GLOBAL HEALTH

Cancer in global health: How do prevention and early detection strategies relate?

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National cancer control plans are needed to stem the rapidly rising global cancer burden. Prevention and early detection are complementary but distinct strategies for cancer control. Some cancers are prevented through behavior and/or environmental modifications that reduce cancer risk, whereas other cancers are more amenable to treatment when they are successfully diagnosed at early stages. Prevention and early detection strategies should be prioritized on the basis of country-specific cancer demographics, modifiable risk factor distribution, and existing treatment resource availability. Following an individualized plan integrating prevention and early detection strategies, deficits can be targeted to strengthen national health systems for cancer control.

A FRAMEWORK FOR CANCER CONTROL

Cancer has become a major cause of global mortality, leading to the emerging recognition that cancer control must become a global health priority. Deaths attributed to neoplasms reached nearly 8 million in 2010, representing ~15% of all global deaths (*1*). Between one-third and one-half of cancers can be prevented through avoidance of known risk factors (*2*). For the remaining 50%, a substantial proportion of cause-specific mortality could be averted through early detection followed by effective treatment. Determining which cancer interventions should be prioritized in the global health agenda has been contentious in the current environment in which noncommunicable diseases (NCDs) receive less than 3% of total donor development assistance for health ($503 million out of $22 billion per year) (*3*).

Data from high-income countries (HICs) indicate that prevention and early-detection programs are cost-effective at reducing cancer mortality (*4*). Nonetheless, translation of these interventions to low- and middle-income countries (LMICs) is difficult. Obstacles to comprehensive cancer control include poor health care infrastructure, competing health priorities, lack of cancer awareness, unabated exposure to carcinogens, inadequate funding, and limited human resources (*5*). Although more than 65% of cancer-related deaths globally occur in LMICs (*6*), only 5% of global health resources are directed toward cancer in those countries (*7*). An effective large-scale global response must be evidence-based and individualized by region.

A general framework for cancer control is to devise plans to (i) prevent cancers that can be prevented, (ii) treat cancers that can be cured, and (iii) palliate cancers for which the first two approaches fail. For cancers that cannot be prevented, treatment efficacy and costs generally hinge on early detection; curative treatment for late-stage disease is more complex and expensive than for early-stage cancer, and cancer recurrence and mortality risks after treatment are substantially increased. For these reasons, it is incumbent on both policy-makers and health care leadership to understand how prevention and early detection differ, how they relate, and how they can be coordinated in a given health care environment in order to improve patient health.

DISTINGUISHING PREVENTION AND EARLY DETECTION

Certain risk factors greatly predispose to cancer development. Primary prevention is achieved by eliminating or minimizing exposure to cancer risk factors and by reducing susceptibility to their effects, avoiding carcinogenesis. Conversely, early detection seeks to identify an existing cancer in the initial stages when a cure is likely. Early detection includes both awareness education and screening (also called secondary prevention). By educating the public about the signs and symptoms of cancer, and then adapting health care systems to permit accurate and prompt cancer diagnosis, early detection becomes a feasible cancer control strategy. Screening goes one step further, by using tests (physical exam, imaging, laboratory tests, or genetic tests) to identify persons with early cancer who have not yet developed symptoms. Screening has the potential to find disease at earlier stages than does awareness education but also requires more health care resources and is generally unavailable and unaffordable for LMICs (*8*).

Cancer control prioritization. National cancer control programs should consider local factors when determining health resource allocation priorities. To develop a national strategy for cancer control, policy-makers must consider specific cancer incidence in their region, the potential for prevention and/or early detection with the most common cancers, the projected efficacy of treatment, and the costs associated with each policy alternative. Objective comparisons can help inform policy-makers about optimal strategies to achieve the best outcomes with available resources (Table 1). In regions where data on existing national programs are absent, global metrics can be used to estimate potential benefits for different strategies.

For cancers with known preventable causes, the relative benefit of a prevention program can be estimated by the population attributable fraction (PAF) associated with the known risk factor that is being targeted for reduction (*9*). The accuracy of PAF as a measure of cancer prevention potential is constrained by biases in exposure recording, poor documentation of actual cancer incidence, and limited quality of evidence used to calculate relative risk (*10*). The correlation of PAF to actual cancer risk reduction magnitude assumes 100% effectiveness in avoiding the stated risk factor, which in practice will not be attainable. Thus, PAF is most helpful in a relative sense for comparing different risk reduction strategies in designing an overall cancer control program.

