



# Report from the Front: a Glimpse at Breast Cancer Research in Low- and Middle-Income Countries

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## Abstract

**Purpose of Review** Breast cancer is increasingly more prevalent in low- and middle-income countries (LMICs) and its biology in these populations may differ from that in more affluent countries. Research in these settings is limited by both societal factors and the lack of resources. Our intent is to review the parameters that limit more extensive research activities in LMICs and potentially investigate options for improvement.

**Findings** LMIC governments have limited infrastructure to support appropriate research and the physicians are overburdened by clinical work. Even the patients fail to see the value of research in some countries. Funding and support from pharmaceutical companies is usually channeled to higher income countries with advanced infrastructure.

**Summary** Recent research demonstrates the multi-faceted problems with the conduct of clinical studies in LMICs. A concerted effort by the state and physicians can lead to the development of conditions conducive to research. Such efforts are of paramount importance as the potential of research activities in LMICs is very significant and capacity building can bring in funding, new medications, and ultimately better care for breast cancer patients in LMICs.

**Keywords** Breast cancer · Clinical research · Limited resources · Infrastructure · Low- and middle-income countries

## Introduction

Non-communicable diseases are on the rise in low- and middle-income countries (LMICs), but still escape the focus of funding and research. Breast cancer is the most common malignancy in

women worldwide and, although the incidence in LMICs is lower than in high-income countries (HICs), over 60% of breast cancer mortality worldwide is attributed to LMICs [1, 2]. Advanced stage at diagnosis, aggressive histology, and limited therapeutic options are to blame. Many LMICs lack resources for

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adequate screening and early diagnosis and for prompt and state-of-the-art therapeutic interventions. It therefore comes as no surprise that despite the abundance of breast cancer cases, there is very little original research being performed in LMICs [3]. A quick PubMed search will reveal very few original articles were the first and last authors work exclusively in LMICs [4]. The obstacles to the conduct of original research in breast cancer and oncology in general can be seen in view of recurring themes, attributable to the society and state, the institution, the physicians, and even the patients themselves. Unfortunately, many LMICs do not have the infrastructure required to conduct research, and, even though research is likely to result in the influx of funds, there is very little appreciation of its value at an institutional level.

## Breast Cancer in Low- and Middle-Income Countries

It is estimated that annual new cancer cases will have probably reached 21 million by 2030, and cancer deaths are expected to have reached 13 million by then. About 70% of incidence and mortality related to cancer will have occurred in low- and middle-income countries [5, 6••].

Breast cancer remains the most common malignancy affecting women worldwide and the leading cause of death related to cancer in females accounting for more than 1.6% of deaths [7]. The burden of breast cancer is expected to have increased by 50% between 2002 and 2020 [8, 9]. This rise in breast cancer rates will be higher in LMICs and this is approximately reflected in a 55% increase in disease incidence and a 58% increase in disease mortality in less than 20 years. Even though breast cancer constitutes a malignancy with good prognosis, especially when it is diagnosed in early stages, with average 5-year survival rate over 75% in most HICs, the survival for breast cancer patients is less favorable in LMICs (average 5-year survival 57%), with the lowest observed in Gambia at 13% [5, 10•].

The increase in breast cancer incidence in LMICs may be associated with lifestyle changes observed over the recent decades mostly in diet, age at first delivery, and duration of breast feeding [11].

A well-organized research would contribute to the improvement of a better understanding of breast cancer molecular subtypes and clinical course and in the establishment of resource-stratified evidence-based guidelines. A quick review in the literature and electronic databases is enough to obtain a clear insight in the multiple challenges and barriers with the conduct of research in low- and middle-income countries.

## The State

Many LMICs lack the organization required to support research. Governments, frequently stagnated by bureaucracy, are burdened

with the acute care of the population with limited funding [12]. Research is seen as an unknown, seemingly frivolous area and/or is viewed with suspicion. There is often no legislation regarding research, or the legislation is too limiting, archaic, and obstructive [13]. Ethics committees (ECs) are rarely available and properly empowered at a country level, and funding, barely adequate for basic primary care, is not available to support investigational efforts. Also lacking are appropriately trained personnel to handle such issues at a state level [13]. Africa for example contributes only 1% of global investment to research and most of its countries contribute less than 0.5% of their national health budget to research [14, 15•, 16, 17•].

Another major issue here is the lack of national registries [18, 19]. A concerted reporting effort could lead to valid descriptive epidemiological studies with better understanding of disease behavior and temporal trends in LMICs. The existing impression is that in sub-Saharan Africa breast cancer is more aggressive and presents in younger women. This profile is not completely proven because of the lack of national registries [20]. Countries with somewhat better infrastructure have managed to conduct epidemiological research or case-control studies to overcome the lack of registries [21•].

## The Institutions

One of the main issues in doing research is the lack of interest from the leading institutions that are theoretically the national research centers. In Albania, for example, such institutions have not been able to perform extensive clinical research despite its obvious potential, not only in scientific development but also in procuring funds. For the last 10 years, Albania's tertiary cancer center has been directly involved in less than 20 studies, mostly global phase III/IV and a few local phase IV for the local branch of a pharmaceutical company (personal communication ML).

