

# High-burden Cancers in Middle-income Countries: A Review of Prevention and Early Detection Strategies Targeting At-risk Populations



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## ABSTRACT

Cancer incidence is rising in low- and especially middle-income countries (MIC), driven primarily by four high-burden cancers (breast, cervix, lung, colorectal). By 2030, more than two-thirds of all cancer deaths will occur in MICs. Prevention and early detection are required alongside efforts to improve access to cancer treatment. Successful strategies for decreasing cancer mortality in high-income countries are not always effective, feasible or affordable in other countries. In this review, we evaluate strategies for prevention and early detection of breast, cervix, lung, and colorectal cancers, focusing on modifiable risk factors and high-risk subpopulations. Tobacco taxation, human papilloma virus vaccination, cervical

cancer screen-and-treat strategies, and efforts to reduce patient and health system-related delays in the early detection of breast and colorectal cancer represent the highest yield strategies for advancing cancer control in many MICs. An initial focus on high-risk populations is appropriate, with increasing population coverage as resources allow. These strategies can deliver significant cancer mortality gains, and serve as a foundation from which countries can develop comprehensive cancer control programs. Investment in national cancer surveillance infrastructure is needed; the absence of national cancer data to identify at-risk groups remains a barrier to the development of context-specific cancer control strategies.

## Introduction

Cancer incidence and mortality are rapidly increasing in low- and especially middle-income countries (MIC), where 75% of global cancer deaths are projected to occur by 2030 (1, 2). Middle-income economies are defined by the World Bank as those in which the gross national income per capita is between \$1,036–12,535 per year (3). They are further subdivided into lower-middle-income (GNI \$1,036–4045) and upper-middle-income (GNI \$4046–12,535) groupings. While countries classified as middle-income economies are highly diverse, they face some common challenges in cancer control.

Economic evaluation suggests most MICs have the financial resources to deliver a basic set of cancer services tailored to domestic health budgets and cancer burden (4).

Rising cancer incidence in MICs has been attributed to population growth, increases in life expectancy and social and economic transitions which are changing the prevalence of major known risk factors for cancer (5). Two defining features of cancer in MICs are the advanced stage of presentation and the high stage-adjusted mortality rate relative to incidence (i.e., case fatality rate; refs. 1, 6, 7). Globally, survival after a cancer diagnosis is highest among women living in the world's wealthiest countries, with an overall incidence to mortality ratio of 0.31, and lowest among males in the poorest regions, with an incidence to mortality ratio of 0.77 (1). Even for cancers associated with the most favourable outcomes, wide discrepancies in survival between countries remain. In the United States, 5-year unadjusted overall survival for breast cancer is 90.2%, compared with only 66% in India and less than 44% in Nigeria (8).

The implementation of population-based cancer prevention, screening and early detection strategies in high-income countries (HIC) over the past 30 years has led to decreases in cancer mortality rates for common cancers including breast (9), cervical (10), prostate (11), colorectal (12), and liver cancer (13). Between 1975 and 2000, earlier detection of breast cancer accounted for almost half of the reduction in breast cancer mortality in the United States, with the remainder due to advances in treatment (9). Similarly, greater than 50% of the

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decrease in colorectal mortality over the same period in the United States is attributed to greater acceptance and uptake of colorectal cancer screening (12). Many preventative and early detection strategies have not yet been evaluated in MICs (4, 14). Population-based screening strategies that have been credited with reducing cancer incidence and mortality in HICs may not yet be effective, feasible, or affordable in many MICs (15). Finally, the ability of screening and early detection policy to improve cancer-specific outcomes is contingent on access to effective treatment. Without addressing inequities in access to multimodal cancer care the potential gains of early detection are significantly curtailed (14, 16). Focusing prevention and early detection efforts initially on high-risk individuals and groups, may allow for targeted risk reduction and stage shifting (17–19), as well as provide an entry point from which countries can develop more comprehensive cancer control programs.

This review explores the opportunities and challenges in the prevention and early detection of breast, cervical, lung, and colorectal cancer, which represent the highest burden cancers (Table 1) in MIC (2). Identifying evidence-based, cost-effective strategies that can be tailored to local resources and system constraints will be critical for reducing the wide gap in cancer outcomes that currently exists between the most developed countries and the rest of the world.

## Improved Cancer Surveillance

Cancer surveillance is the foundation upon which cancer control efforts, including prevention and early detection

**Table 1.** The four highest burden cancers in MICs, 2020.

	Total new cases	Total deaths
Breast	433,060	202,463
Cervical	236,828	189,230
Lung	210,541	146,198
Colorectal	194,954	112,556
<b>All cancers</b>	<b>3,099,791</b>	<b>1,982,660</b>

