Delays in Breast Cancer Detection and Treatment in Developing Countries

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ABSTRACT: Breast cancer is the most common cancer in women in both developed and developing countries and the second most common cancer in the world. Developing countries are increasingly adopting a Western lifestyle, such as changes in diet and delayed first childbirth, lower parity, and shorter periods of breastfeeding, which are important determinants of a higher incidence of breast cancer among those regions. Low- and middle-income countries (LMICs) represent most of the countries with the highest mortality rates, ranging from 40% to 60%. Furthermore, developing countries account for scarce survival data, and the few data available coincide with the observed incidence and mortality differences. Five-year survival rates for breast cancer are much worse for LMICs countries such as Brazil, India, and Algeria in comparison with the United States and Sweden. Paucity of early detection programs explain these poor survival rates, which results in a high proportion of women presenting with late-stage disease, along with lack of adequate diagnosis and treatment facilities. Emphasis is urgently needed on health education, to promote early diagnosis of breast cancer, highlighting the importance of creating more public facilities that provide treatment, which are key components for the improvement in breast cancer care in developing countries.

KEYWORDS: breast cancer, developing countries, delays

Introduction

Breast cancer is the most common cancer in women in both developed and developing countries and the second most common cancer in the world.[1] High-income countries represent most of the countries with top incidence rates, whereas low- and middle-income countries (LMICs) represent most of those with the highest mortality rates. In fact, it is estimated that in 2020, 1.7 million new cases of breast cancer will present in the developing world, and the huge discrepancy in survival chances will continue with most of the breast cancer deaths (70%) occurring in the developing world. Therefore, breast cancer has a tremendous public health significance and because primary prevention is still not available, efforts to promote early detection should be highlighted.

Breast cancer survival rates vary greatly worldwide[2] and developing countries have paucity of data, but the few data available coincide with the observed incidence and mortality differences. 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%) in comparison with the United States (83.9%), Sweden (82.0%), Japan (81.6%), and Australia (80.7%).[3,4] Between 2000 and 2010, an analysis of breast cancer incidence and mortality in Mexico showed that there were 66 405 and 47 832 new cases and deaths, respectively.[5]

The low survival rates in developing countries are explained by scarcity of early detection programs, resulting in a high proportion of women presenting with late-stage disease at diagnosis, along with the lack of adequate diagnosis and treatment facilities[3,6] as well as delays associated with treatment.

One of the most important prognostic factors of survival in breast cancer is the clinical stage at diagnosis.[7] There are 2 accepted classifications: the TNM staging system developed by the American Joint Committee on Cancer (AJCC)[8] and the one proposed by the US National Cancer Institute of Surveillance, Epidemiology, and End Results (SEER) program.[9] However, both classifications have shown a poor survival when breast cancer has spread to distant organs (24.3%-41.8%).[9,10]

For example, most of the patients with breast cancer in India are diagnosed at metastatic and locally advanced stages as a result of scarcity of organized breast cancer screening programs, lack of diagnostic aids, and general indifference toward the health of women within the Indian society.[11] However, a retrospective study performed in Mexico City General Hospital reported a 5-year overall survival (OS) of 58.9% in a cohort of 432 women with breast cancer treated between 1990 and 1999.[12] However, according to a recently published study in Mexico, including 5500 patients with a diagnosis of breast cancer, treated at the National Cancer Institute, between 2007 and 2013, survival increased, but most patients had locally advanced disease at the time of diagnosis (53%, n = 2293).[13]

In this setting, only some regional cancer centers provide multimodality treatment facilities, and comprehensive data and breast cancer statistics remain scarce. Both young and older women are affected by breast cancer, but in developing countries, the affected population entails up to 50% of women younger than 50 years.[4] Also, young patients are

reported to have larger tumor size, more metastatic lymph nodes, and poorer OS.[14–16]

