## Chapter 15

# Need for National Commitments to Cancer Research to Guide Public Health Investment and Practice

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## INTRODUCTION

This chapter is addressed primarily to potential funders of health research at the national, provincial, and state levels. Health research in general, and cancer research in particular, is not a luxury reserved for high-income countries (HICs); it is a necessity for all countries across the income spectrum. The extent and depth of that research may vary by a country's financial situation, and the topics may vary by a country's specific burden of cancers and associated risk factors. Nevertheless, a comprehensive health research plan is foundational to the ability to allocate resources efficiently and effectively, develop human capacity and infrastructure, and identify the appropriate technologies and medicines for health and health services delivery. In short, robust research is essential to building evidence-based cancer prevention and control programs.

In recognition of the foundational nature of research, ministers and representatives of ministries of health, science and technology, agriculture, education, foreign affairs, and international cooperation from 53 countries convened in 2008 in Mali at the Bamako Global Ministerial Forum on Research in Health. Of the 53 participating countries, 38 were low- and middle-income countries (LMICs), according to World Bank criteria. The group issued its Call to Action, which articulates the rationale for supporting research to inform public policy, and sent the Call to Action to the World Health Organization (WHO 2008). The Call to Action recommends that national governments allocate at least 2 percent of the budgets of ministries of health to research and that international development agencies invest at least 5 percent of development assistance funds earmarked for the health sector in research. Box 15.1 highlights many of the principles applicable to cancer research.

Subsequent white papers and policy statements have made clear the importance of research on noncommunicable diseases and cancer to guide public policy and public investment (See Annotated Select Bibliography).

## STAKEHOLDERS AND THEIR KNOWLEDGE NEEDS IN CANCER RESEARCH

There are many stakeholders in cancer prevention and control, including researchers, ministers of health, physicians, other providers, and patients.

The most important stakeholders are the individuals with cancer, their families, patient advocates, and those at risk of cancer. Ministers of health and their colleagues

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**Box 15.1**

### Highlights of the 2008 Bamako Call to Action for Research on Health

- *Adopting comprehensive approaches.* Ensure that research and innovations are interdisciplinary and intersectoral; engage the public sector, private sector, and civil society associations in collaborations.
- *Setting priorities.* Develop the global research agenda in light of national and regional priorities, and encourage national governments to make the development of policies for health research and innovation a priority.
- *Building capacity.* Improve capacity at all relevant levels to foster research and technology transfer, improve the education and training of researchers, integrate research into health systems, and establish systems to evaluate the impact of research.
- *Improving equity.* Make greater equity a key element in the process.

*Source:* WHO 2008.

are also important stakeholders, as are physicians and other members of the health care team who provide care on a daily basis. Additional ministries at the national and state levels often play roles (albeit some of them minor), including the ministries responsible for finance, education, science and technology, agriculture, energy, customs, and foreign affairs. Universities and other academic units, as well as hospitals and clinics in the public and private sectors, have major roles in research.

Nongovernmental organizations are also crucial partners in fostering cancer research. Specialists from many disciplines of research and health are involved, including physicians, nurses, pharmacists, psychologists, social workers, epidemiologists, biostatisticians, basic and translational research scientists, information technologists, and data managers.

The needs of national stakeholders should guide cancer research in each country. One way to recognize those needs is by determining what ministries of health need to know (box 15.2) and what patients and their doctors need to know (box 15.3).

## RESEARCH PRIORITIES IN CANCER

### Health Surveillance and Cancer Surveillance

Making cancer surveillance an integral part of public health surveillance, which collects information on other risk factors and diseases, will greatly facilitate efforts to improve cancer outcomes. More than 20 percent of cancers in LMICs, for example, are associated with chronic viral, bacterial, or helminthic infection (De Martel and others 2012). Comprehensive cancer surveillance, accordingly, requires surveillance of relevant preventive practices, including vaccinations, that can influence the incidence and prevalence of infections linked to cancer. Similarly, cancer and other noncommunicable diseases, such as cardiovascular disease, diabetes, and chronic obstructive pulmonary disease, share a number of common risk factors, such as tobacco use, obesity, poor diet, physical inactivity, alcohol consumption, and environmental pollution. Surveillance for these common risk factors is critical to effective cancer control.

The Institute for Health Metrics and Evaluation (2011) has developed a framework for integrating surveillance systems across health information sources to help decision makers allocate resources and evaluate interventions. The World Health Organization also collects data on a variety of health indicators across diseases through its Global Health Observatory (WHO 2013). Table 15.1 sets out the range of health surveillance systems with relevance for cancer prevention and control. Few countries can afford to collect such health surveillance data on 100 percent of their populations. Nonetheless, through judicious use of cross-sectional surveys in representative populations, cohort studies, and disease and death registries, health policy makers can draft, implement, evaluate, and modify cancer control plans.