Source: GLOBOCAN 2020, International Agency for Research in Cancer (107). Note: Estimates of absolute cancer burden in 2020 across 36 cancer sites in 185 countries or territories is built up in GLOBOCAN using the best available sources of cancer incidence and mortality data within a given country; therefore, validity of the national estimates depends on the degree of representativeness and the quality of source information. Middle-income countries (MICs), as defined by the World Bank Income Group Classification 2020, are: Angola, Algeria, Bangladesh, Benin, Bhutan, Bolivia, Cabo Verde, Cambodia, Cameroon, Comoros, Congo, Rep., Cote d'Ivoire, Djibouti, Egypt, El Salvador, Eswatini, Ghana, Honduras, India, Kenya, Kiribati, Kyrgyz Republic, Lao PDR, Lesotho, Mauritania, Federated States of Micronesia, Moldova, Morocco, Myanmar, Nepal, Nicaragua, Nigeria, Pakistan, Papua New Guinea, Philippines, Sao Tome and Principe, Senegal, Solomon Islands, Sri Lanka, Tanzania, Timor-Leste, Tunisia, Ukraine, Uzbekistan, Vanuatu, Vietnam, West Bank and Gaza, Zambia, Zimbabwe, Albania, American Samoa, Argentina, Armenia, Azerbaijan, Belarus, Bosnia and Herzegovina, Botswana, Brazil, Bulgaria, China, Colombia, Costa Rica, Cuba, Dominica, Dominican Republic, Equatorial Guinea, Ecuador, Fiji, Gabon, Georgia, Grenada, Guatemala, Guyana, Indonesia, Islamic Republic of Iran, Iraq, Jamaica, Kazakhstan, Kosovo, Lebanon, Libya, Malaysia, Maldives, Marshall Islands, Mexico, Montenegro, Namibia, North Macedonia, Paraguay, Peru, Russian Federation, Samoa, Serbia, South Africa, St. Lucia, St Vincent and the Grenadines, Suriname, Thailand, Tonga, Turkey, Turkmenistan, Tuvalu, Venezuela.

strategies, are developed. Cancer risk factors, incidence, mortality, stage of presentation, and outcomes following treatment are poorly characterized or absent in most MICs (20, 21). Population coverage with cancer registries is low in South America (19% of total population covered by a registry), Asia (15%), and Africa (13%), and sampling is predominantly subnational, urban-biased and of variable quality (1, 22). Only one of five countries globally report cancer data of sufficient quality to determine incidence estimates (1, 21). In a recent systematic review on the stage of diagnosis of breast cancer in sub-Saharan Africa (SSA), only one country (i.e., South Africa) had national data on the stage of presentation (23).

The World Health Organization (WHO) lists cancer monitoring through the use of population-based cancer registries as part of its Essential Cancer Package (24). To support lower-middle-income countries (LMIC) develop and improve their cancer surveillance capacity, the International Association for Research on Cancer leads the Global Initiative for Cancer Registry Development (GICR; ref. 25). The GICR provides technical training and support for new population-based cancer registries (PBCR) and has developed open source software (CanReg5) in seven languages to support cancer registry data entry, maintenance, and analysis (26). The GICR regional hub for SSA is administered by the African Cancer Registry Network, which includes 30 members across 19 countries (27). The annual costs of maintaining a registry are estimated at \$USD0.01–USD0.22 per person in the population covered by the registry (25, 28), with incidence data becoming available within 2 years of a registry's establishment (26), making PBCRs a low cost, high value cancer control investment. Despite this, registry development remains underutilized as a cancer control strategy in many countries (25).

## Modifiable Risk Factors As Targets for Prevention Strategies

Countries with limited or modest per-capita health spending often allocate most of their cancer resources to therapeutic care, despite the cost-effectiveness of prevention and early detection (29). Major long-term gains in cancer control for MICs can be achieved at relatively low cost by strengthening prevention strategies for modifiable cancer risk factors (4), which cause half of all cancers worldwide (22). The relative importance of a particular risk factor varies with geography, demography, and development status (5). The Global Burden of Disease consortium identified six broad drivers of cancer incidence in MICs: population growth, population age structures, exposure to environmental risks (e.g., air quality, UV radiation, aflatoxins), shifting behavioral risks (e.g., tobacco, alcohol, sexually transmitted infection, fertility patterns, exercise), new metabolic risks (diet, obesity), and changes due to all other factors (30).

Tobacco use remains the leading preventable cause of cancer worldwide. Smoking prevalence is declining globally, but at a slower rate in both LICs and MICs (5, 22). Strategies aimed at

tobacco cessation and prevention of initiation can have sizeable health and cancer impacts, and achieve relatively quick health gains. Around 90% of the cancer-related risks of smoking can be averted if people quit before the age of 40 years, but unlike in HICs most adults in MICs will only quit after developing cancer and not while healthy (4). The most effective tobacco control strategy for countries at all stages of development is taxation, specifically high excise taxes on tobacco products which promote adult cessation and reduce youth initiation rates. This is especially effective among lower-income and younger populations who are more price sensitive. The Philippines substantially increased excise taxes on tobacco in 2012. Smoking prevalence subsequently fell sharply, with an estimated 3 million fewer smokers 3 years after the law took effect. The greatest declines were seen among the poorest households (31). Furthermore, 80% of the tax revenue generated from this legislation was channeled back into the health budget, allowing the government to increase health insurance coverage to 25 million poor and elderly households (32). Although 168 countries encompassing 90% of the world's population are signatories to the WHO Framework Convention on Tobacco Control (33), which includes price and tax measures to reduce demand for tobacco, excise tobacco taxes are still underutilized in many countries as a primary prevention tool for cancer (and many other noncommunicable diseases; ref. 4).