Major institutions in some countries may at least have an EC, but the ECs are frequently without a regular meeting schedule or standard operating procedures. In Egypt, where some research is initiated in the large academic centers, investigators are concerned about the lack of infrastructure to ensure the quality of the data, thus reducing the likelihood that the research from these centers will be publishable in high impact journals.

## Physicians and Practice Challenges

**Workload** The number of healthcare professionals working in LMICs is limited. All health workers work long hours and usually with little supportive staff. This leaves them with very little time and energy for research work. The levels of physician “burnout” are very high [22].

**Standard of Care Deviations** In order for research to be communicated, data has to be organized in a readily recognizable way, according to universally accepted staging and classification systems.

Science is benchmarked to the standard of care, but LMICs rarely meet this standard. There is a shortage of diagnostic tools used to fully investigate and document the extent of disease. Thus, staging of cancer in LMICs is usually incomplete, due to lack of CT, MRI, PET scanners, and molecular testing. This makes it difficult to conduct meaningful research. For example, how is one to evaluate the role of breast conservation in a country without radiotherapy machines?

**Poor Record Keeping** Poor record keeping is also a challenge for researchers in LMICs. It leads to a loss of valuable clinical and laboratory data, both key factors to the conduct of high level clinical research.

Very few centers have electronic medical record systems with disease coding which allow for good disease tracking and monitoring. Analysis of these records usually allow for the formulation of valuable hypotheses, which can be tested to provide solutions to identified trends and problems. These analyses have been the basis of research for many researchers worldwide [23], but are missing in LMICs.

**Professional Collaborations and Publications** Because LMIC researchers are aware of their limited resources, they are apprehensive about presenting their findings in conferences and in journals that can be easily accessed by their colleagues worldwide [24]. To make matters worse, when researchers in LMICs participate in collaborative research with international partners of HICs, researchers from LMICs have little control over the research agenda, and over the data and samples accumulated from these research projects. Unfortunately, in joint efforts, the academic credit is much more weighted towards the HIC researchers [25]. Collaborative research between LMICs and HICs should presumably enhance capacity building. Often, this is not the case, as the study samples and data are frequently handled and stored by the collaborating center in the HIC. Thus, the centers in the LMICs lose the opportunity to develop human and infrastructural capacity to support future research, addressing their unique healthcare challenges [26]. To make matters worse, the co-authors from the HIC assume the first and corresponding author positions on the publication of the research findings [27].

Yet, another issue is the cost of publication to some journals. This fee is usually significant for researchers from LMICs. These fees may be prohibitively high, while lower cost publications usually have a low impact factor [28].

**Poor Incentive for Research** University work in most of these countries is poorly paying as compared with private clinical work [29]. Most of those working clinically at the medical schools do it out of passion and normally survive on the

earnings from their work outside the academic world. Many of these researchers and academics even self-sponsor to travel to conferences to present their research work with little or no support from their institution.

All of these issues relate to the conduct of the “easiest” type of research, which is clinical research. Laboratory-based research or translational research is much more difficult to conduct as there is absolutely no funding to devote to such activities. Translational research is also difficult to conduct since some of these countries do not even have basic immunohistochemistry for breast tumors, such as estrogen receptors and HER2 [30].

**Brain Drain** Most of the excellent “brains” in LMICs leave their homeland to work in countries where research is supported and advanced. A significant amount of research work from HICs is conducted by the skilled migrants from LMICs [31]. Continuous brain drain resulting in poor retention of trained researchers also contributes to the lack of capacity for research [15]. The lack of trained oncologists particularly in the clinical specialties (surgical, medical, and radiation oncologists, hematologists, specialized oncology nurses etc.) as well other oncology research staff such as basic science researchers and epidemiologists is prevalent in the developing world [32].

The suggestion that results from clinical trials in resource-rich HICs can be extrapolated and applied in resource scarce LMIC settings also serves to discourage support to LMIC researchers from international organizations and pharmaceutical companies in order to build capacity. These assumptions may however be false, as they do not take into account the peculiarities of these settings including potential differences in drug metabolism among members of different races and access to drugs and diagnostic facilities. The importance of the participation of LMICs in clinical trials and of the support of local studies in diseases unique to LMICs should not be underestimated [33].

Finally, collaboration between researchers in institutions within a country/region and across countries/regions is also lagging behind due to cultural, institutional, and geopolitical differences [15, 34]. Having said that, in some LMICs, doctors have started national groups for education and research in oncology. Such groups started collecting data and joined international trials. However, hospitals in LMICs are always crowded with patients on long waiting lists, hoping to start cancer treatment. The research issues would add to the daily workload of the already overworked clinicians. Therefore, in order for these efforts to flourish, there should be time protected for research [10]. Despite these adversities, research is slowly coming of age in some LMICs, with many dedicated doctors, conferences, and research centers now publishing their own data, as well as data collected in collaboration with international research groups like EORTC, ESMO, and ISRS [35].

