

Is Cancer a different Disease in the developing World?

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The mounting rise in figures of non-communicable diseases globally, is noticeably disproportionate in prevalence and mortality in low- and middle-income countries (LMICs). The epidemiologic trend of cancers in LMICs is of distinct apprehension. In 2018, an estimated 18.1 million new cancer cases were diagnosed and 9.6 million cancer deaths occurred. The WHO estimates that by 2040, this will increase to 29.5 million new cancer diagnoses and 16.5 million cancer-related deaths annually.¹ Given the population boom and gradual increase in life expectancy in developing countries, a significant increase in cancer incidence in the developing world is projected. The rising figures of cancer and mortality are set to double, and more than 70% of new cancers will occur in people in the developing world.² In 2030, cancer deaths in LMICs are estimated to increase from 65% to 75%.^{1,3} The higher income countries (HICs) have rising cancer incidence rates, but the mortality rate is significantly higher in lower- and middle-income countries (LMICs) and continue to rise, whereas mortality rates in HICs are either decreasing or stable. Despite a lower incidence, cancer-related mortality is significantly higher in younger patients in LMICs. This has an immense economic impact of premature mortality and lost years of productive life.^{3,4}

The etiology of cancers is somehow different in LMICs, affecting a younger population usually with a more aggressive disease behaviour.⁵ Due to close family system and intra family marriages, there are clusters of genetic cancers. Lifestyle changes as diet and sedentary life are rapidly taking place in the majority of developing countries. Tobacco use is not declining in these countries where protective legislation is weak and the population is less cognizant.⁶ The common cancers in developing countries are often associated with infections by viruses like human papillomavirus (cancer cervix), EBV (NPC, Burkitt lymphoma), HIV (anal, Lung, Skin), Kaposi Sarcoma-Associated Herpesvirus (KSHV), Merkel Cell Polyomavirus (MCPyV), Helicobacter pylori (Gastric CA and MALT lymphoma), Opisthorchis viverrine (Cholangiocarcinoma), Schistosoma haematobium

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(Urinary bladder Cancer), SV40 (Mesothelioma, Brain, Bone) and hepatitis B or C virus (liver cancer).⁷⁻⁹

The relevant cancer data from developing countries and research capacity is practically non-existent. Most cancer registries in these countries do not operate optimally and screening programmes are generally lacking.¹⁰ There is a lack of rational approaches to cancer prevention as Tobacco control. There is deficiency of sustained, integrated, coordinated and comprehensive vaccination programmes with equity in LMICs like HBV and HPV. A majority of cancer patients in the developing countries (75%) have advanced or incurable cancers at presentation and diagnosis.^{9,11} This is anticipated due to lack of awareness and non-availability or delayed access to screening programmes and early detection measures. This delayed advanced stage presentation influences the treatment options and poor outcome to any offered treatment.¹² Often these patients are beyond any successful active cancer directed treatment and are only candidates for treatment with palliative intent.¹³⁻¹⁶ There are, however, few examples of successful cancer initiatives in developing countries with limited financial resources. These can lead to an impact on cancer even in the least developed countries, to bridge the disparities.¹

The diagnostic facilities in LMICs are either lacking or under-utilized due to access, awareness and equity issues. These range from radiology, interventional diagnostic radiology, endoscopic evaluation, pathology, molecular imaging like PET scan, Gallium scan, DOTA Scan, PSMA PET Scan, etc., which are scarcely available. Molecular testing which is now an integral part of diagnosis and treatment are either not accessible or not available like; NGS, Oncotype DX, MI. These delay or misdiagnosis of cancer leads to progressive disease to an advanced stage with unfamiliar symptomatology, unknown often undescribed complications, resistant, refractory disease and unexpected poor outcome compared to HICs.^{13,15,17}