Infection-related cancers, including human papilloma virus (HPV)-related cancers, hepatitis B virus (HBV), and hepatitis C virus (HCV) associated liver cancer, *H. pylori*-associated gastric cancer and HIV-associated Kaposi sarcoma, comprise a significant proportion of the total cancer burden in many LMICs (22, 34). In SSA, infection-related cancers accounted for approximately 28% of all new cancers in 2018, and as many as 50% of new cancers in East African countries (34–36). Vaccination against HBV infection represents one of the major cancer success stories of the past 30 years. Primary prevention of chronic HBV infection through vaccination is now delivered in 183 countries as part of routine childhood vaccination, with 81% global coverage. In lower-income countries HBV vaccination programs are supported by the Global Alliance for Vaccines Initiatives (GAVI; ref. 37). The success of this program has set the stage for vaccination research and development for other infection-related cancers, most notably HPV-related cervical cancer.

The development of a vaccine against high-risk HPV genotypes offers a highly effective primary prevention strategy for cervical cancer, one of the leading causes of cancer mortality among women in LMICs, as well as for HPV-related oral, throat, penile and anal cancers. HPV infection is common among young, sexually active individuals and usually clears without treatment. However persistent HPV infection with the high-risk oncogenic subtypes 16 and 18 accounts for 70% of all cervical cancer cases. Population-level coverage  $\geq 70\%$  of girls ages 9–12 years is considered the most cost-effective strategy for cervical cancer prevention at all development levels (38, 39), and is included in the WHO and Disease Control Priorities

Essential Cancer Packages (4, 24). Current commercially available HPV vaccinations require 2–3 doses over 6–12 months and a temperature-controlled supply chain. This poses a challenge in many LMICs where platforms for reaching and following up adolescents are not well developed and the infrastructure needed to ensure a cold chain is often absent. Moreover, the cultural acceptance of vaccination against sexually-transmitted infection for adolescent girls can be variable, with vaccine acceptability (among parents for their daughters) in SSA countries ranging from 59%–100% in systematic reviews (40).

Delivery of the HPV vaccine to girls in both LICs and MICs with high coverage rates is possible (41). HPV vaccination program coverage in 2019 was  $\geq 90\%$  for two doses in Turkmenistan, Mexico, and Rwanda, and a further 10 MICs have achieved  $\geq 90\%$  coverage for the first dose (41). Cost remains a major barrier to adoption of the HPV vaccine in MICs, particularly those that do not qualify as GAVI eligible (most MICs; refs. 38, 39). Further efforts to improve uptake and coverage in both LICs and MICs must focus on price reduction and programmatic infrastructure, which may be best achieved by embedding HPV vaccination within a platform of adolescent health interventions. Most of the mortality gains from both HPV vaccination will not be realized until the second half of the century (4), given the lag time between vaccination, infection and development or prevention of related cancers. Screening and early detection strategies among individuals at high risk for HPV-related cancer need to be developed alongside vaccination programs to meet country-level and global targets for cervical cancer reductions (42).

As countries transition from a disease burden primarily composed of communicable to noncommunicable diseases, infection-related cancers typically fall, and cancers associated with tobacco, alcohol, diet, and a lack of exercise begin to dominate (35). The relative contribution of these risk factors to the development of breast and colorectal cancer in particular is poorly understood in MICs (5). For example, delayed child-bearing and use of hormone replacement therapy are associated with breast cancer risk in HICs (43, 44). These risk factors have a synergistic effect with elevated BMI, inadequate exercise, and excessive alcohol consumption, but a smaller effect on overall risk compared with genetic and familial risks (44). The effect and relative contribution of these risk factors to breast cancer in LICs and MICs is poorly established (35). Some hormonal risk factors for breast cancer, such as delayed child bearing and age at menarche, are associated with positive development outcomes including access to education for women, and improved nutrition status, and reversing these changes is not desirable. Breast cancer prevention should therefore focus on identifying modifiable risk factors relevant to the local and regional context (45).

In colorectal cancer, well-established dietary risk factors, such as high intake of red and processed meat and low intake of fiber, account for an estimated 5% of cancer deaths worldwide (36, 46). The strength of the association between diet and

colorectal cancer varies by study type, sex, and the timing of dietary exposure across the life course (36). The contribution of these dietary changes to the rising rate of colorectal cancer in MICs is unclear. Large case-control studies are lacking and there is a paucity of data in emerging economies that clearly link diet to cancer risk. Moreover, changing dietary patterns are often accompanied by other major lifestyle changes. The interaction of diet with the colonic microbiome is an area of active research. Following diet exchange, colorectal cancer-associated microbiome changes have been documented in rural SSA (47). However, this has not yet translated into clinically relevant targets (e.g., identification of a higher risk groups for screening).

## Detecting Precancerous Lesions and Asymptomatic Cancers Via Screening

Detection of asymptomatic cancer or precancerous lesions through screening allows for the detection of disease at an earlier stage, when curative treatment is more likely (15, 48). Given the excess burden of advanced-stage disease, many MICs are considering the role of screening within national cancer control plans (48). Screening also features prominently in the 2017 WHO Resolution on Cancer Prevention and Control, which called upon all member states to develop, implement, and monitor programmes for screening, where feasible and cost-effective (49). Organized screening, which defines a targeted population for screening and systematically invites all eligible members of the population to participate, has led to proven mortality reductions for cervical cancer (using cytology-based screening), breast cancer (mammography), and colorectal cancer (stool-based screening and/or colonoscopy) in HICs. Opportunistic screening, or case finding, is provider or patient-driven and occurs on an as-needed basis and typically within the context of national screening guidelines (15).

