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Implementation Science in Cancer Prevention and Control: A framework for research and programs in low and middle-income countries

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Abstract: Implementation Science is a set of tools, principles and methodologies that can be used to bring scientific evidence into action, improve health care quality and delivery and improve public health. As the burden of cancer increases in low- and middle-income countries, it is important to plan cancer control programs that are both evidence-based and delivered in ways that are feasible, cost-effective, contextually appropriate and sustainable. This review presents a framework for using implementation science for cancer control planning and implementation and discusses potential areas of focus for research and programs in low and middle-income countries interested in integrating research into practice and policy.

Keywords: Cancer, global health, implementation, dissemination, training, research methods

Note: The opinions expressed are those of the authors and do not necessarily reflect those of the National Cancer Institute or any other institution.

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Introduction

Cancer is a leading cause of death around the world. Recent world cancer statistics show an increase in the number of new cases of cancer and deaths worldwide from 12.7 million cases and 7.6 million deaths due to cancer in 2008 to 14.1 million new cases of cancer and 8.2 million deaths in 2012. More than half of these new cases and 64.9% of these deaths due to cancer occurred in low- and middle-income countries(1) (LMICs). While population growth and aging contribute to this increase, the burden of cancer in LMICs is also being driven by trends of known and well-studied lifestyle-related risk factors, including tobacco use, harmful use of alcohol, poor diet, and physical inactivity as well as high prevalence rates of infection with cancer-causing microorganisms such as the Human Papilloma Virus (HPV), the cause of cervical cancer and other cancers. Overall, 26% of all cancers in LMICs are associated with infectious agents(2) which are amenable to reduction by vaccination, improved hygiene, and a more favorable risk profile(3). Thus, cancer prevention in LMICs brings multiple challenges: rising numbers of cases, fewer prevention and treatment resources, inadequate treatment infrastructure, lack of access to palliative care and limited availability of care delivery personnel and infrastructure.

It is important to note that there is significant variability between and within world regions in the burden of cancer and the experience of living with cancer. Figure 1 shows data based on the Global Burden of Disease estimates(4). In the two decades ending in 2010, the percentage of deaths due to cancers increased at a higher rate in LMICs as compared to high-income regions of the world. Further, the rate of increase in cancer deaths within many LMICs was also high from 1990 to 2010 – e.g., 36% in China, 42% in India and near doubling in Ethiopia. Even acknowledging the variability in data collection for cancer, the evidence does support the position of cancer advocates that cancer is indeed a disease of the poor and middle-income regions and that action is needed to address this burden(5).

A key challenge to reducing the rising burden of cancer in LMICs comes from barriers to implementing even basic cancer prevention and care practices. Many factors outside the control of individuals contribute to the gap between knowledge and practice. Implementation of effective, evidence-based interventions could reduce the burden of cancers globally. Yet, such interventions are under-used. Many promising health interventions have had only limited impact on the burden of disease in LMICs because of implementation problems that have yet to be identified, researched, and addressed(6). Implementation science begins with evidence and develops strategies to bring these evidence-based interventions to public health settings, to improve access to, and use of, these interventions in populations(6).

We describe the challenges of implementing cancer control programs in LMICs, define implementation science, present a framework to illustrate how it can be applied in the context of global cancer research and practice.

Challenges to Implementing Cancer Control in Low- and Middle-Income Countries

Cancer control involves research and programs in the behavioral, social, and population sciences aimed at developing or improving interventions that independently or in combination with biomedical approaches, reduce cancer risk, incidence, morbidity and mortality, and improve quality of life (7). Cancer prevention and early detection are the key focus areas for cancer control efforts. We acknowledge the importance of cancer diagnosis and treatment in LMICs but do not focus on these areas in this paper.

It should be noted that there is wide variation in implementing cancer control programs within and between LMICs; and generalizations across countries would be inappropriate. Countries in Africa (such as Botswana, Zambia, Rwanda and Kenya) and in Latin America (such as Argentina, Colombia, Chile and Guatemala) have established national cancer control plans or national programs that focus on a particular cancer such as cervical cancer(8, 9). Mexico's Seguro Popular program has helped

improve access to HPV immunization, breast cancer detection and treatment, and has reduced the costs to individual for prevention and treatment of cancer(10). Other countries such as India, have highly advanced treatment centers for cancer and some states in India have very comprehensive cancer screening programs(11). Still others lack basic cancer prevention programs and cancer detection is available only in limited geographical areas(12) and often just to those who are relatively well off financially. Cancer disparities are often stark; rural residents as compared to their urban counterparts as well as those with lower socio-economic status in LMICs are at higher risk for cancer and exposure to cancer risk factors such as tobacco and alcohol use(13). Conversely, those with higher socio-economic status experience lower cancer mortality rates(13, 14). This plurality in the cancer experience presents challenges and opportunities for both aspects of cancer control that we discuss: cancer prevention and cancer detection.