## The Patients

Patients with breast cancer present in very advanced stages in many LMICs. This limits the option for innovative research, as frequently, palliative care is more appropriate. Public perception of clinical trials (CTs) is usually quite negative. Both patients and families feel uncomfortable to participate, even in observational studies [36]. Investigators are not experienced in explaining in lay language the study intricacies to patients and their relatives. Furthermore, lack of information on the Internet regarding local clinical studies adds to the lack of trust and misperception.

Implementation of the ICH-GCP (the International Conference on harmonization—Good Clinical Practice; Food and Drug Administration guidelines) in LMICs, including informed consent, proper documentation, data archiving, and validated methods of data analysis, is lagging behind.

The stigma associated with a cancer diagnosis coupled with mistrust of the pharmaceutical companies further hinders trial accrual. Of patients who do participate in clinical trials, many are lost to follow-up because of the inability to handle the practical aspects of study participation.

Advocacy has been the pillar of scientific advances in breast cancer worldwide and this is yet another area that lags behind in LMICs. This comes coupled with lack of awareness of cancer prevention and of the value of early detection [32]. The stigma associated with a breast cancer diagnosis also inhibits patients from participating in advocacy groups [37]. Public awareness of the disease and its ramifications and therapeutic options is critical in raising trial conduct and patient participation.

A study being conducted to investigate the status of research in Albania shows that, although officially research is the responsibility of the University Hospital Center (UHC) and the University of Medicine (UoM), it was very difficult to identify all approved CTs and their research topics online. Furthermore, there is no information in lay language for the public, or a strategy for public engagement [38]. To make matters worse, it appears that, compared with its neighbors, Albania is conducting very few CTs.

## Little Affinity for Support in the Eyes of the Pharmaceutical Industry

The pharmaceutical industry has been a major driver to research work over the past few decades. LMICs may not be viewed as economically valuable markets for most pharmaceutical companies. They therefore do not invest in research activities in these countries [25]. The questionable quality of data from these countries is also a deterrent for the pharmaceutical companies. Very few clinical trials are ever sponsored in these countries when compared with HICs [39]. On the other hand, LMICs could provide a rich resource of untreated patients in advanced stage, where some new medications can

be tested, thus both providing access to modern medications to those patients and valuable scientific insight to the pharmaceutical research.

Further misconceptions, such as the belief that pharmaceuticals want to exploit patients in LMICs where regulation is not as tight, in order to test new, potentially unsafe, therapies, discourage patients from participating in research [7]. A frequently cited example in the literature is that of a study of breast screening by a clinical examination that took place in the Philippines and was closed prematurely. More than 60% of the women on the study were lost to follow-up after a suspicious finding was detected on the screening examination [40]. Further disbelief stems from the fact that if the tested drugs are proven effective, it is unlikely that LMIC patients will have access to them.

Improving public awareness of breast cancer and exposing the advantages of participating in a clinical trial is essential for increasing breast cancer research in LMICs [41]. Education in this field should focus on reversing the social obstacles and the cultural misbeliefs. Patients should be properly informed that their participation in the research will help them gain access to more appropriate treatment for their illness and better diagnostic processes and a multidisciplinary approach to their disease, thereby ultimately gaining access to better care [40, 42•].

There are many patients, especially in the late stages of the disease, who would be willing to participate in clinical trials, after proper translation and explanation of side effects of the new drug. Many organizations like Reach for Recovery have been established in order to promote the practical and emotional support in women with breast cancer in LMICs and make it clear that a breast cancer diagnosis is not a death sentence [43]. These support groups might have a positive influence on the cancer research agenda.

## Conclusion

Breast cancer constitutes an increasing risk for women in LMICs. The westernization of lifestyle has led to a steadily increasing incidence of the disease without any improvement in mortality, contrary to what is observed in HICs. The cost for appropriate or even basic treatment is prohibitive in some LMICs. The conduct of well-organized research could contribute to the solution of this problem, although there are multiple barriers and challenges to overcome.

Clinical research could reveal etiological factors, molecular alterations between different subtypes, and possible reasons for the different drug pharmacodynamics among populations in LMI and HICs. Moreover, research can lead to the improvements in infrastructure, better social awareness, and the establishment of resource-stratified treatment guidelines. Finally, it could contribute to the training, education, and satisfaction of medical professionals.

The conduct of research in LMICs should obviously respect local culture, ethics, and beliefs and the needs and capabilities of the existing health system. Extensive collaboration with the well-organized research and medical institutions located in HICs should be encouraged.

Research in breast cancer should be supported by the pharmaceutical industry and international organizations, as has occurred for HIV research for many years, within a well-designed legislative framework that at the same time strengthens research and protects citizens [44]. In contrast to what is happening so far, in the design of a clinical trial, investigators should take into account that a regimen may not have the same impact in all populations. Adjustments according to racial differences in the metabolism of medications, nutritional habits, the biology of the disease, the available equipment, and, of course, the presence of co-morbidities, such as infectious diseases that are no longer present in the West, may be needed.

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## Compliance with Ethics Guidelines

**Conflict of Interest** The authors declare that they have no conflict of interest.

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- Of major importance

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