A national system that assigns unique individual identifying numbers or biometrics can be used routinely at all health system encounters and vital registrations of births and deaths to strengthen national health surveillance systems. Such a national identification system can facilitate the linkage of medical records, including records from clinic visits and hospitalizations, immunization records, pathology reports, operative notes, health insurance reimbursement information, and death registration.

### Cancer Registries and Pathologic Diagnosis

**Cancer Registries** The most basic public health oncology question is what is the burden of cancer in a city, a state, a country, or a region? The answer begins with pathology laboratories, where biological specimens for individuals—including blood tests, diagnostic biopsies,

**Box 15.2**

### What Do Ministries of Health Need to Know?

The answers to the following questions are relevant to ministries of health from low-, middle-, and high-income countries.

**What is the burden of cancer in the country?**

- How many cancers are diagnosed each year?
- How many people die from cancer?
- Which are the most common cancers?
- Which geographic regions and populations bear the greatest cancer burden?
- How does the burden of cancer compare with that of other diseases?
- What are the risk factors for cancer in the country?

**What resources are now in place for cancer control?**

- What can be done in the context of the existing health care system to prevent cancer and other common diseases?
- What can be done to screen for and treat cancer?
- How can we help cancer survivors return to being productive members of society?
- What palliative care can we provide?

**What could we do by redeploying existing resources? What else should we be doing and what will it cost?**

- What are the "best buys" for the country in the context of currently available health resources?

and surgical specimens—are evaluated. To these data are added cancers diagnosed on the basis of imaging studies, as well as cancers diagnosed on the basis of physical signs and patient symptoms. The data for individuals diagnosed with cancer can then be added up to give a picture of the overall cancer burden. Cancer registry data can provide descriptive and trend information about the burden of cancer in a population and enable the formation of hypotheses about etiology that can be tested in analytic studies. Cancer registry data also inform the need for cancer diagnosis and treatment facilities and allow the evaluation of cancer control interventions in a population.

Obtaining such data at the country level is difficult and expensive. The traditional approach has been to start small, with one hospital, then expand to a city or county, then to a state or province, and finally to other representative or high-risk populations of interest. Population-based registries may cover a representative portion of the geographic region of interest from which the larger (for example, countrywide) cancer burden can be estimated. Furthermore, population-based registries can be used to evaluate community health interventions in the region.

In the United States, for example, the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program began to capture information on cancer incidence from 14 percent of the country's population in 1973. The scope was subsequently expanded to track additional areas with low-income

**Box 15.3**

### What Do Patients and Doctors Need to Know?

The answers to these questions are relevant for patients, families, and health care providers in low-, middle-, and high-income countries.

- What type of cancer does the patient have?
- What is the extent or stage of the cancer?
- What are the options for treating the cancer and its symptoms?
- How can the patient gain access to appropriate and affordable cancer therapy, treatment of symptoms, survivorship counseling, and supportive care?
- If the treatment works as hoped and the patient is cured of cancer, what steps are needed to help the patient reintegrate into family and work life?
- If the cancer is too advanced for curative therapy or if treatment does not cure the patient, will the patient benefit from palliative care, including pain control?
- How can the patient best gain access to palliative care?

**Table 15.1** Health Surveillance Systems for Noncommunicable Diseases and Cancer Control Planning

***Infections***

- Incidence and prevalence of infections linked to cancer, such as hepatitis B virus (HBV) and C, human papillomavirus (HPV), human immunodeficiency virus (HIV), human T-lymphotropic virus-1, Epstein-Barr virus, human herpesvirus, *Helicobacter pylori*, and liver flukes
- Uptake of prophylactic HBV and HPV vaccines

***Common risk factors for noncommunicable diseases***

- Tobacco use (smoked and oral), including exposure to secondhand smoke
- Lack of proper diets, such as those with more fruits and vegetables and whole grains; exposure to known carcinogens, such as nitrates and high-temperature beverages
- Alcohol intake
- Obesity
- Low activity level

***Availability of, access to, and uptake of cancer screening***

- Preinvasive cervical cancer
- Breast cancer
- Colon cancer

***Cancer registries***

- Type and stage of cancer annotated with demographic data
- Primary treatment and cancer outcome

***Death registries***

- Deaths occurring due to cancer or concurrent disease after diagnosis of cancer

and minority populations; as of 2013, it included approximately 28 percent of the population. The SEER Program collects high-quality, individual-level data on patient demographics, primary tumor site, morphology, stage at diagnosis, first course of treatment, and follow-up for vital status (Howlader and others 2013). A complementary program established through the U.S. Centers for Disease Control and Prevention in 1992 has expanded cancer registries to cover 96 percent of the U.S. population.