Cancer Prevention. Cancer Prevention involves taking action to decrease the chance of getting cancer including reduction of exposure to risk factors and increasing exposures to protective factors. At the individual and population levels, behavior modification efforts can be implemented to create awareness about cancer and motivate risk reducing and preventive behaviors. We acknowledge that for individuals with a higher risk of cancer, options such as preventive surgery (mastectomy or removal of breast, fallopian tubes and ovaries) as well as chemotherapy are also being offered. However, in this paper, we focus on the behavioral and population-based approaches to prevent cancer.

Table 1 outlines five risk factors for cancer at the individual and systems levels in LMICs. Risk factors for cancer at the individual level are those that are associated with behaviors and lifestyle and hence amenable to modification. The five factors that we discuss are tobacco use, exposure to infectious agents associated with cancer, harmful use of alcohol, unhealthy diet and lack of physical activity, and exposure to carcinogens in the environment. Systems level factors are those that pose a barrier to, or facilitate the adoption of behaviors that can reduce and/or eliminate exposure to cancer risk.

We discuss five systems level factors in this paper: access to cancer control information, availability and access to cancer prevention, screening and treatment services; cancer disparities and inequities within a given LMIC; social and cultural factors; and cancer control policies. Ideally, factors at both of these levels should operate together to favor risk reduction, but in many LMICs they do not. For instance, an individual may be motivated to stop smoking but poor or no access to tobacco cessation with the health system poses a barrier to cessation. Similarly, knowledge of early detection is important and useful when there is easy access to cancer screening programs as well as effective follow-through to treatment.

Among the five preventable risk factors, tobacco use remains the single largest preventable cause of cancer in LMICs. Nearly 80% of all smokers live in LMICs (15). In countries such as Indonesia and China, the problem is acute. According to recent global tobacco surveys, 67% of Indonesian men smoke(16). There are 350 million smokers and 740 million passive smokers in China (population 1.35 billion)(17). In South Asia, use of smokeless tobacco (SLT) products is very common; as is oral cancer associated with SLT(18). Indeed, in India, those who use SLT outnumber exclusive smokers by over two-fold(19), and oral cancer associated with tobacco use is a leading cause of cancer among men(20). The global campaign against tobacco, including the provisions set forth by the Framework Convention on Tobacco Control (FCTC), have led to multi-ranged initiatives in many LMICs in tobacco prevention education and taxation(21). However, the implementation of these policies and enforcement of regulation around them is not strong and tobacco control remains a significant cancer prevention challenge. Implementation science research can help identify policy and enforcement gaps and factors influencing them, and recommend guidelines for widespread adoption of effective programs.

Infectious agents, which comprise a second set of remediable risk factors for cancer in LMICs, are preventable; yet over 80% of the cases and the deaths due to cervical cancer occur in LMICs(22). While there are effective vaccines against HPV and HBV (Hepatitis B Virus, associated with liver cancer) infections, issues of access to and cost of these vaccines remain (23) despite studies

demonstrating that vaccine delivery strategies can have a wide reach when tailored to the cultural context (24). Other issues include poor awareness of vaccines available to prevent cancer. In a study in sub-Saharan Africa, authors showed that awareness of the HPV vaccination was very low; but community members when made aware, were willing to participate in a vaccination program (25).

National HPV vaccination programs have been launched in some countries such as Australia and Rwanda(26, 27). In these countries, policy makers have made HPV vaccination program an important investment in cervical cancer control and have launched national programs at their cost (Australia); or used a combination of vaccine donation and negotiations for low price with vaccine manufacturer in order to implement and sustain the program (Rwanda). The role of agencies such as the Global Alliance for Vaccines and Immunizations (GAVI) as well the Pink Ribbon Red Ribbon initiative(28) has been valuable in providing funding, policy guidance and technical assistance, as well as assistance in procurement of vaccines to launch these national programs.

The third cancer risk factor is the harmful use of alcohol which is rising in many LMICs (29). Globally, 6.2% of all male deaths and around 1% of female deaths are attributed to alcohol. While the per capita consumption of alcohol in many LMICs remains low compared to Europe and North America, alcohol risk behaviors such as heavy episodic drinking, and risky patterns of consumption such as drinking to intoxication are increasing in countries in the Russian Federation, Mexico, Pakistan and southern Africa (30). Alcohol also operates in synergy with tobacco to increase risk of esophageal cancers and oral and laryngeal cancers (31, 32). Addressing harmful use of alcohol will benefit not only cancer but reduce other adverse health outcomes. However, in many instances, alcohol, as well as tobacco sales, outlets are managed by the state, rendering control of these substances a difficult ground to traverse(33).

