

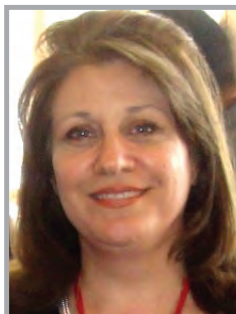
EDITORIAL

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How can we improve survival from breast cancer in developing countries?



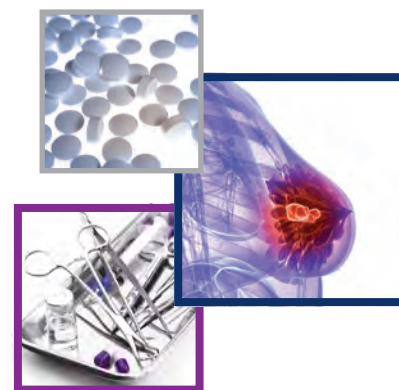
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The 5-year age-standardized population-based breast cancer survival rates in most developing countries vary between 9.5 and 66.0%, which are significantly lower than in high-income countries. This poor survival reflects the limited breast cancer awareness among women and primary care practitioners, advanced clinical presentation and limited capacity for early diagnosis and effective multimodality treatment and a significant proportion of breast cancer patients not accessing care or not completing treatment due to poorly developed and poorly accessible healthcare services or socioeconomic barriers. Critical to improving the early detection of breast cancer and breast cancer survival in developing countries is enhancing the awareness of breast cancer and improving the healthcare infrastructure by:

- Enhancing clinical consultations with symptomatic women;
- Improving the skills of primary care practitioners in clinical suspicion of breast cancer and prompt referral;

- Strengthening the capacity for diagnostic imaging, fine-needle aspiration cytology, histopathology and testing for hormone receptors;
- Improving access to multimodality treatment involving surgery, radiotherapy and adjuvant hormone and chemotherapy.

Breast cancer incidence rates have been steadily increasing in low- and middle-income developing countries (LMICs), with an annual percentage increase of between 1 and 2% [1,2]. The age-standardized incidence rates range from 20 to 70 per 100,000 women in LMICs [2]. Almost half of the 1.4 million estimated new breast cancer cases, two-thirds of 458,000 deaths and 2.4 million of the 5.2 million prevalent cases around the world in 2008 occurred in LMICs [10].

In the absence of specific primary prevention strategies for reducing breast cancer incidence, early detection and prompt treatment is the major control option to improve survival and quality of life and to

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reduce suffering and premature deaths from the disease. Trends in long-term survival are useful to evaluate progress in breast cancer control, since they reflect the impact of awareness, early detection and treatment. The high long-term survival associated with small primary tumors (5 cm or less, T1 or T2 disease), absence of axillary lymph node metastasis (N0 disease) and recent advances in locoregional and systemic adjuvant treatments are well established. However, survival from breast cancer is depressingly low in LMICs, and the challenges to improve outcomes are significant, but they are not impossible to address with appropriate planning and investments.

Survival estimates based on all cancer cases diagnosed in the whole population of a region or country are one of the suitable measures to assess progress in cancer control [3,4,102]. Survival rates of cancer patients registered in population-based cancer registries are the major sources of such data, which reflect the influence of different socioeconomic factors, natural histories, levels of awareness, health-seeking behaviors, early detection practices, availability and accessibility to diagnostics and treatment and the efficiency of public health services. The limited population-based breast cancer survival studies from a few LMICs provide valuable leads for improving breast cancer survival outcomes [3–6,102].

“...survival from breast cancer is depressingly low in low- and middle-income developing countries, and the challenges to improve outcomes are significant, but they are not impossible to address with appropriate planning and investments.”

Population-based 5-year age-standardized relative survival rates for breast cancer cases diagnosed during various time periods between 1990 and 2000 ranged between 9.5% in the Gambia and 82.3% in Tianjin in mainland China. Equivalent figures were 36.1% in Kampala, Uganda and 54.8% in Harare, Zimbabwe (after excluding patients with no follow-up information) [3,4,102]. However, survival in black patients (37.9%) was significantly lower than in white patients (74.4%) in Harare [4,5]. Survival from breast cancer ranged from 25.3 to 48.4% in different populations in India, from 34.7 to 51.9% in the Philippines, from 55.8 to 63.6% in Thailand and from 57.6 to 82.3% in mainland China. Survival rates were 66.0% in Costa Rica,

69.4% in Cuba and 76.6% in Izmir, Turkey [3,4,102]. The 5-year survival rates were 73.9, 90.0 and between 74.3 and 75.5% in Singapore, Hong Kong Special Administrative Region and the Republic of Korea, respectively, which are high-income countries/regions in Asia [3,4,102].

The 5-year survival rates for localized (corresponds mostly to stages I and IIA) cases ranged from 41.1 to 78.6% in different populations in India, from 65.3 to 73.5% in the Philippines, and from 79.5 to 84.1% in Thailand; they were 81.6% in Cuba, 89.9% in Costa Rica and 85.5% in Izmir, Turkey [3,4,102]. The 5-year survival rates for similar cases were 94.9% in Hong Kong and 85.9% in Singapore [3,4,102]. On the other hand, the 5-year survival rates for locally or regionally advanced breast cancer (corresponds to stages IIB and III) varied between 32.8 and 48.9% in India and in the Philippines; they ranged from 58.9 to 66.9% in Cuba and Thailand and from 77.1 to 79.1% in Costa Rica, Singapore and Hong Kong [3,4,102].