Population-based screening requires high levels of coverage to be effective, is expensive and can rapidly deplete cancer-focused resources in countries with limited per-capita health spending (4). Delivery of screening programs requires a complete diagnostic and treatment referral pathway to be in place and accessible by those being screened, to realize the potential benefits of early detection. This represents a major barrier to implementing organized screening in many MICs, where health system infrastructure and supporting processes are still developing (15). A country's health system must first be able to manage symptomatic cancers. The processes of designing and implementing a national screening programme in MICs is beyond the scope of this review but is well described elsewhere (48).

One approach for MICs that are committed to building cancer screening programs, is to start by targeting high-risk individuals (15, 48). However, defining and capturing high-risk individuals for targeted cancer screening in MICs can be challenging. Traditional models have often relied on the

identification of at-risk populations based on a single demographic, environmental or genetic risk factor (e.g., HPV infection and cervical cancer). A greater understanding of country-specific cancer risk factors and risk factor interactions is needed to allow for the creation of predictive models (50). The use of existing health care platforms or programs, for example, those focused on child and maternal health or infectious diseases, to deliver opportunistic cancer screening (e.g., cervical cancer screening) to at risk populations has been successful in Zambia, Tanzania, and Botswana (51). However, these programs often do not reach all eligible individuals and may exacerbate existing inequities in access to care (48).

Cervical cancer screening is the most established form of cancer screening in LMICs and is well supported by population-based studies and randomized controlled trials. In both LICs and MICs screening using cytology, as is done in HICs, is being displaced by HPV testing as a primary screening technology (38). HPV testing represents a more feasible, cost-effective approach, with better sensitivity than cytology and fewer rounds of screening required to achieve comparable mortality reductions (52). A large randomized trial in rural India (53) demonstrated that a single round of HPV screening in women ages 30–59 years reduces advanced cervical cancer incidence and mortality. Another randomized trial in Tamil Nadu, India documented a 35% reduction in cervical cancer mortality after screening with visual inspection with acetic acid (54).

The WHO cervical cancer elimination strategy calls for cervical screening at 35 and 45 years of age for 70% of the eligible population in LMICs by 2030. It is estimated that this will reduce mortality by 34% (23%–38%; ref. 55). Currently, cervical cancer screening in MICs falls well short of this target. In a study of 55 LMICs (of which 53 were MICs), the median lifetime prevalence of self-reported cervical cancer screening (i.e., cytology or HPV-based) was 43% (range, 0.3%–97%; ref. 56). Attempts to increase opportunistic screening (e.g., during antenatal care) and targeted screening of those at highest risk for HPV-related cancer are strategies that can increase coverage in the absence of an organized screening program. The use of mobile Health technology including text message reminders and social media campaigns targeted to higher risk women have also been employed in some countries (57), with small studies suggesting improvement in uptake and follow-up (58).

Women with HIV, especially those with low CD4 counts, are at the highest risk for persistent HPV infection and progression to cervical cancer (59) and are one well-defined high-risk population that benefit from short-interval targeted screening in all countries (29). HPV testing or VIA can be delivered by leveraging existing HIV infrastructure and programs, something Zambia has been doing since 2006 via its Cervical Cancer Prevention Program (Table 2; ref. 60). Smoking tobacco is another major risk factor for the development of cervical cancer and should be included in risk prediction models. A recent meta-model using data from China identified 17 risk factors for

**Table 2.** Prevention and early detection of high burden cancers in MICs: examples of feasible, cost-effective, interventions, target population, health system delivery level and country case examples.

	Target population	Delivery level	Country Examples
<b>Improved cancer surveillance in MICs</b>			
Population-based cancer registries	All cancer cases in a defined population catchment area	National and subnational level, with central coordination	Zimbabwe National Cancer Registry, Kampala Cancer Registry (subnational) (34)
Participation in epidemiologic and clinical studies of cancer risk factors	General population in LMICs	Community-based research	H3 Africa consortium on molecular epidemiology and risk factors for NCDs (108)
<b>Prevention of modifiable risk factors</b>			
Tobacco taxation	General population, current and potential future tobacco users	National, through legislation increasing excise taxes on tobacco	Philippines—introduction of high excise tobacco taxes in 2012 led to an estimated 3 million fewer smokers within 3 years (31)
HPV vaccination	Girls ages 9–12 years	Primary care/community based  School based for those enrolled	A number of MICs including Zambia and Ethiopia have introduced community and school-based HPV vaccination program over the past 10 years, achieving >90% coverage (109)
<b>Targeted and opportunistic cancer screening</b>			
POC diagnostics: HPV testing	Sexually active women, with focus on high-risk subpopulations: HIV(+), sex workers, tobacco users	Primary care or community based	Argentina—used an existing network of trained CHWs to implement self-collection HPV tests among high-risk groups to increase coverage 4-fold (110)
Screen & treat: VIA + HPV testing	As above	Primary care or community based	Zambia: since 2006 Zambia has used its HIV program infrastructure to introduce the Cervical Cancer Prevention Program, a nurse driven screen and treat program which initially focused on women with HIV and later expanded coverage to other women, reaching 58,000 women within its first 5 years (60)
Clinical breast examination (conditional recommendation)	Women ages 30 years+	Primary care or community based	Malawi—delivery of CBE through trained lay women, implemented in primary care health clinics among women presenting for reasons other than a breast concern (70)
Familial/hereditary risk stratification	First-degree relatives of patients with breast, colorectal cancers	Primary care (family history screening tools), secondary/tertiary care (familial cancer registries, kindred studies)	Nigeria—first-degree relative (FDR) registry maintained within African Research Group for Oncology's multi-site hospital-based colorectal cancer registry. FDRs in registry invited to participate in high-risk screening studies (111)
<b>Earlier detection of symptomatic cancers</b>			
Risk stratification tools	Symptomatic patients on first contact with health provider	Primary care	Nigeria—development of a cardinal symptoms tool for colorectal cancer, to prompt referral for further investigation of symptoms (92)
Public awareness campaigns	General population	Community based	Rwanda (a LIC) introduced a public awareness campaign for women's cancers in 2020 as part of its National Cancer Control Plan (112)
Provider education	Community health workers, primary care	Community health and primary care facilities	Peru: Community-based Program for Breast Health, a collaboration between PATH, the Peruvian Ministry of Health, the National Cancer Institute (Lima), and the Regional Cancer Institute (Trujillo). Phased implementation of public and primary care provider education on breast cancer diagnosis improved capacity for early diagnosis among first-level health workers (113)
POC diagnostics	Symptomatic patients presenting to primary care or a first-level hospital	All levels of the health system but targeted at primary care, first-level hospitals without advanced imaging and pathology capacity	Nigeria—prospective evaluation of urine-based POC testing for colorectal cancer using metabolomics (114)