**Role of Laboratories and Anatomic Pathology** Accuracy in histopathologic diagnosis of tumor specimens from surgery or biopsy is required to make the correct diagnosis for any one person's cancer and help that person and health care providers make the appropriate treatment decision. In addition, accuracy in histopathologic diagnosis is also required to ensure the accuracy of cancer incidence data in cancer registries. Biological specimens must be processed promptly, shortly after removal from the human body. Pathology laboratories require trained histotechnicians and cytotechnicians, as well as functioning instrumentation and a reliable supply chain for the equipment needed to process specimens, such as formalin, glass slides, and diagnostic reagents. Trained pathologists must be available to review the processed material, whether onsite, at central laboratories, or from remote sites via telepathology.

When a person is diagnosed with cancer, it is important to determine the aggressiveness of the specific cancer and whether the cancer has spread from the original site of origin to other parts of the body. This additional information is used to assign a stage to the cancer, which generally ranges from stage I (the earliest stage, which in many cases can be cured with standard therapy) to stage IV (the most advanced stage, which is most difficult to treat effectively). The ability to assign a stage to newly diagnosed cases requires linking the pathology report to clinical data. Without data on the extent of the disease or stage, it is not possible to provide appropriate treatment or determine the success of interventions intended to diagnose cancer at earlier stages when the cancer is more successfully treated.

**Biobanking** Biobanks and biological resource centers constitute key components of cancer research. To understand the biological basis of cancer; to develop biomarkers for cancer risk, early detection, and prognosis; and to determine the most appropriate cancer treatment based on precise diagnosis of tumor characteristics, it is necessary to have access to clinically annotated biologic specimens of cancer and normal tissue (Vaught, Henderson, and Compton 2012). Until recently, some analyses required special preparation of specimens, such as fresh frozen tissue. More recent developments in molecular pathology permit many studies to be done on formalin-fixed, paraffin-embedded tissue.

To make progress in cancer research as quickly as possible, it is important to be able to facilitate the collection and analysis of such specimens. Some specimens may need to be shipped to global or regional core laboratories for analysis using standardized protocols. In other cases, the primary analysis may be done in the country of origin, with a small number of samples exchanged among countries for standardization and quality control of the laboratory techniques. National or state regulations that prohibit any shipment of specimens outside the country or region of origin may preclude efficient analysis of those specimens and delay progress in research needed for cancer control.

Given the increasing need to pool data and biospecimens from consortia of studies around the world to achieve adequate sample size and statistical power, countries with rigid rules for data- and biospecimen-sharing will be at a disadvantage in the ability to participate in cutting-edge cancer research (NRC 2011; Thun, Hoover, and Hunter 2012). Although it is clear that regulations must be in place for the appropriate use of all samples when shared outside national boundaries, facilitating processes for the timely sharing of biological specimens will enhance research for all.

### Linking Death Registration Systems to Cancer Registration Systems

Functioning national, regional, or sample-area death registration systems are critical to a country's ability to monitor its burden of all diseases. In areas covered by cancer registries, accurate death registration information may serve as an important source of cancer-case finding. In general, cancer registrars routinely search hospital medical records for the initial diagnosis and pathology report of medically certified cancer deaths.

Linking information on individuals diagnosed with cancer to death registries also greatly facilitates the computation of rates of cancer survival (for example, case-fatality rates) by tumor site and stage of disease, which otherwise would require expensive and time-consuming active follow-up of individuals diagnosed with cancer. As noted, the use of unique individual patient identifiers can help to link the diagnosis of cancer with patient follow-up and, ultimately, the death of that individual. In the absence of cancer registries, the cancer burden of a country can be estimated by the cancer mortality rate, if cause-of-death data are available (Boyle and Levin 2008; Jensen and others 1991).

A less costly and less precise alternative approach to obtaining the medically certified cause of death is that of the verbal autopsy, in which trained health workers interview the members of a household in which a death has occurred about the symptoms of the deceased person (Institute for Health Metrics and Evaluation 2011). Dikshit and others (2012) have reported the successful use of the verbal autopsy in the Million Death Study in India to estimate mortality from cancer and other diseases.