Breast Cancer Detection

Breast cancer screening modalities include screening mammography, clinical breast examination, and breast self-examination (BSE). The efficiency and effectiveness of each of these strategies should be considered in the context of resource availability and population-based need, which also determines the primary goal of a screening program. The least expensive early detection screening method is BSE because it does not require advanced technology neither physician intervention. Nonetheless, randomized trials have not shown improvement in breast cancer mortality despite the increasing literature available on BSE, suggesting that this modality should only be encouraged as part of awareness programs and not for decreasing mortality.[17]

However, the only single modality that has demonstrated an improvement in breast cancer mortality with prospective randomized trials is screening mammography, however, its cost is prohibitive in many settings,[18] such as limited resource institutions. Cazap et al[19] performed a survey which indicated that most Latin American countries had no guidelines for mammography screening. Therefore, when screening mammography is used in LMICs, target populations and screening intervals need to consider what is optimal for the overall population acknowledging available resources.[20] Furthermore, the incidence of younger women with breast cancer is higher in most developing countries, and despite breast cancer incidence rates are supposed to be lower in younger women, meaning that screening programs will have a lower yield in terms of cases detected per 1000 women screened, the resources used for screening this target population should be carefully considered. When introducing mammography screening, highlights should be made to initiate in a limited age group of women in which age-specific incidence rates indicate that it is likely to be most productive; then, as the program gains experience, it could expand to additional age groups.[20] The age-specific incidence rates of breast cancer in each country, the available resources, and information regarding the effectiveness of screening in various age groups to determine the appropriate targets for mammography screening must be considered by those responsible for screening programs locally.

Furthermore, despite international guidelines providing an overview of the fundamental points and principles that should support any quality breast cancer screening or diagnostic service, such as the *European Guidelines for Quality Assurance in Breast Cancer Screening and Diagnosis*, were developed within the Europe against Cancer Programme,[21] these are not always applied in developing countries.

Delays in Breast Cancer

Despite acknowledging diagnosis and treatment delay as a deleterious factor for survival of patients with breast cancer, there is a lack of studies investigating the reasons correlates with a better survival has been accepted since the beginning of the 20th century, even before the existence of scientific evidence. Dr William Halsted, an American surgeon whose contributions have influenced surgical principles to this day, known for the introduction of the radical mastectomy, wrote at the end of the 19th century that the cure of breast cancer was not possible, but, if operated on early, quite probable.[22]

For almost 70 years, research studies about delays were contradictory, either supporting or rejecting an association with survival. However, the point of view of physicians, researchers, and patients for about 100 years has been avoiding medical attention when cancer symptoms are discovered.

In 1999, Richards and colleagues[23] clarified the relationship between global delay and survival, performing a meta-analysis including observational studies published between 1907 and 1996. They demonstrated that women with global delays longer than 3 months had shorter survival compared with women who started treatment within the first 3 months of symptom discovery. To date, this study is the strongest published evidence available.

Moreover, care delay has been subdivided into patient delay (PD) and health system delay (SD).[24] According to Caplan,[25] PD corresponds to delay in seeking medical attention after breast cancer symptoms and SD is a delay in the health care system. Therefore, care or global delay is usually divided into PD and SD.

The definition of global delay in the oncology field is more than 3 months between symptom discovery by the patient and the beginning of treatment, and it is now known that longer delays associate with reduced survival.[23] This is explained by many facts; for example, it has been shown that even cells from in situ carcinoma can metastasize,[26] highlighting how important a delay of 3 to 6 months in the clinical phase of the disease could be. On the one hand, delays between 3 and 6 months would probably not have an impact on survival, but, on the other hand, it has been documented that delay time increases along with the probability of clinical progression,[27] which has been shown to decrease survival.[28] Even though the natural history of breast cancer is unpredictable and heterogeneous,[29] studies have shown a reduction in mortality with earlier diagnosis.[30] Thus, as long as breast cancer cannot be prevented, efforts should aim early and adequate diagnosis and treatment.