The mortality-to-incidence ratio (MIR) can be calculated as a crude estimate of case fatality for each cancer subtype—that is, the likelihood that an individual with a specific malignancy will die as a direct result of that illness. MIR provides insight into the status of current early detection and treatment in a country. If there is a substantial difference between MIR for specific cancers in a given country as compared with HICs, then improved diagnostic and treatment services may be warranted. MIR is subject to limitations, including variations in cancer incidence over time, the quality of cancer registries, and regional variation

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Table 1. Incidence, prevention potential, screening effectiveness, and mortality-to-incidence ratio differences for the 10 most frequent cancers around the globe. Data are from (*6*). The PAFs were calculated in LMICs when available (*9, 24, 27*). Screening percentages reflect estimated mortality decline with effective screening based on published screening trial statistics (*18, 25, 28, 29*). Screening modalities exist for each of the listed cancer subtypes but may not be cost-effective or efficacious in many circumstances. The MIR reflects the effectiveness of current diagnosis and treatment in very high human development regions as defined by the International Agency for Research on Cancer (*6, 24*). Differences in MIR between HICs and LMICs provide a gross index of potential improvement with investment in early detection and treatment resources. Health policy priority is determined via a comparison of PAF (which could be addressed with maximal prevention investment) versus screening availability with associated mortality reduction versus potential improvements in MIR. These generalized policy recommendations are subject to interpretation and could be altered depending on an individual country's situation and specific resource constraints.

Cancer type	Relative incidence in LMICs (%)	Prevention potential (PAF) (%)	Screening effectiveness (estimated mortality benefit, %)	MIR in HICs (%)	Difference in MIR between HICs and LMICs (%)	Health policy priority
Breast	15.6	21	Yes (20–40)	22	28	Early detection and treatment
Prostate	5.1	0	No* (0–30)	18	64	Treatment
Lung	4.1	74	Unknown (0–20)	82	7	Prevention
Colorectum	4.2	13-15	Yes (12–32)	42	34	Early detection and treatment
Cervix uteri	11.7	95–100	Yes (20–70)	42	19	Prevention > early detection
Stomach	3.7	69	No†	56	38	Prevention > treatment
Liver	5.3	81	No*	86	9	Prevention
Corpus uteri	1.3	37	No*	19	20	Prevention > treatment
Ovary	2.2	12	No*	67	9	Additional research
Esophagus	4.9	46–58	No*	81	11	Prevention

*Screening for esophageal, uterine, ovarian, and prostate cancers is advised only for high-risk patient cohorts. †Gastric screening may be indicated in countries that have a particularly high gastric cancer burden (for example, in Japan).

in tumor biology (*11*). The use of MIR as a population-based cancer control statistic should proceed with the understanding that it will not specifically reveal where service deficiencies exist along the spectrum from early diagnosis to treatment. However, it can serve as a valuable metric in both LMICs and HICs to reflect the overall quality of cancer services and may be useful in following cancer outcome changes over time (*12*).

For national cancer control planning, PAF and MIR can function as instructive indicators, revealing differences in local disease patterns that may guide policy-makers on how to best invest in prevention and/or early-detection and treatment programs. The process of program planning should be evidence-based, should be individualized to a country's needs and circumstances, and should evolve based on resources and changing outcomes over time.

Prevention. Effective prevention programs require multisectoral investment and should target modifiable risk factors that cause substantial disease burden (Table 1). In HICs, programs and policies focused on tobacco avoidance and weight management could do more to mitigate cancer than any other measure (*13*). Despite the potential benefits, less than 4% of public health care budgets in the United States, Canada, and Europe is spent on cancer prevention, perhaps reflecting poorly formulated health priorities, limited political will, and insufficiently persuasive evidence supporting the establishment of national prevention programs (*14*). Promoting healthy behavior is particularly challenging when it counters the economic interests of commercial industries and the lifestyle choices of a populace (*2*, *15*). The success of prevention is invisible; the possibility of a high personal and financial return is theoretical.

Pharmacologic and surgical interventions receive the most research and media attention as methods to prevent cancer. Approved medications such as tamoxifen (breast cancer), aspirin (breast and colon cancer), celecoxib (colorectal cancer), and finasteride (prostate cancer) have varying degrees of acceptance, in part because of the limited prospective data supporting their use and the somewhat uncertain overall risk-benefit profiles (*16*). Invasive procedures, such as prophylactic mastectomies, have increased in volume in recent years without definitive evidence of cancer-related mortality benefits for the general population (*17*). More prospective studies are warranted to validate these clinical interventions as cost-effective prevention strategies.

Prevention programs are further challenged by fragmented health care services that have been slow to adapt to changing behavioral trends and technology (Table 2) (*2*). In LMICs, approximately 2 million cancer cases per year caused by infectious agents could be prevented through vaccination, improved hygiene, sanitation, and infection treatment protocols (*9*). Health ministries could structure preventative efforts, including vaccination programs, tobacco control legislation, and "junk-food" taxes, in accordance with socioeconomic context, willingness to change, and popula-

Table 2. Prevention program types. The estimated PAF provides an indirect measure of the potential impact for a given prevention program. HPV, human papilloma virus; HCC, hepatocellular carcinoma.