The potential of curative treatment seems limited as the cancers that predominate in LMICs are stomach, liver, and lung; which are relatively refractory to treatment. There are concerns and questions about timely and quality standard of cancer care centres, encompassing surgical, medical and radiotherapy treatment.^{1,11} There are further issues of human resource development and training,

capacity building, expansion of infrastructure, procurement of latest machines, and modernized sophisticated technology like cryosurgery, robotic surgery, transplant, interventional therapeutic radiology techniques, laser therapy, Radio isotope therapy (Lutetium, Actinium), proton beam therapy, etc. In many places there is inadequate access of medications. Generic, biosimilars, or unsatisfactory manufactured products are used due to cost; having concerns of questionable efficacy and higher toxicity. This adds to patients' health, safety, equity, and suffering often impairing treatment outcome due to treatment interruption, dose modifications and discontinuation. The updated treatment like targeted therapy, immunotherapy, CART-T, bone marrow transplant, and gene therapy are not easily accessible due to cost and affordability. The use of artificial intelligence, digital pathology, computational medicine in cancer management is a distant reality. Curative treatment is crucial but in the developing world, around 80% have late-stage incurable disease at the outset. Palliative care and pain control are also far from ideal and majority of patients are forced to live with pain and suffering. Health professionals have an ethical duty to prevent avoidable suffering by effective pain relief, but unfortunately access to palliative care is often limited.^{4,15,18}

Cancer research at present is strongly inclined and steered by high-income countries (HICs). The HICs have different cancer epidemiology, research priorities, competence, scope, infrastructure and health systems than LMICs. There is minimal research conducted in, and applicable to the problems of low- and middle-income countries (LMICs). This discord in knowledge, data generation and application need to be rebalanced. Implementing these current research findings in LMICs is unlikely to yield optimal or desired outcomes in this setting.^{9,11} There is a need to urgently scale up locally relevant cancer research in these countries. Strengthening research is imperative for long-term benefit and sustainability. This may fill the disparities to address the scorching issues in cancer care in LMICs.¹⁵

Breast cancer is the most common cancer in women in both developed and developing countries. In developing countries, 50% of breast cancer patients were younger than 50 years age.^{2,5,15} The Western lifestyle, delayed first childbirth, lower parity, and shorter periods of breastfeeding make breast cancer different and distinct in HICs and LMICs. Five-year survival rates for breast cancer are much worse for LMIC countries such as Brazil (58.4%), India (52%), Algeria (38.8%), and Gambia (12%) compared to United States (83.9%), Sweden (82.0%), Japan (81.6%),

and Australia (80.7%). In Libyan women with breast cancer, the median delay in diagnosis was 7.5 months, and 56% were diagnosed after 6 months. In Uganda, the median delay to the first medical consultation was 13 months.^{5,14} A diagnosis delay of >3 months is associated with positive lymph nodes, larger tumours, late clinical stages, and distant metastasis. The mortality rates are higher and survival rates are lower in breast cancer, as reported from LMICs of Asia.¹⁹ Scarcity of early detection programmes, later stage presentation, access to standard diagnostics and treatment contribute to these poor survival rates.^{20,21} Emphasis is urgently needed on health education, promote early diagnosis of breast cancer, and importance of creating more advanced treatment facilities, which are key components for the improvement in breast cancer care and survival.⁵ In developing countries, only very few facilities provide early, multimodality protocol-based treatments in line with international guidelines. Most patients with breast cancer receive inadequate treatment due to scarcity of high-quality infrastructure, a direct effect of deficient financial resources.^{5,19} The low survival rates are further confounded by social taboos not to disclose or discuss the diagnosis.

The top five cancers in developed countries are lung, colorectum, breast, stomach, and prostate cancer; while in developing countries these are stomach, lung, liver, breast, and cervix.¹¹ Cancer MIR (Mortality to Incidence ratio) in high-income countries (0.47) was significantly lower than that of middle/low-income countries (0.64), with a significant p-value of < 0.001.¹⁰ LMICs with the least access to health care are more likely to have the underestimation of cancer death, as many cancer patients die without seeing a physician. Additionally, the number of physicians trained to diagnose and treat cancer are not adequate, as the focus is on training more primary care physicians. Cancer mortality and survival rates essentially depend upon awareness, early presentation, and oncologic infrastructure; which warrants sustainable, coordinated and comprehensive cancer control programmes with assistance from local communities. Sustainability and cost-effectiveness are important in facilitating effective cancer management by optimal resource utilization. Accessibility to cancer medicine either free or at affordable prices or universal coverage of health expenditures must be ensured by the governments in LMICs.¹³ Overall financial resources and healthcare infrastructure are strongly associated with cancer MIR in high-income countries. This suggests a greater importance of healthcare system structure and equality in lower income countries vs. level of resources in HICs.