The fourth risk factor comprises behaviors related to diet and physical activity. While obesity has not yet reached epidemic proportions in LMICs as it has in many high-income countries, it is increasing. A

recent study notes that in the three decades starting in 1980 obesity rates have increased in children and adolescents in LMICs – 8.1% to 12.9% in boys and 8.4% to 13.4% in girls(34). There is a wide diversity in rates of obesity between countries surveyed as well as between genders in the countries surveyed. The demographic and nutrition transitions taking place in many low income countries are resulting in changes in lifestyle, and diet that may be contributing to increasing obesity(35). The roles of these diet, physical activity and obesity factors in cancer risk in LMICs need further study(36).

The fifth risk factor for cancer is exposure to environmental carcinogens, including indoor and outdoor air pollution, both serious problems in some LMICs. Measures taken in high-income countries including controlling outdoor air pollution, banning asbestos and imposition of controls on other toxic agents and chemicals have been successful in limiting these exposures. Available figures, acknowledging variability between countries in exposure assessment, estimate that between 7% and 19% of cancers globally are attributable to environmental carcinogens(37). For ambient air pollution alone, the Global Burden of Disease 2010 project estimate for lung cancer is 223,000 attributable deaths(38). While these estimates do not capture second hand smoke, the results from the Global Adult Tobacco Survey (GATS) suggest that SHS poses a significant environmental risk for cancer. Reported exposure to SHS at home in this survey ranged from 17.3% in Mexico to 73.1% in Vietnam; and was high in various environments such as work places, restaurants, health care facilities and public transportation(39). Effective regulatory strategies, educating communities about these exposures, and working with corporations to realize prevention and control of these environmental and occupational exposures are some recommendations suggested by experts. However, individuals in LMICs may be limited in the actions they can take as the changes needed to reduce exposure need to be made at the systems level through government action.

Systems level changes, when made, can influence exposure to all risk factors. As shown in Table 1, there are five factors at this level. First, access to information about risks of exposure is particularly

limited in LMICs. Availability and wide dissemination of cancer prevention information might increase awareness and facilitate early detection, promote civil society leadership, and raise policy maker attention to these risk factors. Second, availability and access to cancer prevention and screening programs remains a challenge because of a combination of lack of trained personnel and infrastructure, costs and systems to track screened patients to ensure completion of treatment. The third systems level factor is the role of cancer disparities within LMICs. Care for cancer remains largely concentrated in large urban centers, and typically members of high socio-economic classes have higher access to prevention, screening and care. Fourth, the role of social and cultural factors that affect exposure to cancer risk has not gained much attention in cancer control in LMICs. Stigma is high and poses a burden on care seeking and social support. This disproportionately affects women who already experience gender-based discrimination in several LMICs. (40). Finally, the role of policy level changes is critical. Cancer control policies can facilitate access and equity to much needed services. Particularly, in order to limit environmental exposures, change in occupational health policies, regulations to limit emission from diesel-fuelled vehicles, and policies to facilitate clean air as well as clean cooking sources are necessary to realize cancer control in the long run(41)

Cancer Detection. Indeed, systems level changes are necessary not only to realize cancer prevention but also cancer detection goals. Cancer detection refers to services and programs that offer screening for cancers allowing for the detection of cancer at an early stage of the disease so that it can be managed effectively. It is estimated that only 5% of women in LMICs as compared to 75% of women in high income countries have had cancer screening at any given time(42). Cervical cancer screening in LMICs overall is estimated to cover only 19% of those women needing this service, as compared to 63% in high income countries; coverage ranging from 1% in Bangladesh to 67% in Brazil(43). Cervical pre-cancerous lesions go undetected resulting in very late stage presentation for treatment. The Pap Smear test to detect cervical cancer, standard in the high-income countries is not widely available, in LMICs. When it is, the human resources for cytology, pathology and diagnostic systems needed to

complete a timely diagnosis are often lacking. As the entire spectrum of services from screening, diagnosis and linkage to treatment is unavailable in many LMICs, researchers and practitioners have explored alternative approaches and to screening. Visual inspection of the cervix with acetic acid (VIA) or Lugol's Iodine (VILI) followed by treatment referral; VIA followed by immediate treatment (called cervical cancer see-and-treat); and self-collection of vaginal samples followed by HPV DNA analysis are some approaches being evaluated in LMICs(44-46) which might be implemented at low cost. VIA followed by referral and treatment and has been shown to reduce cervical cancer incidence by 25% and mortality by 30% in community-based randomized trials(44, 47).