Etiology	Carcinogenic risk factor (associated PAF)	Overall PAF (%)	Risk reduction programs	Key multisectoral partners	Estimated cost-effectiveness
Infectious etiologies	HPV (cervical cancer 90–100%)* Hepatitis B and C (HCC 77%)* *H. pylori* (gastric cancer 75%)*	18	Vaccinations	Health care workers Pharmaceutical companies Legislative bodies	Very cost-effective
Behavioral factors	Tobacco (30%)† Obesity (20%)† Diet (5%)† Alcohol (4%)†	66	Tobacco cessation Exercise programs Public education and outreach	General population (health literacy) Legislative bodies Health care workers	Very cost-effective
Environmental factors	Air pollution Aflatoxins	4	Environmental regulations	Legislative bodies Business sector	Potentially cost-effective
Clinical interventions	Chemoprevention (such as tamoxifen, aspirin, celecoxib, or finasteride) Surgical procedures (such as prophylactic mastectomy or prophylactic oophorectomy)	N/A	Insurance coverage for correctly selected individuals at elevated risk	Health care workers Pharmaceutical companies General population	Cost-effective

*Percentage reflects PAF for a single cancer type (for example, 90 to 100% of cervical cancer can be avoided with universal vaccination). †Percentage reflects PAF for multiple cancer types (for example, reducing obesity can decrease incidence of up to 20% of cancers).

tion health literacy. Multisectoral collaboration and increased public health education are critical to strengthening service delivery and regulatory frameworks, which ultimately could reduce cancer burden at the population level.

One example of prevention is lung cancer, which results in more deaths than any other malignancy (*6*). Prevention through tobacco avoidance remains the most effective intervention, reducing disease burden globally by 70%. The U.S. National Lung Screening Trial demonstrated a 20% mortality benefit for those undergoing three annual CT screenings between 55 and 74 years old (*18*). The cost-effectiveness of CT screening is between International Standard Dollar (ISD) $110,000 to $169,000 per quality-adjusted life year (QALY), which contrasts with a single smoking cessation therapy program with an assumed 1-year 8% abstinence rate, which has a cost-effectiveness of ISD $20,800 to $23,900 per QALY (*19*). Lung cancer treatment, even in maximal resource environments, results in cure for less than 20% as measured with MIR (*6*). Given the high cost and limited efficacy of early detection, lung cancer prevention should remain a global health policy priority. With the aligned support of public health experts, policy-makers, and advocates, the World Health Organization (WHO) Framework Convention on Tobacco Control has successfully shaped effective tobacco prevention programs, allowing for regional adaptation and resulting in successful implementation (*20*).

Early detection. Not all cancers can be prevented. Although tumor cell production may have an inherent stochastic nature relating to the number of cell divisions and biological "bad luck" (*21*), early detection for many cancers can improve outcome by identifying disease at less advanced stages when it is more likely to respond to therapy. The effectiveness of early detection programs is contingent on many of the same processes required for successful prevention programs. The combination of increased health literacy, augmented health service utilization, strengthened public health communication, and improved primary health care access can achieve maximal population coverage. However, for early-detection programs to be ultimately successful in reducing cancer burden in LMICs, they must be linked to accessible and affordable treatments. Although early detection programs require substantial resources to maintain, inaction bears an intangible cost in lost human productivity and lives. If a country's MIR is a reasonable estimate of cancer-specific case-fatality rates, then there is a missed opportunity to cure nearly one in three cancer patients in LMICs (Table 1) (*6*).

Successful early-detection platforms can be divided into two groups: awareness education for early diagnosis (patient-identified cancers) and screening programs (health system–identified cancers). In low-resource settings, early detection is hindered by the lack of knowledge about cancer and the fatalistic belief that it cannot be cured. In sub-Saharan Africa, less than 40% of individuals are aware of cancer as a disease entity, and less than 20% of the at-risk populations know of cancer screening tests that may be available to them (*13*). Awareness campaigns empower the population to understand health concerns and advocate for themselves. Early diagnosis also requires a mature health care system with health care personnel who have been trained to correctly identify cancer symptoms and can provide diagnostic services.

Screening programs can be difficult to develop and may require high levels of investment to maintain. Implementation of screening programs must be commensurate with available human resources and professional

expertise, diagnostic services, and appropriate treatment access. Effective screening programs should reach at least 70% of an at-risk population. These programs demand infrastructure for follow-up and treatment for positively screened patients, and they need quality assurance measurements at each step (*22*, *23*). Screening implementation should minimize the potential harms of overdiagnosis and overtreatment (identification of and therapeutic intervention for cancers that would never cause symptoms during the patient's natural lifetime), which themselves incur personal and financial costs. The complex decision about which early-detection programs should be established and how they will be maintained over time comes from well-informed policy-makers.