Brazil has undergone significant demographic, social, and economic transitions over the past 30 years and is now an upper middle-income country, though considerable subnational inequity exists in health and socioeconomic indices. It has also experienced an epidemiologic transition with a marked increase in breast cancer incidence from an age-standardized rate of 54.7 (95% UI, 45.5–60.3) per 100,000 in 1990 to 74.0 (95% UI, 61.9–85.86) in 2015.<sup>115</sup> Breast cancer screening using clinical breast exam and biennial mammography for women ages 50–69 years was recommended by the Ministry of Health in Brazil for the first time in 2004 as part of a policy aimed at earlier detection of breast cancer. This policy was supported by cost-effectiveness analysis demonstrating favourable cost-effectiveness ratios for cities and states in Brazil with average or above average breast cancer incidence rates.<sup>116</sup> Evaluating the implementation, uptake, and impact of the Brazilian breast cancer screening policy may have valuable lessons for other countries at similar stages of economic growth and health system development.

The Brazilian National Health Service (SUS) is the sole provider of health care coverage for a majority (~70%) of the Brazilian population. A significant increase in breast cancer screening coverage under the SUS occurred in the first 5 years after the policy took effect, but with wide variation across regions and states. More recently screening coverage under the SUS has stabilized nationally at ~24.2% (from 14% in 2008) with wide subnational variation persisting.<sup>117</sup> Despite the modest increase in screening coverage, a national hospital-based registry study evaluating stage of presentation over the 10 years following the introduction of the policy showed no change in the stage of presentation of breast cancer, with the incidence of late stage breast cancer remaining constant at around 40% of new presentations per year.<sup>63</sup> Although the overall breast cancer mortality rate and the population-based mortality to incidence ratio fell during that same period, improvements in mortality may have been driven by access to better treatment rather than by down staging as a result of screening. Population wide implementation appears to have been the major barrier to greater screening coverage. Although the 2004 Ministry of Health recommendation was for population based screening, implementation was opportunistic only.<sup>117</sup> Critically, follow up after the detection of a lesion suspicious for cancer on screening mammography was very low - only 27% for women ages 50–59 years and 63% for those ages 60–69 years - which limits the potential for down staging despite earlier detection.<sup>63</sup> Furthermore over half of all women with breast cancer over the study time period were diagnosed outside the target screening age, reflecting the importance of choosing screening age groups that reflect local demography and epidemiology, rather than those validated in high-income countries with older populations. However, a separate state level analysis of the impact of opportunistic mammography in Sao Paulo did suggest downstaging following the introduction of the policy in the state, which may reflect state-level differences in access to screening, breast cancer incidence and diagnostic and treatment infrastructure.<sup>118</sup>

**Figure 1.**

Mammographic screening for breast cancer in MICs: lessons learned from Brazil.

cervical cancer for inclusion in a clinical predictive model to guide screening for individual patients that may be more generalizable to other MIC settings than predictive models from HICs (50).

The rising incidence of breast cancer in MICs has focused attention on the role of early detection and screening in nascent cancer care systems. Clinicians, policy-makers, and patients are increasingly aware of the excess mortality associated with advanced stage of presentation and the relative success of mammography-based screening in reducing mortality in HICs (61). Earlier detection, timely referral, and treatment of symptomatic breast cancer should be considered a prerequisite to screening in all countries and should be prioritized over efforts to introduce screening programs (62). Even in the presence of robust cancer diagnostic and treatment services, the overall incidence of breast cancer is still lower in MICs than in HICs, which can significantly modify the cost-benefit and benefit-to-harm ratio for screening (15).

Existing data from MICs do not support a role for breast cancer screening in reducing cancer-specific survival or overall mortality with either clinical breast exam (CBE) or mammography (15). The impact of organized or opportunistic breast cancer screening on clinical stage shifting (which may represent an earlier surrogate for survival in the presence of appropriate treatment), in LMICs is mixed. A recent national population-based analysis from Brazil did not show a measurable impact on the incidence of late-stage breast cancer ten years after the introduction of a policy recommending

mammographic screening for women ages 50–69 years, which may be explained by low coverage rates, inequitable access and low follow-up after a concerning screening finding (63). These experiences are explored in **Fig. 1**. Measurable success in stage shifting has been reported with opportunistic mammography-based screening in postmenopausal women in Malaysia, an upper MIC, although this program has yet to demonstrate a positive impact on overall mortality (64). Mammography also requires specialized imaging infrastructure and its utility as a screening modality is dependent on image quality and interpretation (4). Thus, mammographic screening has not been shown to be cost-effective in LMICs or low-income countries, and is supported by only weak economic data in select upper MICs (65, 66).