## Cancer Epidemiology

The application of sound epidemiologic methods is indispensable in cancer research. Experimental and observational studies have yielded much of the current knowledge about causation, prevention, and intervention; epidemiologic studies conducted using cancer registry data have made significant contributions to the understanding of rates and trends. Cancer registries provide descriptive data that reveal important patterns and trends in the burden of cancer in defined populations. Registry data help to generate hypotheses that guide epidemiologic investigations that can identify potential causative factors, rule out false associations, define the nature of the dose-response relationship, identify co-factors and, in some cases, identify explanations for late-stage diagnosis. Increasingly, epidemiology studies incorporate molecular biology in their design to help better define outcome (cancer subtypes at a given site can vary greatly) and exposure with relevant biomarkers and to identify genetic and other molecular risk factors.

### Case-Control Studies

A great deal of knowledge on cancer epidemiology is generated by case-control studies, which identify cancer cases using cancer registries or hospitals and other points of care and sample controls from the source population of cases. These epidemiologic investigations may require rapid case finding by study personnel, in-depth interviews of cases, and controls by trained interviewers to assess exposure information, environmental sampling, and collection and analysis of biospecimens at core laboratories. Case-control studies are efficient and generally less costly than cohort studies, particularly in the study of rare outcomes (Rothman, Greenland, and Lash 2008). Challenges include the potential for biases, such as differential recall, and the challenge of measuring exposures or assessing biomarkers of environmental exposure before the time of cancer diagnosis, thereby making it difficult to assess temporality (Wild 2009).

**Cohort Studies**

Cohort studies can overcome some of the limitations of case-control and cross-sectional study designs by enabling the measurement of exposures at the time of cohort enrollment, often years or decades before cancer development and diagnosis (Breslow and Day 1987; Rothman and Greenland 2008). Exposure assessment can be determined before the onset of disease and thereby limit the potential for recall bias and other types of bias inherent to case-control studies.

Cohort studies also contribute to health surveillance by providing the opportunity to obtain repeated measures of multiple exposures and potential confounding factors and to measure changes in these factors over time. Cohort studies enable estimation of the incidence of outcomes of interest, including infections, premalignant lesions, cancers, and comorbid conditions. Follow-up of cohorts requires long-term commitment, for supporting the study infrastructure and team, as well as for building and maintaining trust between the research team and the participants in the cohort. Recent developments in information technology, including the increased uptake of mobile telephones and Internet access, have facilitated the development and maintenance of study cohort enrollment and follow-up.

A cohort may be used to study multiple health endpoints and multiple exposures; new endpoints may be added over time, and data and biospecimens from multiple cohorts can be pooled to obtain greater statistical power. Thun and others (2013), for example, pooled data from seven cohorts to analyze the long-term impact of cigarette smoking in the United States. Another example is the 2004 formation of the International Childhood Cancer Cohort Consortium to assemble birth and child cohorts around the world to prospectively collect information on early life exposures and childhood cancers. This effort resulted from the recognition that single studies lacked the statistical power to study childhood cancers that are rare. It also provided evidence that pre-conception and in utero exposures may be important determinants of subsequent risk of childhood and adult cancers (Brown and others 2007).

Some adult cohorts that have made seminal contributions to cancer epidemiology include the following:

- The prospective cohort study of British doctors (Doll and Hill 1954)
- The American Cancer Society Cancer Prevention Studies (Calle and others 2002; Hammond 1966; Thun and others 1997)
- The United Kingdom Million Women Study (Million Women Study Collaborative Group 1999)
- The Japan Life Span Study (Sakata and others 2012)
- The Nurses' Health Study (Colditz, Manson, and Hankinson 1997) (box 15.4)

More recently formed cohorts in LMICs include the following:

- The China Kadoorie Biobank, which includes 500,000 adults from urban and rural areas in China (Chen and others 2011) (box 15.5)
- A separate cohort of 220,000 men in China (Chen and others 2012)
- A cohort of 150,000 women and men in Mexico City (Kuri-Morales and others 2009)
- The Chennai Prospective Study of 500,000 adults in Tamil Nadu, India (Gajalakshmi and others 2007; Gajalakshmi, Whitlock, and Peto 2012)

**Box 15.4**

### Cohort Study: The Nurses' Health Studies

The Nurses' Health Study (2014a) comprises two cohorts of registered female nurses that enrolled more than 115,000 nurses in the United States. The first cohort began in 1976 and the second in 1989. These long-term epidemiologic studies were originally designed to assess risk factors for two major chronic diseases in women, namely, cancer and cardiovascular disease. Due to the large sample size, the extensive data available on each participant, and associated biological specimens, the investigators have also been able to study risk factors for many other chronic diseases, including diabetes mellitus, stroke, osteoporosis, mental health, and connective tissue disease. The Nurses' Health Study coordinating center is recruiting a third cohort of 100,000 nurses. Participant registration and follow-up will be conducted entirely via Internet communication (Nurses' Health Study 2014b).