Burden of breast cancer in LMICs is increasing, marked by a younger age of onset and more advanced presentation on diagnosis(48). Early detection methods such as mammography may not be practical given costs, and international expert groups such as the Breast Health Global Initiative(BHGI) advocate resource-specific, as well as age-specific screening guidelines(49). Breast health education programs are strongly advocated to inform communities in LMICs about risk factors and early detection(50). For cervical cancer and breast cancer, the use of trained community health workers in countries such as Bangladesh, Botswana and Sudan been has shown to increase referral rates and to build awareness about the importance of early detection(51-53).

Oral cancer screening trials that have targeted high-risk users of tobacco for screening and used trained community health workers for detection have also demonstrated efficacy in LMICs(47). There are also reports of use of screening technologies to visualize the mouth, detect lesions and link to treatment that suggest practical application in LMICs(54). The Institute of Medicine estimates that 80% of cancers in LMICs may be incurable when they are detected(55). In order to promote early detection, approaches that utilize community resources for early detection and link them effectively to diagnostic and treatment centers may be important to consider.

The systems level factors discussed in Table 1 also influence an individual's ability to seek screening for cancer. Information about the types of cancers, which are amenable to early detection, and the availability of local resources where an individual can go to get screened is either not offered or is not widely disseminated. Typically, screening facilities are located in major hospitals in urban areas or in clinics in large towns. Patients travel to these cities at their own cost and often there is poor linkage between centers and community clinics to manage treatment and care. The poor and vulnerable are most affected and this inequity in access to early detection of cancer needs to be addressed. The use of validated screening methods is constrained by cost, limited availability of trained personnel, other acute diseases challenging health care providers, as well as lack of systematic planning and evaluation of available services and future needs (42). Finally, the lack of policy and national guidelines for cancer screening or the poor implementation of the ones that exist is another systems level limiting factor for cancer control.

Cancer Control Costs in LMICs. In many LMICs, it is important to recognize that while cancer burden is increasing, cancer is just one among several health challenges that policy makers face in the context of limited financial resources. However, not all cancer control approaches are a drain on financial resources. Relative to other cancer control areas, prevention education is not resource intensive, can utilize already available human and community resources, but is not widely available in many LMICs. It is arguably the most reachable 'low hanging fruit' for cancer control in LMICs. Vaccination is another intervention that can be implemented with a potential of high public health impact. Costs of introducing the HPV vaccine, recurrent costs of administration, and fully immunizing a girl with three doses ranged from US \$1.49 to \$18.94 in an analysis of data from five LMICs (India, Peru, Uganda, Tanzania and Vietnam)(56). Recently, the Global Alliance of Vaccines and Immunization (GAVI), a global initiative to facilitate access to vaccinations announced plans to make the HPV vaccine available at a cost of \$4.50 per dose(57). The comparable cost in the United States is estimated at \$130 to \$140(58). While not all LMICs are eligible for the GAVI price, the World Health Organization is working with governments to

discuss pricing and procurement(57). Public health benefit can also be gained from the implementation and dissemination of cancer screening programs such as VIA-based screening followed by treatment. This approach has been piloted and is now being widely disseminated and adopted by countries in Africa(59). Indeed, modeling studies based on data from some LMICs note that the most cost-effective cervical cancer screening methods are those that effectively link screened women to treatment and suggest that a one- or two-visit VIA or HPV DNA screening test starting at 35 years of age might reduce cervical cancer lifetime risk by 25 to 36%(60). There is need for more evidence on breast cancer control in LMICs and what is cost-effective in some countries may not be so in others(61). Modeling studies also suggest that breast health education through mass media awareness, for example, may be more cost-effective compared to mammography, but also note that there is poor data on cost of these interventions in LMICs(61, 62)

Implementation Science: Definition and Conceptual Framework

Implementation Science could be a critical tool in addressing these gaps. It involves methods for integrating scientific evidence into practice and policy to benefit public health (63) (64) (65) (6). Research in implementation science investigates and addresses factors (individual and health systems level) that pose barriers to achieving public health benefit and explores alternative and innovative approaches to health care delivery and practice (66). Frameworks to guide this research consider these different levels of influence on cancer prevention and control outcomes. Figure 2 draws from one such framework, the Evidence Integration Triangle(67), and uses it as a model for understanding cancer control research in the LMIC context. This framework posits that implementation science research is useful in planning evidence-based cancer control programs, providing guidance in implementation of these programs, and in conducting evaluations of programs to inform national policies and considers the community, health systems and policy level factors in the process.