CBE is a universal tool in breast cancer detection and surveillance. In most HICs, it is no longer recommended as a screening modality but used as an adjunct in diagnosis and surveillance. However, in countries where mammography-based screening is not available, CBE continues to be investigated as a primary screening modality (15, 67). Two large cluster randomized trials in India (68) are currently evaluating CBE performed by trained primary health workers compared with breast cancer awareness education alone (15). Recent results from the Mumbai trial demonstrated that CBE led to a nonsignificant 15% reduction in breast cancer mortality overall, but a significant reduction in women ages >50 (69). Estimates of CBE specificity in a screening setting are also

needed, as smaller observational studies suggest highly variable performance, which may place an unmanageable burden on diagnostic facilities (70). A recent economic analysis of screening modalities for breast cancer outside of HICs concluded that both the evidence base for recommending mammography or CBE, and defining at-risk populations for targeted screening is limited and of low quality (66). In the absence of high-quality experimental evidence, opportunistic screening with CBE by trained primary or community health workers has been conditionally recommended by the Breast Health Global Initiative where mammography is not feasible (62). The WHO has advocated for a focus on earlier detection of symptomatic cancers rather than the introduction of resource-intensive screening in the absence of a strong health system (16, 67).

The Disease Control Priorities (DCP) Network, which synthesizes evidence on the cost-effectiveness and feasibility of interventions for high burden cancers in LMICs have made several recommendations on screening. Only opportunistic and targeted high-risk cervical cancer screening is considered to meet the criteria for inclusion in the DCP “best buy” interventions for essential cancer care (4). CBE by trained health workers may be a viable option in MICs but a lack of high-quality longer-term evidence of its impact prevented its inclusion within the essential package. Interestingly, even where targeted screening of at-risk groups has been offered in MICs uptake is often low, and patient follow-up after a suspicious screening finding variable (67). A systematic review suggested that a lack of knowledge about cancer and an understanding of the role of screening in early detection and cure were the key barriers to participation (71). This reinforces the need for education and public awareness as a core tenant of cancer control efforts and should be viewed as a prerequisite for the adoption of screening policy or programs.

## Genetic Risk Factors and Targeted Screening/Early Detection

Identification of individuals and families at high risk for cancer based on familial and hereditary risk factors offers the opportunity for targeted screening and early detection. Very little is known about the proportion of common cancers with a hereditary basis in MICs and across geographic regions owing to a lack of cancer registry data, challenges with obtaining family histories and cause of death. For patients who present with clinical risk factors for a heritable syndrome, there is a dearth of affordable genetic testing, counselling, and follow-up (72). Although hereditary causes are likely to constitute only a small proportion of total cancer cases in MICs, genetic mutations associated with cancer syndromes (e.g., BRCA1/2) confer some of the highest lifetime risks for the development of cancer. Identification of patients and first-degree relatives at risk through clinical criteria, or where feasible genetic testing, would facilitate opportunities for targeted screening and early detection. With decreasing costs, multigene panel testing (e.g., for BRCA1/2, CHEK2, ATM, PALB2) is a cost-effective strat-

egy in high-income countries compared with genetic testing for BRCA1/BRCA2 alone (73), but the cost and availability of next-generation sequencing and gene panel testing remains prohibitively expensive in many LMICs (72, 74, 75). Development of locally validated risk assessment tools for identifying patients who should undergo further genetic testing is needed alongside increased access to genetic services. This will require strengthening public and private capacity for genetic and molecular analyses. Building that capacity in parallel with cancer registries may be an actionable starting point. In Malaysia, offering BRCA mutation testing to patients with early-stage breast cancer with risk factors on a locally validated risk assessment tool has been shown to be cost-effective compared with routine clinical screening (76). However, without a substantial price adjustment, BRCA testing is out of reach for most patients in lower-middle and low-income countries. For this reason, the Breast Health Global Initiative, which provides resource-stratified guidelines for breast cancer, recommends BRCA testing only in maximally resourced settings (77).

Hereditary and familial risk factors are more common in colorectal cancer than in breast and cervical cancer. The prevalence and penetrance of hereditary colorectal cancer syndromes (e.g., Lynch syndrome) are again poorly characterized in most MICs. A multi-center study from Nigeria demonstrated a higher proportion of microsatellite instability (i.e., 28%) and a lower rate of APC mutation in microsatellite stable disease compared with contemporary series from high-income countries. Unique germline risk loci have also recently been identified for patients with colorectal cancer in East Asia compared with European patients with colorectal cancer, suggesting hereditary and familial risks may vary across racial, ethnic, and geographic regions (78). Translating these findings into clinical risk stratification tools will require a greater emphasis on cancer registry development and case-control studies that incorporate family history, molecular epidemiology, and evaluation of targeted screening strategies that include first-degree relatives in MICs (79).

