prognosis than those with advanced disease. The sensitivity of oral visual inspection to detect lesions varies from 58% to 62% and the specificity ranges from 98% to 99% [47–50]. A 33% reduction [odds ratio 0.67 (95% confidence interval 0.46–0.95)] in the risk of advanced oral cancer was observed in a case–control study of oral screening in Cuba [51]. A significant 34% reduction in oral cancer mortality has been observed among the tobacco or alcohol users in a randomized oral cancer screening trial in Southern India [52], supporting the routine use of visual screening among users of tobacco or alcohol both, in addition to primary prevention efforts in reducing oral cancer mortality.

**cancer downstaging**

Improved awareness among the public and health care providers, supported by accessible health services, are conducive for the early clinical diagnosis of head and neck, breast, cervix and large-bowel cancers among others. There is evidence for such clinical downstaging of breast [53] and cervical cancer [54] in LMIC. A major research priority is to evaluate the impact of improving awareness and health services on clinical downstaging of cancers in different additional health care settings in LMIC.

**cancer management**

The minimum basic facilities required for diagnosis and staging and to indicate treatment options and prognosis include histopathology, imaging with conventional radiology, ultrasonography and basic endoscopy. Unfortunately, even these basic services are not widely available in public health services in many LMIC, particularly in sub-Saharan Africa.

Surgery plays an important role in the management of many solid tumors such as breast, head and neck, gastrointestinal, genitourinary and soft tissue cancers and removal of tumor mass is often curative for many localized cancers. Increasingly more cancers are surgically managed by specialist surgical oncologists in HIC, whereas cancer surgery is still widely carried out by general surgeons in most LMIC. Although surgery is the most widely feasible cancer treatment modality, lack of skilled surgeons and training programs have greatly impeded the availability of basic cancer surgery services (for breast, cervix and ovarian cancers and excision biopsy) in many countries in sub-Saharan Africa.

Radiotherapy is mainly used to treat solid tumors such as cervix, breast, head and neck, uterus, brain and soft tissue sarcomas. The dose to each site depends on a number of factors including the type of cancer and whether there are tissues and organs nearby that may be damaged by radiation. There have been considerable advances, refinements and sophistication in radiotherapeutic equipment and techniques which has driven the capital costs enormously in recent years. Replication of such sophisticated radiotherapeutic infrastructure and services as they exist in health care settings of HIC is neither feasible/affordable nor absolutely essential for delivering basic and effective services in impoverished health care settings such as in sub-Saharan Africa. It is important to highlight in this juncture that even basic radiotherapy services (telecobalt external beam therapy, preloaded brachytherapy, radiation physics and manual treatment planning services) are not available in >30 countries in the world (most of them in sub-Saharan Africa) [55].

Several new chemotherapeutic molecules have been recently developed which have escalated treatment costs enormously for minimal incremental benefits. It is not feasible and affordable and not necessary to follow in LMIC the expensive models of cancer chemotherapy, including hormone therapy, practiced in HIC. Development of nationally or regionally affordable yet evidence-based and effective treatment policies is vital for cost-effective treatment options in LMIC.

Palliative care refers to medical care aiming at relief from suffering, pain and other distressful symptoms from generally incurably advanced cancer as well as psychological and spiritual care. It is usually provided by a team involving doctors, nurses and social workers. A large proportion of cancers in LMIC are currently diagnosed in advanced stages and thus palliative care is an important component of the overall cancer control strategy. The three-step analgesic approach and the availability of oral morphine have significantly advanced pain relief and judicious use of surgical, radiotherapeutic and pharmacological approaches has greatly improved relief of distressing symptoms due to obstruction, pressure, growth and ulceration of cancers. However, progress is not uniform throughout LMIC.

Appropriate policies as part of a national or regional cancer control plan and political commitment by national or regional governments to vertical investments in infrastructure and human resources are critical to develop and sustain basic cancer management services in LMIC. It is impossible to develop services without vertical financial investments through a dedicated budget line on an ongoing basis and this is glaringly lacking in those countries with no or meager cancer treatment services. A model which has been instrumental in developing cancer management services and human resources in many countries such as India, China, Thailand, Egypt, Algeria, Morocco, Singapore, South Korea, Brazil, Peru, Colombia, Mexico and Cuba among others has been the organization of comprehensive cancer centers in capital cities and in regions such as provincial capitals and districts. Countries like Thailand and South Korea and states in India such as Kerala, Tamil Nadu and Maharashtra among others have considerably augmented equitable access to cancer services at the country level by developing several regional cancer centers. This model has contributed to developing and extending cancer services and later directing important investments in primary prevention and early detection efforts. Planned development of cancer centers in LMIC with no or limited cancer management will go a long way in seeing these services established in a time-bound fashion. Commercial influences and aggressive marketing practices by pharmaceutical industry may be an impediment for the development of rational, affordable, equitably accessible and cost-effective cancer management services in poor-resource settings. This is a paradoxical situation leading to the rapid depletion of the limited resources.

A recent additional development in developing and augmenting cancer services is the Programme of Action for Cancer Therapy (PACT) created by the International Atomic
Energy Agency in collaboration with WHO and other agencies in response to the lack of cancer care and control services in many LMIC [56]. PACT aims to raise awareness, to assess needs, to develop realistic cancer control plans with national government commitments as demonstration projects, and to raise funds for cancer control. In fact, this is the first real action-based international attempt to help countries to develop services. Model demonstration programs are being developed in six countries (Albania, Tanzania, Yemen, Sri Lanka, Vietnam and Nicaragua) under the PACT project.