As suggested in Figure 2, implementation science research comes into play after evidence is gathered. Evidence for cancer prevention and control is gathered from the full spectrum of cancer research: basic science, etiological research, randomized trials of screening and therapy, studies of determinants of outcomes, naturalistic experiments and observational studies as well as controlled assessments of effectiveness. The gulf between research and actual care is illustrated by the contrast between efficacy that is achieved in a clinical trial, e.g., of a therapeutic agent or device, and the effectiveness achieved in the real world. Efficacy is typically assessed under the controlled circumstances of the randomized controlled trial(68). In the case of observational study designs, evidence is gathered by instituting rigorous monitoring and evaluation processes with careful attention to selection of controls and adjustments for potential confounding factors. In both of these study designs, protocols are implemented and followed, quality is monitored and assured, and participants often are selected to be homogeneous, highly motivated to participate and to be adherent. The results of rigorously analyzed trial data typically form the basis for recommendations based on the paradigm of evidence-based medicine.

However, when effective cancer control interventions are brought into real-world clinical and public health settings, the basis for analysis and evaluation moves to large, heterogeneous populations and settings(69). In these real life settings, as shown in Figure 2, there are three levels of influence on cancer control programs - the community, the health system and the policy milieu. We discuss how implementation science research considers these levels in planning implementing and evaluating cancer control programs.

Planning Cancer Control Programs. When used to plan cancer control programs, implementation science research conducts assessment of existing programs and policies, and of key institutions and stakeholders who can influence implementation of evidence. In planning cancer control programs, the role of existing resources in the community can be better understood. Traditional healers, practitioners of alternate systems of medicine and community-based health volunteers and workers might be the first

point of contact for a health consult in an LMIC setting particularly in rural areas. Understanding their strengths and limitations, and exploring how to integrate their efforts into cancer control is important. Research is also needed to understand practical functions of a health system. Health systems, refer to the organizational infrastructure, health care providers and health information systems that deliver care, gather data and provide operational evidence of program progress in the public health sector(70). Assessments of available health care personnel and infrastructure, their expertise and training needs is also essential in order to plan a program that can be practically implemented. Other data that needs to be collected for planning include identifying units of health care delivery – clinics, hospitals, public vs. private sector units- and linkages that exist or that can be created between them. Finally, as we seek to plan evidence-based programs, training policy makers as well as program implementers and bureaucrats in the health and financial sectors about how to understand and use evidence from research is a large unmet need. This can help guide the allocation of scarce resources in a strategic manner.

Guiding Program Implementation. Implementation Science research is needed to develop approaches to implement evidence-based interventions in ways that consider the ground realities of the LMIC setting. This involves participation from community members and leaders and seeks input from various disciplines in public health practice and research. This type of research also identifies barriers and facilitators at the community level that need to be considered to implement a program. These include data collection on individual, social as well as structural level influences (influences beyond individual control such as location of residence, availability of transportation and health care). These structural influences are part of the social determinants of health which WHO recommends receive consideration in implementing programs(71). Research on these factors can help highlight knowledge deficits, understand care-seeking behaviors and barriers, and identify strategies for care delivery and improvements of care quality.

Seeking feedback from providers and patients on service delivery including patient flow, patient navigation, record keeping and follow-up are some examples of areas of inquiry. Here, the role of task shifting is noteworthy. Task shifting refers to a practice in health care delivery where non-traditional providers are trained to offer a service that was hitherto being offered by a more traditional provider such as a physician or a nurse(72). This type of reorganization of the work force utilizes available resources in a community and is being used in LMICs in cancer research to offer education, screening and provide linkage to treatment. Finally, identifying monitoring systems at all levels of the program is key to informing program implementation. This includes developing or tailoring data collection instruments and systems to the program and the community it serves.

Conducting Program Evaluation to Inform Policy. Finally, implementation science can help evaluate ongoing programs. This kind of evaluation is best done longitudinally so that indicators of progress and best practices can be documented. The results can provide guidance to policy makers and program planners about effective components that can be widely disseminated for broader public health outreach. For instance, following the Framework Convention for Tobacco Control – the first international treaty to respond to the globalization of the tobacco epidemic- makes several recommendations and offers guidelines to control and prevent tobacco. These include guidelines for reducing tobacco demand, taxation and pricing of tobacco products, dealing with transnational tobacco companies as well as prevention education(73) Many countries have become signatories to this treaty and developed policies and programs for tobacco control based on these recommendations (73). However, in practice these are not being effectively implemented or enforced in all countries(74). For instance, smokeless tobacco use (SLT) is widely prevalent in India, particularly among women. Implementation science can help understand patterns of use of SLT among various segments of the population and lead to recommendations for community education programs. It can also assess the types of SLT products available, compile sales and consumption data and provide data on the scale of the problem.