Last but not the least there are limitations in Quality and Access to Cancer Services in Developing Countries for the patients. There are issues of cost, effectiveness, Accessibility, Equity, Sustainability and economic efficiency. These inequality in developing vs. LMICs definitely influence patient management outcome. In developing countries, poor infrastructure to intervene timely and to deliver basic care may jeopardize treatment of cancer. The pain relief and palliative care to cancer cases and other terminally ill patients is a demanding cost-effective option as in developing countries, as over 60% patients die from the disease. To reduce the suffering is a benefit without the requirement of any sophisticated technology. Back in the 1980s, WHO established the Cancer Pain programme and forty-three years later, palliative care still struggles to gain priority with policy-makers.⁶

In LMICs the population explosion and exposure to risk factors has increased the new cancer cases significantly in recent years.¹³ Early diagnosis of cancers is important for fruitful treatment options and lack of access to early diagnosis results in higher mortality rates.¹³ Besides, the insufficient prevention, detection and treatment of infectious diseases also increases the risk of some cancers. If the age-specific rates of cancers remain the same, then just because of rising population and changing demographics, the cancer burden will increase to 2.1 million new cases and 1.4 million deaths by 2040 in Africa.¹³ Cancer burden in African countries would increase even more than the predicted values by 2040 unless a holistic approach to cancer management and control is adopted.¹³ The burden of childhood cancers in LMICs of 183 countries surveyed, is around 80% of the global burden of childhood cancers.¹³ They have not been able to allocate sufficient monetary resources to implement comprehensive prevention strategies at primary, secondary, and tertiary levels.¹³ The major cancer treatment modalities in LMICs are scarcely available in a timely manner and are associated with prohibitive costs¹³ We found that life expectancy, maternal education, fertility rate, availability of pathology services, bone marrow transplantation capacity, availability of treatment services (chemotherapy, radiotherapy, or surgery), number of pharmacists per 10,000 population, country income level, and out-of-pocket health expenditure were significantly associated with cancer mortality for children in LMICs. The highest levels of vulnerability were found in sub-Saharan Africa.¹⁴

The opioid crisis in developing countries illustrates the importance of understanding, nature and levels of cancer pain, and barriers to effective cancer pain management.¹⁰

The accessibility of cancer treatment procedures and medicines is quite low in LMICs due to the high prices, low income, low health insurance and low public health spending. Patients at low-income levels can't afford the costly medicine and cancer treatments, thereby leading to therapy abandonment.¹⁸

There was broad consensus that efforts and scarce resources in developing countries should focus first and foremost on prevention and awareness and secondly on early detection. Treatment and research were considered lower priorities in resource constrained settings. However, prevention cannot stand alone without proper cancer surveillance and cancer control systems.¹ There is a need to improve health services for cancer control in developing countries. In LMICs facing more advanced disease, there is a need to improve treatment outcome by improving access and affordability, value-based care and health economics, treatment quality improvement, implementation of research and leveraging technology to improve cancer control. LMICs need to have collaboration and commitment from governments, policy makers, funding agencies, health care organizations and leaders, researchers and the public.⁴ Current resources and much-needed investments must be optimally managed. To achieve this, there are four key priorities: (1) Capacity building in oncology health services research, policy and planning relevant to developing countries (2) Development of high-quality health data sources (3) More oncology-related economic evaluations in developing countries (4) Exploration of high-quality models of cancer control in developing countries.

Strengthening research capacity at individual, organizational, network and policy levels is important for long-term benefit and sustainability. Governments, policy makers, funding agencies, health care organizations and leaders, researchers and the public should work together and show strong commitment to promote cancer research in LMICs.² They must work together and show strong commitment.^{2,4}

There are wide differences in developing LMICs countries and ICs countries in terms of tumour genetics, genetically determined cancer, age at diagnosis, dissimilar etiological factors, access to screening programmes, early diagnosis, availability of diagnostic facilities, timely access to care, late advanced stage presentation, availability of sophisticated/state of the art treatment according to international guidelines and recommendations, non-availability of workforce and infrastructure, inadequate cancer control programme, scarcity of pain management and palliative care facilities, and investment in cancer care. These differences are translated in the care delivered

to the patients influencing tumour biology, behaviour, treatment options, complications, and treatment outcome or survival. This makes cancer an altogether different disease from presentation to outcome in LMICs compared to HICs, as long as this bridge is persistent and wide and difficult to be filled.

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