**Box 15.5**

### Cohort Study: The China Kadoorie Biobank

The China Kadoorie Biobank includes 500,000 adults recruited between 2004 and 2008 from 10 regions in China, urban and rural (Chen and others 2011). All participants are being followed for hospital admissions, as well as cause-specific morbidity and mortality. Already, studies have been published on respiratory disease, depression, anxiety, diabetes, cardiovascular disease, alcohol consumption, physical activity, and obesity, and interactions among these factors within the cohort (Bragg and others 2014; Chen and others 2014; Du and others 2013; Lewington and others 2012; Mezuk and others 2013; Millwood and others 2013; Zhang and others 2013).

The studies have found, for example, that self-reported diabetes was associated with a doubling of the odds of prevalent cardiovascular disease (Bragg and others 2014); that only one in three individuals with prior cardiovascular disease was routinely treated with any proven secondary preventive drugs (Chen and others 2014); that drinking alcohol was positively correlated with regular smoking, increased blood pressure, and increased heart rate (Millwood and others 2013); that major depression and generalized anxiety disorder are associated with type 2 diabetes mellitus (Mezuk and others 2013); and that exhaled carbon monoxide can be used as a biomarker for assessing current smoking and exposure to indoor household air pollution (Zhang and others 2013).

## Health Communications

Health communications contribute in a number of critical areas needed in cancer research (National Cancer Institute 2004). First is the need to communicate the importance of health research to the media, policy makers, and the general public. Without community recognition of the need for health research, without appropriate levels of funding, and without a regulatory framework that facilitates the health research needed to guide public policy and public investment in health, health research cannot take place.

Second is the need to understand how best to communicate to individuals, families, and communities that research findings support public health recommendations and guidance. One clear example is how best to communicate the health risks associated with tobacco use, alcohol abuse, and physical inactivity. Ideally, such communication should lead to changes in behavior that reduce the risk of cancer and other chronic diseases. Other examples are communication regarding recommended regimens for approved vaccines that prevent chronic infections associated with cancer, such as those for hepatitis B virus (HBV) and human papillomavirus (HPV), and recommendations for routine cancer screening.

Third is the need to identify ways to help communities understand cancer. This includes understanding that some cancers can be prevented, that some cancers are amenable to screening, and that many cancers can be treated successfully if diagnosed early. Such education and communication may help to overcome the stigma of cancer, particularly in settings where cancers are typically diagnosed at late stages with poor prognoses.

Different communication strategies may be needed for different populations, based on language, levels of literacy and health literacy, access to health care, socioeconomic status, cultural sensitivities, and other factors. The development and validation of effective cancer-related health communication strategies is key to developing and implementing research that can facilitate cancer prevention and control.

## Implementation Science

Effective means of implementing cancer prevention; population-based screening; and timely and accurate cancer diagnosis, treatment, and symptom management are needed to improve cancer control. The U.S. National Cancer Institute has developed a website (http://cancercontrolplanet.cancer.gov) with links to effective cancer control interventions, including a database of research-tested intervention programs developed in partnership with the Substance Abuse

Box 15.6

### What Questions Can Implementation Science Answer?

Implementation science can help obtain answers to the following questions for cancer prevention and control:

- Which tobacco control programs are most effective for specific populations?
- What are the most cost-effective ways to ensure that as many children as possible are vaccinated for HBV and HPV?
- What is the most effective way to screen for and treat preinvasive HPV-related cervical neoplasia?
- What is the most effective way to screen for colon cancer?
- What is the most effective way to provide palliative care, including pain control?
- What are the most effective ways to ensure quality control across the cancer spectrum, from screening to treatment to survivorship care?

and Mental Health Services Administration (National Cancer Institute 2013).

Different approaches may be needed for different regions in the same country and between countries, based on existing health resources, cultural norms, and other factors. In some cases, task shifting of responsibilities from doctors to nurses, other health professionals, and lay community health workers or from nurses to community health workers may be required. The principles of implementation science can guide public health interventions for cancer control and facilitate their routine evaluation and modification, as needed, to achieve the goals (Madon and others 2007). Although more research is needed in all the areas mentioned, much is already known to be able to implement cancer control strategies to reduce the burden of cancer (box 15.6).