In programs to prevent HIV transmission from parent to children, supported by the United States President's Emergency Program for AIDS Relief (PEPFAR), implementation science research has helped develop guidelines to improve delivery of these programs. Feedback about health care quality, patient follow-up methods, needs for physician training as well as supply chain and HIV diagnostic concerns were among them (75-77). Based on these and similar findings, the PEPFAR has adopted an implementation science framework to enhance the effectiveness of its programs in LMICs(78). PEPFAR envisions that such a framework will hasten adoption of evidence-based interventions, promote operations research that can improve delivery and design of HIV prevention programs and increase the scale and outreach of program delivery.

Implementation Science Research for Global Cancer Prevention and Control

How can the framework in Figure 2 guide cancer research in LMICs? We offer two focus areas for research in implementation science - community-based research and health systems research- that can help plan, guide implementation, and inform evaluation of cancer control programs. Table 2 outlines possible implementation science research questions.

Community Based Research in Cancer Control Implementation. Primary prevention programs can bring cancer into the public discourse and frame it as a preventable and manageable condition while compiling and providing information on community-based resources for care seeking and management. Research to develop prevention education programs can understand misperceptions and knowledge gaps, that can then inform program content for various audiences (youth, married men and women, health care providers. Here, it is important to address the role of stigma in seeking cancer screening as well as treatment, and understand the role community-based opinion leaders in education efforts.

Research is also needed to understand approaches to plan and implement vaccination programs against infectious agents causing cancer. Particularly for HPV vaccination, understanding the social and cultural factors influencing participation of young girls and boys is critical. Implementation research

can also investigate ways that utilize mobile technologies to help in cancer prevention and detection. Several mobile health (mhealth) initiatives that utilize cell phone and communications technology have demonstrated the reach and relevance of communicating health information through this medium in high income countries(79). In LMICs, telecommunications-based approaches have been used for cancer patient navigation and follow-up, video consultations with experts in urban settings, as well as digital record reviews. (53, 80) Given the high rate of adoption of telecommunications technology in LMICs, mhealth and may offer a practical approach to cancer control.

In cancer detection, community-based research can help identify barriers and facilitators to participation in screening programs; and identify key individuals and institutions who can play a role in mobilizing efforts to expanding such programs such as school teachers and health workers. In many instances, traditional healers and other practitioners are the first points of contacts for patients with cancer(81). Understanding ways to engage these individuals, utilize their credibility within the community for cancer prevention and screening is important. Further, research is needed to understand how cancer services can be introduced as part of ongoing public health programs. The effort of the Pink Ribbon Red Ribbon program of integrating women's cancers into ongoing HIV prevention and treatment services is a case in point(28, 82). As cancer is one among the many public health challenges facing LMICs, research to understand how existing disease control infrastructure and expertise can be utilized for cancer control will help optimize scarce resources. Another focus area in low resource settings is research to develop low cost technologies to detect cancer. The recent announcement from the National Cancer Institute (NCI) on low cost technologies for global health is an example of emphasis placed on developing appropriate technologies for cancer screening that are relevant, feasible and sustainable in LMICs and which can help foster cross-country partnerships in cancer control(83). NCI program announcements in dissemination research as well as the US Centers for Disease Control and Prevention's (CDC) efforts in training and capacity building for cancer control are also noteworthy(84, 85).

Given the high rates of individuals in LMICs who seek care only at very late stages, it is important to understand the access, availability and possibilities of expansion of palliative care programs. A recent study called palliative care a 'painful inequity' and called for research to understand best ways to roll out palliative care programs(86). Community-based approaches to palliative care serve to educate communities as well as empower survivors and are integral to cancer control efforts.

Health systems research can highlight gaps and strengths in the organizational apparatus as well as human resources that deliver cancer prevention and detection services. Understanding gaps in medical curricula, needs for refresher training, roles and responsibilities of nurses, and other health center staff, in addition to physicians are important to explore, as well as feasible options for addressing these gaps. Studies are also needed to understand how lessons from small projects can be applied to larger settings. Many projects draw lessons on implementing evidence but do not move beyond the communities in the study. Evaluation studies of ongoing projects can highlight effective components and delivery strategies that can inform wide scale dissemination. Research is needed to test linkages between screening and treatment centers where they exist. Loss to follow-up after screening is a challenge in LMICs and understanding practical ways for patient follow-up and navigation is important.