## Earlier Diagnosis of Symptomatic Cancers

Delays in receiving cancer care have been described at three points: delays in seeking care, delays in reaching care, and delays in receiving appropriate diagnosis and treatment. Many factors contribute to delays in seeking care (the time from recognizing a symptom to seeking health care for it)—including health literacy, fear, stigma, financial, and geographic barriers (80–83). These are well covered in other reviews (84). Delays in diagnosis following initial symptomatic presentation to a health provider can also significantly impact cancer outcomes.

Diagnostic delays (i.e., from first consultation with a health provider to diagnosis) have consistently been reported as the greatest contributor to overall delays for breast cancer in MICs (85–88). In studies from Brazil and Mexico, the average

delay between symptomatic presentation to a doctor, and a diagnosis of breast cancer was 6–7 months (86, 87). Delays in histologic diagnosis after biopsy explained up to 3–4 months of this delay. Referral delays were longer in patients presenting with earlier stages of disease. In India, a mean delay of 2 months was seen after first presentation with symptomatic locally advanced breast cancer, with greater delays reported by patients from rural areas, lower education level, and those who had consulted an unregistered traditional medicine provider first (86). Several opportunities exist for reducing diagnostic delays in symptomatic individuals in MICs, and are summarized in **Table 2**.

Clinical stage shifting through the earlier diagnosis of symptomatic cancers in MICs has received far less attention than asymptomatic screening in the literature and policy discourse. However, delays in diagnosis following presentation to a health care provider with cancer-specific symptoms represents a considerable opportunity for improvement within existing systems of care. Strategies to improve early detection for cervical, breast, and colorectal cancer have been shown to be cost-effective in upper and lower MICs, comparable with other commonly funded public health interventions (4), and associated with sizeable mortality reduction (17, 42, 89). For example, it is estimated that approximately 1/3 of all breast cancer deaths in SSA in the next decade could be prevented through earlier detection and improved access to treatment (89). In MICs, the estimated marginal costs of a package of interventions aimed at earlier detection and treatment of breast cancer ranges from \$USD0.43–\$1.29 per capita, and \$USD0.29–0.87 per capita for cervical cancer (4).

Not all patients that present with symptoms of cancer will have advanced disease. Symptomatic presentations with a palpable mass in breast cancer or rectal bleeding in colorectal cancer are common in earlier stage disease. Promoting awareness and recognition of cancer presentations at the time of first contact with a health provider—usually at a community or primary care level—and then ensuring appropriate and timely referral represents a tangible means for reducing supply side delays. This requires provider education of “red flag” symptoms for common, high burden cancers. National and subnational data on demographic, familial and environmental risk factors that increase the pre-test probability of a cancer diagnosis are needed in many MICs to better inform provider education efforts. For example, colorectal cancer presents at a younger age than in HICs, increasing the probability that rectal bleeding in a younger patient is not from benign causes. The development of referral guidelines can support appropriate and timely investigation and referral of symptomatic patients, while minimizing unnecessary resource utilization. Patient navigation services are still rare in MICs, and almost exclusively based in tertiary referral centers where they have been used to facilitate linkages with follow-up services, provide counselling, coordinate appointments, and maintain communication with patients and families (90, 91). Expansion of these concepts into community and first referral sites may mitigate early delays and

loss to follow-up prior to a definitive diagnosis and serve to support patients through their cancer diagnosis and treatment journey.

The development of simple risk stratification models based on patients’ clinical symptoms may assist in earlier detection of colorectal cancer at the primary care level in MICs. The combination of self-reported rectal bleeding with change in bowel habit and/or weight loss predicted the likelihood of colorectal cancer in a Nigerian cohort of patients whose presenting complaint was rectal bleeding (92). In countries with scarce endoscopy capacity and high rates of noncolorectal cancer-associated rectal bleeding (e.g., haemorrhoids, parasitic disease), both underreferral and overreferral can have significant negative impacts on waiting times and patient outcomes. Validated cancer-specific family history tools that are self-administered are in use in a number of HICs in both primary care and specialist settings (93). The role for locally developed family history tools in contexts where large immediate and extended families are common but the cause of death are often unknown or not disclosed to other family members requires further investigation. As efforts to deliver noncommunicable disease management through primary care platforms increase in MICs, there is clearly opportunity to include education on common cancer-specific symptoms as part of provider training and public health campaigns.

Point of care (POC) testing can provide rapid results at the time of clinical encounter to inform clinical decision-making, diagnosis, and early referrals. In MICs it can overcome some of the diagnostic limitations of a weak health system (94) and allow for testing in the absence of traditional laboratories. POC testing has been successfully delivered at scale in both LICs and MICs for infectious diseases such as HIV, malaria, and tuberculosis (95), but remains an underdeveloped area globally for cancer. This is in part because of the heavy reliance on advanced imaging techniques and histopathology for cancer diagnosis which are widely available and accessible in HICs, and a paucity of peripheral cancer biomarkers that can be used for screening and diagnostic purposes. The development of POC HPV testing, which can detect high grade precancerous cervical lesions with higher sensitivity and comparable specificity to conventional cytology, represents the most promising POC test for cancer screening of asymptomatic women in MICs. While POC HPV tests have not been fully validated in the clinical setting, promising initial field results are emerging. In addition, POC HPV testing has been developed for self-collected vaginal specimens, which would greatly decrease the resource burden associated with clinician screening (96). A meta-analysis suggests that while clinician-collected samples are still the gold standard, acceptable sensitivity and specificity can be reliably achieved with self-collection (97). A major benefit of POC HPV testing is that it can be combined with same-day treatment of precancerous lesions (e.g., with cryotherapy) as part of single visit “screen and treat” strategies, improving uptake of treatment and reducing the follow-up burden on both patients and providers (98).