An example of a cancer subtype requiring an early detection strategy is breast cancer. Only 21% of breast cancers can be prevented even in the most favorable conditions (*24*). Conversely, early detection and effective treatment of breast cancer have had a more substantial impact on breast cancer survival (*25*). In LMICs, early detection should emphasize breast awareness [cost-effective ratio (CER) of U.S. dollar (USD) $1299 per disability-adjusted life year (DALY)] and clinical breast exam (CER USD $1364 per DALY) resulting in 12 to 55% reduction in breast cancer deaths as initial steps toward the development of resource-appropriate programs (*23*, *26*). The annual expenditure for nationwide screening mammography in one LMIC (Ghana) is approximately USD $800,000 per year per 100,000 women screened, constituting a 1.75% increase in health care cost per capita, which may be prohibitive in financially constrained health care budgets (*26*). Investment in breast cancer control should be directed toward early detection and effective treatment in a resource-stratified manner as outlined by the Breast Health Global Initiative (*23*).

INTEGRATION OF CARE

Resources are most effective when distributed in ways that strengthen the entire health system, integrating cancer care with the management of other diseases to avoid service duplication (*7*). Cancer prevention and early detection can improve cancer outcomes while also strengthening larger health networks for better management of other chronic diseases in the NCD framework. Prevention requires health education and empowerment; media campaigns can drive legislative reform and also communicate key awareness messages to strengthen early detection. Screening mandates a strong primary care network, which strengthens health care delivery across the board.

Diagonal integration models emphasize coordinated development of programs, collective action, and collaboration between the cancer community and other disease-specific groups (*12*). Close integration between cancer, other NCDs, and communicable diseases can achieve realistic goals during a patient's lifetime by augmenting health system capacity across disease spectrums. Existing platforms in areas where infectious diseases are endemic can be leveraged to provide the framework for prevention (for example, vaccinations) and early detection (for example, use of community health workers and health screening with history and physical exam). To manage the growing and complex disease burden, services for NCDs must be integrated, must have multisectoral involvement, and must be designed according to local resource availability.

Health program planning that only prioritizes isolated short-term projects to validate outcomes may overlook the benefits of prevention and early-detection programs. Program longevity depends on its integration within a larger health system to secure long-term funding, collaboration across all sectors, and sustainability. Quality assurance assessments and continuous quality improvement are necessities to yield wide-scale implementation success. The early integration of successful pilot projects by using multisectoral partnerships to facilitate scaling-up can help mitigate these substantial challenges.

A graduated resource-stratified national cancer control plan can be designed to prioritize programs and ensure integration of prevention and early detection. For example, at the primary care level, low-cost, high-impact programs should be developed, such as strengthening vaccination services and providing training to health care personnel on early cancer signs and symptoms. Ministry of Health efforts can be made to develop cancer registries and referral networks while promoting WHO Framework Convention on Tobacco Control and vaccination programs as legislative maneuvers (*20*). These coordinated interventions can strengthen national comprehensive cancer care by laying the framework for prevention and early-detection services linked to the capacity to diagnose and treat disease.

WHAT DOES THE FUTURE HOLD?

As life expectancy has been increasing globally, there has been an epidemiologic transition away from risk factors for childhood communicable disease toward risk factors for NCDs (*1*). This resultant shift requires investments to be made more broadly in health systems, rather than siloed disease-specific models that may be more prevalent among communicable disease management programs. Investment in human resources, an integral part of early detection and treatment, is an important next step given the deficits in trained health care providers.

Scientific advancements from genetics and molecular epidemiology combined with novel diagnostic tools are likely to usher in a new era of prevention and early-detection strategies. The future is ripe with opportunities to prevent and detect cancer at the earliest stages. The human papillomavirus (HPV) vaccine has appropriately shifted the emphasis on cervical cancer care toward prevention; however, novel methods for cervical cancer remain relevant to the millions of women who remain at risk for cervical cancer and are being effectively introduced into LMICs.

Programs should build on existing capacities and infrastructures, generate investments from key stakeholders, and identify barriers to effective implementation. A successfully implemented cancer control plan can reduce the burden of cancer and other NCDs, especially if progress is monitored with appropriate metrics and outcomes are evaluated and fed back into adaptively redesigning the programs, sustaining health benefits for future generations.

Moving forward, we should not allow a schism to form between prevention and early detection in cancer care prioritization; quite the opposite, our objective should be the promotion of an integrated framework for cancer control interventions, recognizing that systems for both prevention and early detection are needed globally. The history of public health has shown that when programs are developed in isolation for complex problems, the outcomes are not durable. Cancer, like HIV/AIDS and countless other disease processes, requires prevention, early diagnosis, treatment, and palliation for comprehensive, patient-centered control. It takes coordinated action on the individual and population level to succeed—that is our call to action.

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