Conclusion. As the global burden of cancer and the prevalence of its risk factors increase, approaches to reducing this burden must involve a process of matching knowledge and scientific advances with need for intervention. The following are some broad summary recommendations for cancer control:

- A focus on prevention education is both necessary and an important first step to raising public awareness about cancer. Cancer remains to be viewed as a death sentence in many LMICs and there is stigma associated with cancer that disallows interaction with health care providers. This focus on prevention has been adopted with many other disease outcomes such as HIV/AIDS prevention early in the process of disease control, and has resulted in positive effects

on care seeking and disease management. It has also facilitated the development of a strong advocacy network, and involvement of policy makers. It is time for cancer control efforts to employ implementation science research and plan programs that offer this needed service.

- HPV vaccination is being successfully implemented with international assistance in some countries. This is an important investment in the health of young girls and boys in LMICs.
- As we have discussed, low-cost approaches for cancer control are available. Though not perfect, these technologies can potentially help reduce high and unnecessary burden of these preventable cancers in LMICs.
- Strengthening the linkage between screening and treatment is imperative to cancer control and amenable to innovative approaches in implementation research.
- Research to understand shifting of tasks among the existing health care workforce toward cancer control can guide program development.
- Gaining support from the international community for efforts in LMICs is critical. This can be done through partnerships, skills building workshops, as well as joint program development. The National Institutes of Health (NIH) has developed programs with middle-income countries such as China and India to develop joint funding programs, thus leveraging resources where they are available. Such models can enhance collaborative research and also address cancer priorities both in LMICs and bring lessons from these studies to underserved areas of high income countries(87, 88).

The consideration of multiple levels, as well as ability to develop pragmatic approaches suggests that implementation science has much to offer to cancer control practitioners and researchers working in LMICs. Programs based on evidence from research are urgently needed for cancer control.

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Table 1. Risk Factors for Cancer: Individual and Health Systems Level Considerations for Cancer Control in Low and Middle Income Countries.

Risk Factor	Brief Notes on Risk Factors and Systems Level Considerations
Individual Level 1.Tobacco Use 2.Infectious Agents 3.Harmful Use of Alcohol 4.Lack of Physical Activity and Unhealthy Diet 5.Environmental Exposures	<p>80% of all smokers in the world live in LMICs. Smokeless tobacco use is widely prevalent and on the increase in South Asia.</p> <p>Three agents contribute to the burden of cancer in LMICs: Human Papilloma Virus, causal agent in cervical cancer; Hepatitis B and C viruses associated with liver cancer; <i>Helicobacter pylori</i> , a bacteria associated with stomach cancer.</p> <p>According to WHO, 5-year trends of alcohol consumption show an increase in Southeast Asia and Africa regions and reports of underage drinking show a 71% increase in alcohol use among 13-15 year olds.</p> <p>In the decade ending 2007, combined prevalence of obesity and overweight has grown by 0.4% per year. Among women from 42 countries participating in a study on nutrition, 19 percent of rural women and 37.2 percent of urban women were overweight or obese</p> <p>WHO estimates suggest that the proportion of global cancer attributable environmental carcinogens ranges from 7 to 19%</p>
Systems Level 1.Access to Cancer Control Information 2.Availability and Access to Cancer Prevention and Screening 3.Cancer Disparities and Inequities 4.Social/Cultural Factors 5.Cancer Control Policies	<p>Cancer Prevention Education programs at national and community levels are limited in many LMICs. This impedes timely care seeking</p> <p>Cancer screening modalities that work in high-income countries have been difficult to implement and sustain given the cost of screening, lack trained personnel to administer screening, conduct diagnostics and maintain equipment. Systems to track screened patients to ensure treatment completion are inefficient.</p> <p>In many LMICs, cancer services are available at a high cost in select centers in the private sector. Most patients, and particularly poor patients are typically diagnosed late and/or unable to afford treatment.</p> <p>High levels of stigma, Delayed care seeking due to stigma and other cultural factors</p> <p>Policy and national guidelines are either non-existent, or where present poorly enforced.</p>

Table 2. Implementation Science Research in Cancer Control: Possible Research Focus Areas

Type of Implementation Science Research	Possible Focus Areas for Research
Community-Based Research	<p>Developing appropriate prevention education interventions - content and delivery strategies in the community to inform about cancer risk and prevention, types of cancer and care seeking for cancer.</p> <p>Understanding the role of stigma in cancer prevention and screening</p> <p>Understanding practical strategies for delivering HPV and HBV vaccination. For HPV, considering the sociocultural implications of vaccinating young girls and boys in such a program</p> <p>Exploring role of technology in cancer prevention and early detection(e.g., use of mhealth technologies in cancer prevention)</p> <p>Understanding barriers and facilitators to participation in cancer screening programs</p> <p>Developing practical strategies to integrate cancer detection into ongoing disease control programs</p> <p>Developing Low-Cost and Sustainable Strategies for detection</p>
Health Systems Research	<p>Developing and testing content of training programs for frontline health staff (doctors, nurses and other health workers) in cancer screening. Understanding novel task shifting options in cancer screening</p> <p>Operations Research to understand organizational limitations and facilitators to expand program outreach (dissemination)</p> <p>Evaluating systems to understand what needs for improvement including development of screening to treatment follow-up systems, systems for patient navigation</p>