The use of visual inspection with acetic acid (VIA) as a POC test for diagnosing cervical cancer and high-grade precancer changes has fallen out of favor as a leading strategy for cervical cancer screening in LICs and MICs with the emergence of HPV testing. In a landmark Indian randomized trial, HPV testing was superior to no screening, cytology-based, and VIA screening in reducing advanced presentation and mortality from cervical cancer (53). However, VIA may still represent a cost-effective strategy where HPV testing is unaffordable and cytopathology infrastructure is not available. Although operator dependent, VIA can be performed by primary care staff, is inexpensive, can be combined in a single visit with cryotherapy treatment. In the presence of good training and sustained quality assurance, is an effective method to prevent cervical cancer (54, 99).

Finally, the role of digitization of pathology and imaging, which allows reading and interpretation of biopsies and images remotely in the absence of local capacity, and the use of artificial intelligence (AI) to detect precancerous and cancerous lesions, hold promise for overcoming major human resource limitations in MICs (18, 100). The use of an AI-based program in conjunction with handheld ultrasound for triage of breast masses by minimally trained health workers in Mexico is one example under evaluation (101). However the clinical application of AI in cancer diagnostics remains in its infancy, and the utility, cost-effectiveness and feasibility for cancer detection have not yet been proven (102).

## Screening, Early Detection, and Access to Health Care Resources

Screening and early detection are only effective if treatment is available once latent disease is identified. Effective treatment is contingent on services being both physically accessible and affordable (103). In many MICs, effective health insurance coverage for cancer care is lacking. In Nigeria, only 5% of the population is covered by some form of prepaid health insurance (103) and cancer is often covered later within universal health coverage expansion pathways (104). There is emerging evidence to suggest that screening behavior and cancer management are dictated by income (105). In the absence of a comprehensive health insurance system (i.e., public, private, or mixed), the efficacy of opportunistic and organized screening is lost to inequitable access to treatment services. Inadequate health services infrastructure, including systems to ensure timely definitive diagnosis, follow-up and treatment after a screen-detected finding, have been described as major barriers to successful implementation in several MICs attempting to introduce mammographic screening. Indeed, women lost to follow-up after a screen-detected cancer finding, and prior to either definitive diagnosis or treatment, has been reported in studies investigating the role of screening in LMICs (63, 106). In a study evaluating the effectiveness of screening mammography in Jakarta, of the 1,100 women screened, 14 cancers were detected, but only 6 women returned for treatment (106). This

may reflect structural, sociocultural, personal, and financial barriers to accessing care (62) that need to be addressed prior to, or at least alongside, the introduction of screening programs. For the benefits of screening to be realized, patients must undergo further investigation and treatment.

## Conclusion

Population coverage with proven, cost-effective prevention and early detection strategies for high burden cancers is a cornerstone of effective cancer control. Direct national and subnational estimates of cancer incidence, prevalence, and mortality are a critical first step in cancer control efforts. Without robust local data, it is challenging to identify context-specific cancer risk factors and at-risk subpopulations for targeted interventions. In lower MICs and many upper MICs, the major modifiable risk factors for cancer continue to be infection (especially HPV) and tobacco. Large gains in infection- and tobacco-related cancer incidence and mortality can be made in a relatively short time, using proven, affordable, prevention strategies including HPV vaccination of at-risk groups, and tobacco taxation. These remain underutilized levers for cancer control in many MICs and should be considered priorities moving forward.

Presentation with advanced stage cancers, where the opportunity for curative care is greatly diminished, is far more common in LICs and MICs. Efforts to improve earlier detection and treatment of symptomatic cancers can provide marked mortality reductions in settings where advanced presentation is common, and are affordable and cost-effective in upper and lower MICs where breast cancer incidence is highest. Early detection strategies include increasing public and provider awareness of cancer symptoms and curability and increasing access to providers trained in CBE for breast concerns. Coupled with efforts to strengthen the diagnostic and referral pathways at the health systems level, these should be considered core components of cancer stage shifting and cancer control in MICs. This should be appropriately supported by national cancer policy, as well as financial and technical resources. Innovations in POC diagnostic tools, particularly those that reduce delays between first presentation, definitive diagnosis and treatment may provide answers to some existing challenges, in much the way HPV testing and “screen and treat” approaches have changed the landscape for cervical cancer (Table 2).

Although the role of screening programs has received much attention in global cancer dialogue it is not the only, nor the most important, mechanism for earlier cancer detection. Screening of at risk groups in MICs is well supported by high-quality evidence for cervical cancer, but has not been shown to be clinically or cost-effective at reducing cancer-specific survival or overall mortality in MICs for other common cancers. Additional trial results coupled with economic analysis are needed before drawing firm conclusions on the role of CBE in breast cancer screening.

Cancer prevention and early detection strategies cannot occur in isolation. Dedicated resources for the expansion of diagnostic and treatment services are also required, as not all cancers can be prevented, and without this the benefits of earlier diagnosis will be lost. Investment in cancer surveillance mechanisms will be critical for understanding national and subnational needs, and for monitoring the effectiveness of cancer control investments. By considering the continuum of cancer care required, and viewing cancer surveillance, prevention, screening, and early detection as processes rather than discrete events, countries will be better placed to

balance investments and efforts to scale-up across the cancer system.

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