## Cancer Research Collaboration

### National Level

To optimize country-level outcomes, national policy makers will need to consider the essential elements of and necessary conditions for health research that require a comprehensive approach that includes the following:

- Achieving a consensus that health research deserves the appropriate funding and strategies for implementation, as the Bamako Call to Action advocates
- Developing and implementing mechanisms for transparent and objective evaluation and prioritization of clinical research studies
- Establishing systems for ethical, regulatory, and scientific reviews so that research can be conducted in a timely manner and clinical studies can be completed expeditiously
- Revising customs inspections and policies to remove restrictions on the importation of drugs, devices, and reagents for health research
- Developing mechanisms and resources for the efficient and inexpensive acquisition of drugs, devices, and reagents for health research
- Providing financial support—possibly from national governments, state governments, nongovernmental organizations, or a combination—for the infrastructure for public clinical trials, including protocol development, regulatory management, routine medical expenses of patients, data management, quality assurance, biobanking, biostatistics, and informatics
- Integrating clinical research into national health systems
- Integrating education about clinical research into education and training of health care providers

### Local Level

It is important to assist the institutional leadership at the local level—whether hospital, clinic, or university—to appreciate the importance of health research. Doctors, nurses, pharmacists, and specialists from other relevant disciplines need protected time to conduct clinical research. Academic tracks could be established to foster research and reward individuals for conducting clinical research. In some cases, money could be earmarked to pay for the additional costs associated with research. These costs may include additional imaging studies or specimen processing that may not be required for routine clinical care. The local study sites also need the appropriate financial and technical resources for clinical research management, biobanking, and informatics.

### Research Training

For research to have a significant impact on health, governments in LMICs and HICs need to invest in training future scientists, clinicians, public health professionals, and physician-scientists. Such investments in training professionals in the range of relevant disciplines and helping them to maintain and strengthen their research skills require effective coordination that may involve government ministries responsible for education, health, science and technology, and human resources, as well as academic institutions, hospitals, clinics, nongovernmental organizations, and professional societies.

Principles of health research can be integrated into the core curriculums of schools of medicine, nursing, public health, pharmacy, and allied health sciences, as well as university programs for basic sciences and social sciences. This integration will ensure that all individuals involved in research with relevance for health learn about the conduct of health research and appreciate the need for such research.

Biostatisticians are a critical component of the research team, as are basic and translational research scientists, social scientists, health economists, and health communicators. There is a great need, particularly among young scientists in low-resource settings, for opportunities to participate in high-quality cancer research and to have access to nurturing mentors, whether local or remote.

Other allied areas in which training and mentorship are critically needed are the ethical conduct of cancer research, research subject protection, scientific writing for preparation of research proposals and manuscripts, and responsible study and financial management.

#### International Collaboration

International collaboration in cancer research spans capacity building and joint research projects. There are many examples of North-South and South-South projects to build capacity in health and cancer research. Institutional “twinning” has been particularly successful in this regard. Joint research projects can facilitate training opportunities for investigators in LMICs. Two recent reports from the Organisation for Economic Co-operation and Development’s Global Science Forum highlight the need for international collaboration in clinical research to address many important health questions (OECD 2011, 2013).

The facilitation of such collaboration requires an effective national commitment to health research as well as a commitment to facilitate international collaboration (Trimble and others 2009). International research collaboration may require allowing specimens to be shipped to a regional or global core laboratory, as well as pooling relevant information in an international database. Timely scientific and ethical review is critical for national studies, particularly for international collaboration (Abrams and others 2013). International partnerships in cancer research require the timely recognition of scientific opportunities, available resources and study conditions, strengths of research partners, integrity, persistence, and commitment of all partners in jointly overcoming barriers to accomplish research objectives.

#### Industry Collaboration

Many aspects of cancer control, including prevention with vaccines, screening, diagnosis, treatment, and symptom management, require reliable drugs, devices, and reagents. Many areas of cancer need better, more effective, more accessible, and less costly drugs, devices, and reagents. Partnering with industry will facilitate the development and validation of novel products, as well as help to ensure a reliable supply chain to bring products shown to be beneficial to routine clinical practice. Once a product is developed and tested, it will be important to work with industry partners to make the product available and affordable on a population basis. Such public-private partnering is an integral component of developing and translating innovations in cancer research to clinical care and public health.