Figure 1. Trends in Percent of Cancer Deaths in World Regions from 1990 to 2010: The Diversity of the Cancer Experience

**Figure 2. Getting from Scientific Evidence to Public Health Practice: Role of Implementation
Science Research**

Figure 1

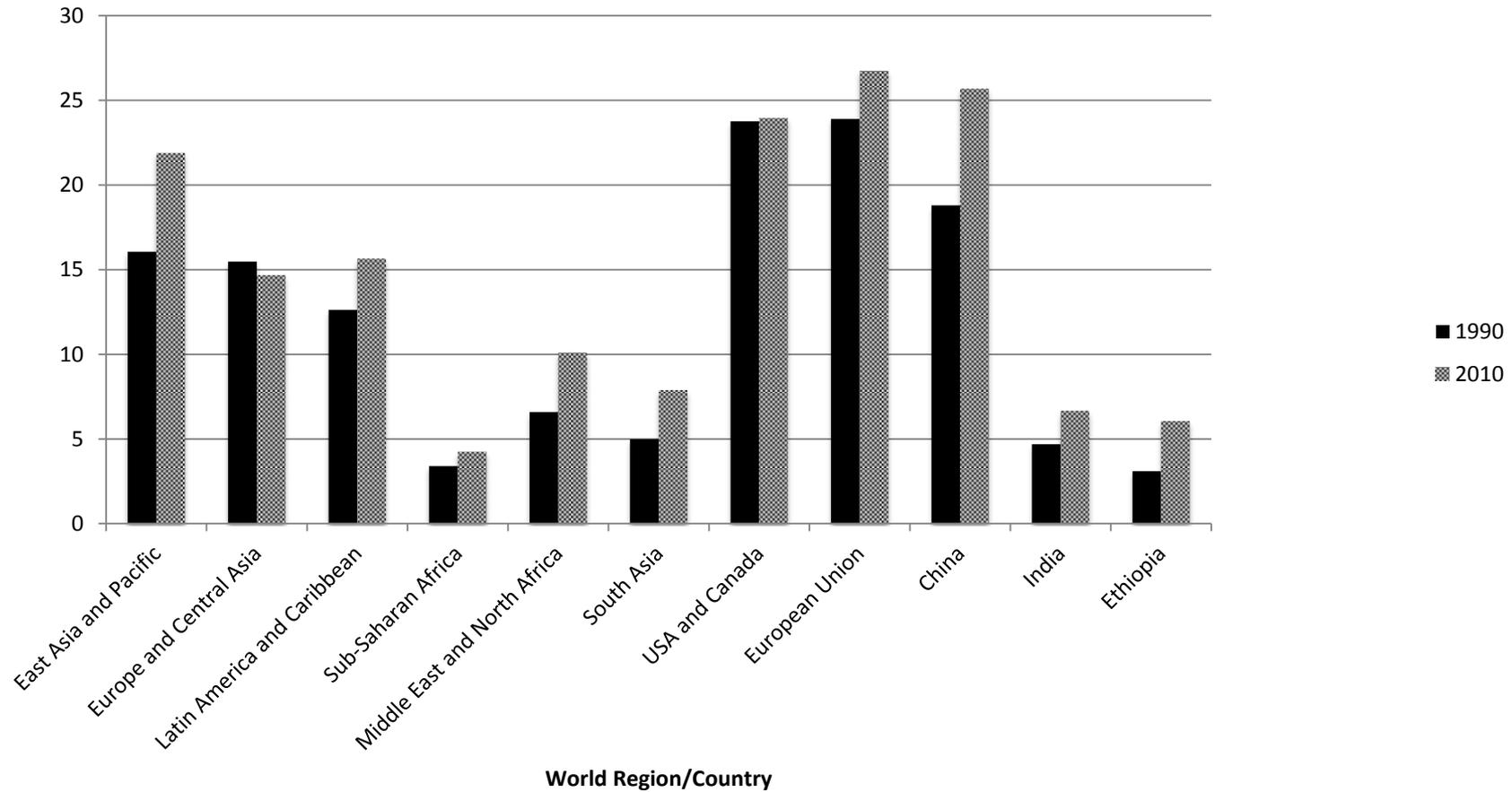


Figure 2