Two delays were described by Pack and Gallo in 1938. They defined PD as an interval of 3 months or longer between symptom detection and medical attention. Health care system delay was described when the interval between the first medical consultation and treatment was too long. According to these authors, a month was considered optimal for the physician to start treatment. Both delays have been arbitrarily established but widely accepted. Along with this model, any delay between symptom detection and first medical consultation has been attributed to the patient, and delay after medical attention is considered a responsibility of the medical team. This concept has been recently questioned by many authors, stating that it is

a reductionist and dualistic model, based exclusively on its relationship with survival, and that it only considers delays as independent factors, which has conditioned its study individually.

Patient delay has been further studied. Different quantitative studies have found that advanced age, being single, Hispanic or black, and a low educational attainment, are associated factors. Other qualitative studies have found different associated factors: socioeconomic level, transportation, perception of competitive priorities (work, childcare, home tasks, etc), and lack of knowledge to health care access. Regarding symptom interpretation, once detecting abnormal changes in the breast, patients usually try to find alternative and possible explanations. Therefore, it is frequent that initially symptoms are perceived as normal alterations or they establish other hypothesis to acknowledge those symptoms. Also, other studies reporting perception of risk of breast cancer have demonstrated that most women underestimate their risk to develop this disease. However, emotions such as fear, sadness, and worrying about diagnosis and possible treatments influence initiative to seek medical attention. So, fear has been associated with delay; it can either accelerate seeking medical attention or cause a delay. Mechanisms determining patients' decision are still unknown.

Health system delay has been less studied. One of the main reasons is that the main medical model traditionally attributes health issues and paucity of attention to the patients without considering the influence of social and structural factors and inequity, which conditions to a differential distribution of disease, quality of attention, and health care access. Associated factors have established that some characteristics might be younger age and presenting unspecific symptoms, both make it harder to the physician to achieve a diagnosis. Socioeconomic level as a factor for medical team delay remains controversial; perhaps, it has not been studied properly because of its affection in accessibility and acceptability of the health system, and this would be responsible of the inequity suffered by minorities and vulnerable population.

Studies from different countries have estimated a global delay in breast cancer of 17%[31] in specific population in Germany to up to 42.5%[32] in a regional hospital sample in Tehran, Iran. Piñeros et al[33] performed a study among Colombian women diagnosed with breast cancer, reporting high frequency of advanced-stage disease. Patient delay was observed in 20.3% and related factors included older age and lack of social security. Another study reported diagnosis delay in Libyan women with breast cancer.[34] The median diagnosis delay was 7.5 months, accounting 56% of patients diagnosed within a period longer than 6 months. Diagnosis delay of >3 months was associated with positive lymph nodes, larger tumors, late clinical stages, and metastasis.

In Uganda,[35] the median delay to the first medical consultation was 13 months (1-127), similar to another study published in 2014, reporting 12 months.[36] The previous information contrasts with studies done in developed countries where median delay to the first medical consultations was 9 to 61 days.[29,37,38] Moreover, in Mexico, global delays vary from 5 to 8.4 months, and PD and SD vary widely according to patients' characteristics, detection method, and the institution.[39–41]

Breast cancer delay is not only associated with a reduced survival time but it also conveys a greater risk of needing more aggressive treatments. Hence, sometimes, the longer the delay, the more likely it is to perform mastectomies instead of conservative surgeries, along with more toxic or extended treatment.[42] Patients diagnosed with advanced disease have also shown to have important psychological morbidity.[43] All these aspects strongly affect the patient's quality of life.

Factors related to breast cancer delay

Ramirez et al[44] reported in their systematic review that single marital status and advanced age were the only socio-demographic factors that seemed to be strongly associated with PD. However, further studies continue to obtain contradictory results. For instance, presenting breast symptoms different from a lump and the patient's initial interpretation of her symptoms as not important have a strong influence on delay; other factors that seem to be of great importance are low education and ethnicity. A recently published study of a cohort of Mexican women with breast cancer reported that patient interval was statistically associated with marital status (shorter interval in married women) $P = .04$ and socioeconomic level (longer interval in low levels) $P = .045$. It was not associated with age, occupation, or education attainment ($P = .74$, $P = .3$, and $P = .18$, respectively).[41]