## CERVICAL CANCER: EXEMPLAR OF INTEGRATED RESEARCH

Cervical cancer provides a sterling example of how cancer research in virology, immunology, epidemiology, clinical care, behavioral sciences, and implementation science has led to effective cancer prevention and control. Much of this work occurred because of international collaborations that allowed appropriate sharing of research material, data, and expertise.

### Epidemiology and Biology

The link between chronic HPV infection and cervical cancer was established by zur Hausen and colleagues in the early 1990s, building on earlier experimental work that strongly suggested the possibility that the two were linked (Reid 1983; zur Hausen and de Villiers 1994). Muñoz and others (2002) confirmed that HPV was responsible for more than 99 percent of cervical cancers globally. Epidemiologic studies have also permitted the identification of additional co-risk factors for cervical cancer, including exposure to tobacco smoke, both firsthand and secondhand, chronic immunosuppression, multiparity, long-term use of oral contraceptives, and high-risk male partners (Schiffman and Hildesheim 2006).

### Development of Vaccines to Prevent HPV Infection

The identification of HPV as a necessary causative agent led to the development of vaccines to prevent HPV infection and cervical cancer. Two vaccines to prevent HPV infection demonstrated efficacy and safety in phase III and IV studies (Schiller, Castellsagué, and Garland 2012). Both agents have been widely approved by drug regulatory authorities, including the U.S. Food and Drug Administration and the European Medicines Agency. The rollout of these vaccines to prevent HPV infection required a progression of clinical research studies, first to confirm primary efficacy, then to validate in different populations, followed by public health investigations to determine how best to deliver and encourage uptake of the new vaccines to prevent HPV infection and cervical cancer (Program for Appropriate Technology in Health 2012).

These investigations incorporated studies of messaging, including how best to communicate to parents the health benefits that the new vaccine offers to their daughters; studies comparing on-the-ground vaccine delivery programs, such as school-based versus clinic-based HPV vaccination programs; and comparisons and studies of different dosing schedules for HPV vaccines (Galagan and others 2013; Lamontagne, Barge, and others 2011; Lamontagne, Thiem, and others 2013). Australia, which has a national reporting system for HPV-associated warts in addition to a national registry for vaccinations, has been able to document significant decreases in HPV infection and genital warts among teenagers and young adults following the widespread introduction of the vaccine (Read and others 2011; Tabizi and others 2012). Several second-generation vaccines to prevent HPV infection are under development, with the goal of addressing the issue of type-restricted protection and decreasing the cost of production.

### HPV Diagnostics for Cervical Cancer Screening

Based on the understanding of the link between chronic oncogenic HPV infection and cervical neoplasia, new diagnostic tests have been developed to target the virus, including evidence of active infection with high-risk HPV types, as well as evidence of HPV integration. DNA-based tests detect the presence or absence of the HPV virus genome. DNA testing for high-risk HPV types has a high sensitivity for the detection of high-grade cervical intraepithelial neoplasia and cervical cancer (Arbyn and others 2012). The great advantages are that HPV detection assays are automated and objective and have a greater reproducibility than cytology; as such, they are a promising screening test in LMICs, which may lack skilled personnel. Sankaranarayanan and others (2009) found that a single round of testing for HPV was associated with a significant reduction in the risk of advanced cervical cancer and death from cervical cancer among rural women in India. In this study, which accrued 131,746 women ages 30–59 years in 52 villages, the other two screening arms—cytologic testing and visual inspection of the cervix with acetic acid—did not demonstrate significant reductions in the risk of advanced cervical cancer and deaths from cervical cancer.

### Unanswered Questions in HPV-Associated Neoplasia and Cervical Cancer Control

Based on the body of research to date, as well as the extensive programs for control of HPV-associated neoplasia, many critical research questions remain unanswered (Schiller and Lowy 2014) (box 15.7). These questions span a variety of scientific areas, including the following:

- Behavioral sciences
- Health communications
- Health services research
- Immunology
- Implementation science
- Prevention

**Box 15.7**

### Ongoing Research Questions in HPV and Cervical Cancer Control

The tremendous progress in HPV and cervical cancer control can be taken even further as these still outstanding research questions are addressed. The following cervical cancer research agenda provides opportunities for scientists in all interested countries.