An evaluation of treatment interventions that are specifically tailored to the needs and conditions of LMIC would be useful, including controlled trials wherever possible. Formulation of evidence-based yet locally feasible treatment protocols for major cancers and evaluation of their adherence and effectiveness is a critical step to ensure cost-effective and affordable treatment services and for harmonizing uniform treatment practices in LMIC. Such protocols have been developed in countries such as Malaysia, certain regions in India and Brazil, Morocco, Oman, Colombia and Peru. Treatment costs can be considerably escalated, especially with the availability of advanced and sophisticated treatment techniques in each cancer treatment modality and expensive new molecules in cancer chemotherapy and because of the aggressive marketing pursued by the pharmaceutical industry and unwarranted commercial influences. The utmost care needs to be taken to keep the costs affordable while delivering diagnostic and treatment services in LMIC.

There is a lack of studies providing information about the current structure and organization of primary, secondary and tertiary care in specific LMIC, with the ultimate aim of modeling and implementing cancer diagnosis and treatment delivery systems that are either integrated with or supplement existing care delivery systems. Studies of this type are needed to ensure that there is a balance, for example, between resources devoted to early detection, diagnosis and treatment. The disappointing performance of cervical cancer screening programs in many LMIC has been due in part to the lack of effective diagnostic follow-up and treatment following screening.

**conclusions**

Cancer research is growing in many LMIC, and extensive partnership programs have been established by international organizations such as International Agency for Research on Cancer [57] and the International Network for Cancer Treatment and Research [58], as well as major national cancer centers and agencies, to foster collaborations between HIC and LMIC. Modern centers have been established in several LMIC, where research is conducted in cutting-edge fields such as molecular biology and genetics. One prominent example is the Advanced Centre for Treatment, Research and Education in Cancer, which has been recently established in New Mumbai by the Tata Memorial Centre [59]. This is certainly a positive trend and would contribute to the general economic and technological development of these countries, in addition to contributing to the global effort of understanding the causes and the mechanisms of cancer and developing effective approaches to combat it.

Despite these positive changes, active research on different aspects of cancer control remains marginal in most LMIC. Most of the research literature on cancer control in LMIC is dominated by descriptive epidemiology, on the basis of registries and case–control studies assessing the risk factors. There are relatively few studies addressing the efficacy of early detection approaches and of treatment protocols, the country-specific cost-effectiveness of various interventions and the clinical utility and cost-effectiveness of innovative health care and communication technologies such as computerized image reading or telemedicine facilitating long-distance consultations. For remote localities or small low-income countries, training and employing local expertise or advanced equipment for every aspect of cancer control may not be necessary if advanced communication and information technology could be used to facilitate virtual collaboration. Cancer control interventions that

<table>
<thead>
<tr>
<th>Area of research</th>
<th>Examples</th>
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<tr>
<td>Cancer registration</td>
<td>Establishment of regional cancer registries of high quality in low-income regions, in particular in sub-Saharan Africa.</td>
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<tr>
<td>Tobacco control</td>
<td>MPower program of the World Health Organization [60], a comprehensive strategy targeted toward LMIC, including six policy measures that have been proven to be effective in the fight against tobacco: (i) monitor tobacco use and prevention policies; (ii) protect people from tobacco smoke; (iii) offer help to quit tobacco use; (iv) warn about the dangers of tobacco; (v) enforce bans on tobacco advertising, promotion and sponsorship and (vi) raise taxes on tobacco; research on effectiveness of these strategies in LMIC.</td>
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<tr>
<td>Vaccination</td>
<td>Research on novel vaccines (e.g. against H. pylori) and on strategies for the implementation of vaccination campaigns, in partnership with the pharmaceutical industry to overcome the current financial constraints.</td>
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<tr>
<td>Prevention of overweight and obesity</td>
<td>Promotion of healthy nutrition and adequate physical activity, in particular targeted to the youth; research on the determinants of overweight in LMIC and of strategies to prevent it.</td>
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<tr>
<td>Screening</td>
<td>Development of novel screening methods for cancers with high incidence in LMIC (e.g. esophageal and liver cancer).</td>
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<tr>
<td>Downstaging</td>
<td>Research on determinants of downstaging of cancer diagnosis, in particular for oral, breast and cervical cancer.</td>
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<tr>
<td>Treatment</td>
<td>Establishment of clinical research studies in LMIC.</td>
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<tr>
<td>Capacity building</td>
<td>Concerted efforts on capacity building [61], focused on the challenges, difficulties and opportunities encountered in LMIC; efforts to minimize loss of trained personnel.</td>
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</table>

LMIC, low- and medium-income countries.
appear to be cost-effective in HIC may not be in LMIC, even with the lower cost of providing health services taken into account. Already completed research in cancer control in different low-resource settings, particularly on cancer patterns, patterns of care, survival outcomes, accuracy and effectiveness of early detection approaches for cervix, breast and oral cancers and limited clinical research on effective treatments of cancers such as childhood lymphomas and leukemia, head and neck and cervical cancers, have contributed enormously to the current understanding of the effectiveness, available resources and cost of many cancer control interventions, however incomplete and uncertain it is, as well as for formulating and refining cancer control interventions in LMIC. LMIC should heavily rely on pilot research programs in focused geographical areas or specific facilities with known and well-characterized target populations while introducing new interventions and before scaling up to regional or national programs for further improvements in cancer control. A well-defined country-specific research agenda will provide valuable information on the feasibility, efficacy and cost-effectiveness of various cancer control interventions in these countries. Several priority areas can be identified for future research on cancer control in LMIC; these are listed in Table 2.

The burden of cancer in LMIC is expected to increase in the next decades, largely because of the ageing of the population. While this trend is—at least in part—unavoidable, and will represent a formidable burden on the health systems of these countries, application of current knowledge and results of research in the key areas outlined above would contribute to limit its impact. Cancer research in LMIC, and specifically cancer prevention research, should be brought high in the medical and public health agenda both at the national and international level.

references