The survival of breast cancer patients in most developing countries, where such data are not available, is likely to be lower than the survival observed in the above LMIC populations, given the lack of early detection programs and the poorly developed cancer health services, as exemplified by the fact that a quarter of sub-Saharan African countries have no or extremely limited access to any form of anticancer therapy. Overall and stage-specific survival rates were lower in low- and lower-middle-income countries and in rural areas where breast cancer awareness is low, health services are inadequately developed and women have less access to diagnosis and treatment as compared with upper-middle-income countries and urban areas. The survival difference between black and white patients in Zimbabwe further exemplifies the impact of socioeconomic differences and affordability and access to health services. However, the higher survival rates associated with early breast cancer cases as compared with those of locally advanced cancers in LMICs indicate that the survival prospects for breast cancer can be substantially improved by increasing the proportion of early cancer detection, leading to both downstaging and downsizing of tumors within clinical stages.

It is instructive to compare the survival experiences from LMICs with those of high-income western countries. There has been steady improvement in breast cancer survival in high-income countries in Europe, Australia,

Singapore, Hong Kong, the Republic of Korea and North America over the last three decades due to improved awareness, widespread mammography screening, earlier diagnosis and improved locoregional and systemic treatment [3,4,7–9,102,103]. The 5-year survival rates of all cases and those of localized, regional and distant breast cancers diagnosed during 1993–2000 in the US populations included in the Surveillance, Epidemiology and End Results (SEER) program were 86.3, 96.1, 77.5 and 22.5%, respectively [7]. Five-year survival increased from 60.8% in 1975 to 78.8% in 2004 among black patients and from 76.5 to 91.4% among white patients in the SEER populations [103]. There was a 6–19% improvement in 5- and 10-year breast cancer survival in Europe and Australia over the last two decades [8,9].

The variation in survival outcomes described above is mostly due to differences in awareness, availability and access to early detection and treatment, although some misclassification in the categorization of clinical stages cannot be ruled out. The low level of awareness regarding the symptoms, signs and curability of breast cancer, delay in seeking diagnosis and care after symptoms due to socioeconomic and cultural barriers, fear and denial, and lack of early detection initiatives leads to advanced clinical stages at diagnosis and a significant proportion of breast cancer patients not accessing care or not completing treatment due to inadequate and poorly accessible health services. These, combined with the crippling and highly significant out-of-pocket healthcare expenditure, contribute to the low survival rates in LMICs [3,4,10,102].

The following have great potential to improve early detection and survival from breast cancer in LMICs:

- Provision of histopathology services, including hormone receptor testing;
 - Provision of multidisciplinary treatment comprising surgery, radiotherapy and adjuvant systemic treatments [3,4,102].
- Mammography screening programs are not feasible in LMICs given their limited health-care resources and infrastructure. The efficacy of organized CBE screening of asymptomatic women in reducing breast cancer mortality is not yet known and is currently being evaluated in randomized clinical trials [11,12]. Implementation of CBE-based organized screening programs for asymptomatic women in LMICs should wait until evidence from the trials indicates that it is a cost-effective strategy for downstaging and reducing breast cancer mortality. On the other hand, there is evidence that enhanced awareness about breast cancer signs and symptoms, high cure rates, cost savings, high quality of life associated with early disease detection and the opportunities to learn from breast cancer survivors played important roles in improving early diagnosis and survival in high-income countries before widespread mammography screening [3,4,13–15,102].
- Improving capacity for diagnostic imaging, histopathology and hormone receptor testing will result in accurate staging and appropriate treatment choices. Even a simple stratification of breast cancers based on estrogen receptor (ER) testing without detailed molecular sub-categorization can very much improve overall care for breast cancer patients. Improving the availability and access to surgery, radiotherapy and adjuvant hormone therapy and chemotherapy in health services is critically important to improve breast cancer survival in LMICs. Surgery is central to breast cancer management and radiotherapy after breast-preserving surgery or mastectomy in axillary node-positive patients improves survival [4,102]. Approximately 5 years of adjuvant hormone therapy with tamoxifen in ER-positive patients and adjuvant chemotherapy in women with axillary node-positive tumors or large primary tumors both reduce deaths by 30% [16]. Tamoxifen has no effect on breast cancer mortality in ER-negative disease [17], and hence ER testing will avoid unnecessary treatment with tamoxifen in ER-negative women. In low-income countries, even introducing an affordable and time-tested adjuvant chemotherapy regimen, such as the combination of cyclophosphamide, methotrexate and

5-fluorouracil (CMF; although its effectiveness is marginally lower than anthracycline- or taxane-based regimens, which are considerably more expensive than CMF), can improve survival of locally and regionally advanced breast cancers, especially considering the low costs and the recent suggestion that CMF might be effective in the treatment of triple receptor-negative patients [18].

“Political commitment and planned and phased investment of national resources ... are vital to improve breast cancer outcomes in the overall context of cancer control in low- and middle-income developing countries.”

It is a stark reality that cancer healthcare services are so dismally developed in many LMICs that diagnostic and treatment care do not exist in some countries. The extremely poor survival in the Gambia (as might be the case in many sub-Saharan African countries) reflects a depressing reality and extreme inadequacy of diagnostic and treatment capacity in public health services (nonavailability of histopathology, radiotherapy,

hormone therapy and chemotherapy). In fact, almost all sub-Saharan African countries, with the exception of South Africa and a few low-income countries in Asia and Central America, have invested very little to improve their cancer healthcare capacity and infrastructure in the last four decades. Political commitment and planned and phased investment of national resources in creating community breast awareness, appropriate healthcare financing mechanisms to limit out-of-pocket healthcare expenditures and in strengthening diagnostic and treatment infrastructure and resources are vital to improve breast cancer outcomes in the overall context of cancer control in LMICs.

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