- *Prevention, health services research, and immunology.* How can the cost of the currently available prophylactic HPV vaccine regimen be reduced? Are one or two doses as effective as three? Will additional booster doses be needed and when?
- *Prevention, implementation science, and health communications.* What combination of feasibility and affordability would convince policy makers in LMICs to introduce and fund population-based prophylactic HPV vaccination?

box continues next page

**Box 15.7** (continued)

- *Health communications, prevention, behavioral sciences, and implementation science.* What are the critical components in educational programs for parents considering whether to permit their daughters and sons to undergo prophylactic HPV vaccination?
- *Prevention, virology, and immunology.* What is needed to develop second-generation prophylactic HPV vaccines that provide protection against infection from more HPV subtypes than included in the first-generation HPV vaccines?
- *Screening and virology.* What is needed to develop effective screening strategies for HPV-associated neoplasia of the oropharynx and anus?
- *Screening, health services research, and implementation science.* What types of infrastructure, human resource capacity, and logistical support are needed to scale up existing and new cervical neoplasia screening and treatment services at multiple levels of the health system to meet the needs of urban and rural populations?
- *Screening and virology.* What is the feasibility of developing inexpensive, highly sensitive, and highly specific HPV-based tests to use as a primary screen for cervical neoplasia and chronic HPV infection in low-resource settings?
- *Screening, health services research, and implementation science.* How can population-based screening for cervical neoplasia or chronic HPV infection be more effectively integrated into maternal-child health programs, programs caring for HIV-positive individuals, well-woman programs, and programs screening for other noncommunicable diseases, such as diabetes, hypertension, and breast cancer?
- *Health communications, screening, behavioral sciences, and implementation science.* What measures can be taken to ensure that no woman found to have an abnormal screening result is lost to follow-up?
- *Treatment.* What can be done to improve current ablative therapy for preinvasive cervical and anal cancer?
- *Immunology and treatment.* Can therapeutic HPV immunization strategies be developed to prevent the development of neoplasia in individuals already infected with HPV, as well as to complement or replace ablative therapy for HPV-associated neoplasia?
- *Treatment and implementation science.* How can current therapy, including surgery, radiation, chemoradiation, and neoadjuvant chemotherapy, be improved for women with invasive cervical cancer?
- *Treatment, behavioral sciences, and implementation science.* How can the quality of life best be maintained and enhanced in cervical cancer survivors, including bowel, bladder, and sexual function, as well as physical intimacy?
- *Symptom management, behavioral sciences, and implementation science.* How can palliative care be delivered most effectively to women diagnosed with late-stage or recurrent cervical cancer?

- Screening
- Symptom management
- Treatment
- Virology.

## CONCLUSIONS: "BEST BUYS" FOR CANCER RESEARCH

What are the "best buys" for cancer research in LMICs? Where should ministers of health, ministers of science and technology, and other funders of research begin?

- Robust health surveillance systems, including surveillance of cancer risk factors, cancer registries, and cancer-associated deaths, are critical to effective decision making for prevention and control, as well as priorities in cancer research.
- Next is implementation science focused on how to deliver interventions that have been shown to be effective. Perhaps the most effective method of cancer prevention is tobacco control. Countries at all levels of income could sponsor research focused on how best to reduce or eliminate use of tobacco. This research should include public policy, public education, and smoking cessation initiatives.
- For LMICs burdened with liver cancer or cervical cancer, implementation science focused on expanding routine administration of HBV and HPV vaccinations is appropriate. For countries at all levels of development,

implementation science in effective methods to deliver palliative care is critical. Educational and training programs for health care professionals and community health workers would benefit from the inclusion of the principles of health research. How best to educate and retain health care workers at all levels is also an appropriate area for research.

- Countries with the ability to conduct programs for cancer screening, early diagnosis, and treatment could expand implementation science research to cover these areas, as well as tobacco control and preventive vaccines. Timely topics for research also include cost-effective strategies to screen for cervical, colon, oral, esophageal, stomach, and skin cancers; to evaluate breast masses; and to provide potentially curative therapy for preinvasive and invasive cancer.
- The next area for research, as national resources permit, encompasses cancer epidemiology and biology. Improved understanding of the risk and protective factors for specific cancers, as well as their molecular biology, is essential to design effective interventions for prevention, screening, early diagnosis, and treatment. For example, the epidemiology and biology of prostate cancer is not sufficiently well understood to prevent it, screen for it, or know how best to treat it. Similarly, the ability to make progress on cancer control for many cancers linked to chronic infection and inflammation requires better elucidation of the salient biology, natural history, co-factors, and protective factors.

## NOTE

World Bank income classifications as of July 2014 are as follows, based on estimates of gross national income per capita for 2013:

- Low-income countries: US$1,045 or less
- Middle-income countries:
    - a) Lower-middle-income: US$1,046–US$4,125
    - b) Upper-middle-income: US$4,126–US$12,745
- High-income countries: US$12,746 or more

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