Improving Breast Cancer Survival

The ideal goal would be reducing the incidence of breast cancer; nonetheless, the options are limited and long term, particularly for the developing world. Some lifestyle changes, such as exercise and healthy meals, or avoidance of postmenopausal hormone replacement therapy, can have an important impact on breast cancer incidence.[45,46] Every effort should aim to limit these risk factors and thus breast cancer risk. However, even with strong efforts aimed at prevention, the incidence of breast cancer is likely to increase in most developing countries due to changes in reproductive patterns as well as diminished physical activity and increased life expectancy.

Another priority should be increasing survival rates, as earlier detection and timely treatments would likely result in substantial improvements in survival, especially in developing countries. Education about breast cancer and increased health care coverage could produce improvement in survival rates as observed in developed regions. Regarding education, this is definitely a key first step in implementing breast health programs. The approach and scope of health care education programs determine the success of early detection, measured by presenting stages at diagnosis. Kreps[47] established that these education programs must emphasize that breast cancer is often

curable when it is detected early, diagnosed accurately, and treated appropriately. To optimize success in this context, education needs to adapt to the potential cultural barriers surrounding breast cancer diagnosis within countries, emphasizing on low- and middle-income regions.

Research regarding why patients with breast cancer are diagnosed in advanced stages in developing countries remains scarce. Studies performed in the developed countries show an association of delays greater than 3 months between symptom discovery and treatment start (global delay) with advanced clinical stage of breast cancer. Moreover, reduced survival is associated with delays longer than 3 months. Delay influences disease progression, which in turn affects survival. Furthermore, there are large knowledge gaps in the description of breast cancer structure and process in most developing regions, and where information is available, it demonstrates a picture of great need in access to care and quality of care to improve outcomes in breast cancer. Therefore, investment in breast cancer control for most developing countries is urgently needed because increasing screening coverage is a solid step toward reducing breast cancer mortality across the developing world. Mammography is currently the standard of care in breast screening. Early detection and appropriate diagnosis are critical to achieving a favorable breast cancer outcome, and mammography screening has been shown in many clinical studies to reduce breast cancer mortality by at least 20%. But to support any screening program, sustainable funds, project management, physicians trained on breast cancer, and affordable care are mandatory. Developing countries have limited health care resources and use different strategies to diagnose breast cancer. Most of the population depends on the public health care system, which affects the diagnosis of the tumor. Thus, the indicators observed in developed countries cannot be directly compared with those observed in developing countries because the health care infrastructures in developing countries are deficient. In the past decade, cancer health care programs started gaining priority in LMICs; however, late stage at diagnosis remains a boundary to improving breast cancer outcomes and diminishes the importance of early detection. In some developing countries, screening mammograms are not affordable for all the population of women at risk, and the coverage of the screening provided by the health system is insufficient.

Conclusions

In developing countries, only few centers provide early, multimodality protocol-based treatments for breast cancer; thus, most patients with breast cancer receive inadequate treatment due to scarcity of high-quality infrastructure because of the lack of financial resources. This review highlights that there is a need to emphasize on breast cancer education, promoting early diagnosis of breast cancer, and the provision of more public facilities for breast cancer treatment, which can be expected to bring about the much needed improvement in breast cancer care in low- and middle-income regions. Research on delay should aim to identify factors in developing countries that can be locally modified to create public policy programs directed to improve breast cancer medical attention to reduce mortality rates.

Author Contributions

MMR-F and EL-R analyzed the data and agree with manuscript results and conclusions. MMR-F wrote the first draft of the manuscript and jointly developed the structure and arguments for the paper. EL-R contributed to the writing of the manuscript, made critical revisions, and approved final version. All authors reviewed and approved the final manuscript.

Disclosures and Ethics

As a requirement of publication, authors have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality, and protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. None of the authors have conflict of interests. The external blind peer reviewers report no conflicts of interest.

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