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Global challenges in breast cancer detection and treatment☆

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ABSTRACT

Breast cancer represents an urgent global priority. While this is a universal issue, and as the burden of the disease is increasing globally, current estimates indicate that in the next couple of decades, much of the incidence and mortality related to breast cancer will be seen in underserved populations. The fragile and ill-prepared healthcare systems in low- and middle-income countries (LMIC) need to address this challenge and find solutions with their limited resources. Significant disparities can be identified in stage at presentation as the ability to detect the disease in earlier stages is compromised in these scenarios leading to worse outcomes associated to late diagnoses. Furthermore, access to healthcare in general and to basic surgical, radiotherapy and systemic care is suboptimal additionally limiting treatment results. With a small portion of their budget allocated to healthcare, LMIC need to make the most of their resources prioritizing cost-effective strategies that could offer the best possible results. Countries that invest in women's health do develop into healthier, more educated, and importantly, more productive societies with benefits seen across generations. Finally, recognition of inequities should stimulate a concerted effort engaging all involved stakeholders to find context-adapted solutions to improve healthcare outcomes.

1. Introduction

An urgent and growing worldwide problem, cancer is a leading cause of morbidity and mortality and is currently responsible for one in six global deaths [1]. In 2018, there were 18.1 million new cases and 9.6 million deaths, figures that are expected to increase in the next few decades [2]. With the ongoing epidemiological transition, where infectious and transmissible diseases are being controlled and life expectancy is increasing, non-communicable chronic diseases (NCDs), among which cancer, are taking center stage. Of all deaths from NCDs approximately 30% will be due to cancer [2].

While cancer will have impact in all populations, the consequences should be analyzed considering the important inequities we observe in healthcare around the world. Disparities in resource allocation, established infrastructure, organization and access to healthcare will certainly lead to a higher cancer fatality rate in low- and middle-income countries (LMIC) where the population is particularly vulnerable, diagnoses are made a later-stages of the disease and access to care remains an important challenge.

Within this grim scenario, breast cancer should be the focus of very particular attention. The disease is responsible for more than 2 million new cases every year and in 2018, accounted for 11.6% of all cancer cases and 24.2% of cases in women representing the highest incidence among all cancers and the leading cause of mortality (6.6%) in women worldwide [3].

A careful analysis of development indicators and mortality-to-incidence ratios identifies significant differences among countries and a perverse relationship worth emphasizing. Consistently, LMIC countries have lower (but increasing) breast cancer incidence and higher mortality rates as compared to high-income countries (HIC) [4]. It is in the low resource scenarios where most of the cases and most of the mortality should be expected in the next few decades and where concerted efforts should attempt to decrease the impact of the disease. It has been estimated that in 20 years, more than 60% of the new breast cancer cases and 70% of related deaths will be seen in LMIC [5,6].

While impressive progress has been seen and outcomes are improving for breast cancer, advances in most LMIC have been slow, emphasizing global inequalities. Significant reductions in mortality in HIC over the last few decades have not been observed in underserved populations in LMIC [3,7]. Particularly extraordinary, and a definite statement that better outcomes are possible, a 39% reduction in breast cancer mortality from 1991 through 2015 has been reported in the

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United States [8]. Similar significant improvements in breast cancer results have been documented in other developed countries [7].

There are important challenges addressing breast cancer at a global level indicating critical disparities. Recent information from the World Health Organization (WHO) indicates that although 70% of countries have established cancer guidelines and 62% report screening programs, at the same time, 40% report important management and treatment access restrictions and less than half have palliative care plans [9,10].

This is obviously a complex problem involving multiple stakeholders and several aspects to consider. Focusing on the most important, we could argue that access to healthcare, late-stage diagnosis and lack of timely and appropriate diagnostic and treatment procedures are probably on the top of the list. Somehow these issues are all intimately related. Here, we briefly discuss several disparities related to breast cancer detection and treatment.

2. Breast cancer diagnosis, early detection and screening

Unquestionably, short of prevention, the most important prognostic element for breast cancer is an early diagnosis. A timely diagnosis has a positive impact in the final outcome of the disease. Notably, and according to current knowledge on the causes of cancer, most of the recommended preventive strategies (tobacco control, vaccines to prevent infections, reducing occupational exposures and air pollution, among others) do not apply specifically to breast cancer [3]. However, some risk-reducing strategies such as encouraging breastfeeding, reducing alcohol consumption and prevention of obesity should be promoted in public awareness campaigns and are an important aspect of any cancer control program [11].

As any other mostly chronic disease, an early breast cancer detection should consider two very clear clinical scenarios. Either the diagnosis is made by a screening test that identifies the disease before it causes symptoms in an asymptomatic patient or alternatively, is the result of the early investigation of a patient's complain or a physical exam finding.

Late-stage diagnosis of breast cancer is more frequent in LMIC. Available evidence indicates that 70% of breast cancer patients in HIC present with stages I-II, while consistently, less than 50% of those diagnosed in LMIC have early stages [12].

Adding more complexity and heterogeneity to the discussion, discrepancies can also be found within the same country. Fragmented healthcare systems result in unequal access in different populations leading to different outcomes. In Brazil for example, data form the AMAZONA-III trial, shows that while more than 80% of privately insured patients are diagnosed with stage I-II breast cancers, in the majority of the population, covered by the public system, more than 40% are diagnosed with advanced, stage III and IV breast cancers [13].

While early diagnosis of symptomatic patients and screening of asymptomatic individuals are two potential approaches for early detection these two strategies have different costs and requirements for success and should be applied according to the specific regional context [14–16].

Screening mammographs reduce the proportion of higher stage at diagnosis and have demonstrated reduction in breast cancer mortality, but screening programs may not be ideally applicable to resource-limited healthcare systems [12]. Screening programs require high investments, are difficult to implement and naturally involve large number of patients.

Although these programs have been successful in HIC, it is vital to remember that not all solutions for the same problem are applicable across different settings. In this particular case, the best solution should be tailored and adapted to the specific resource restrictions where it will be implemented. Furthermore, and very importantly, the heated discussion on overdiagnosis associated with screening mammography although applicable to HIC, does not apply to breast cancer control in LMIC and should not misdirect the discussion. In a scenario of limited resources this particular debate is not applicable as any strategy to detect cases at earlier stages remains a dire need.

On the other hand, timely evaluation of symptomatic patients is another strategy to consider. There are well defined requirements for a successful early detection program in a given situation. As a first step, increasing awareness and improving health literacy and patient education are certainly initial objectives achievable in all scenarios. Culturally conscious and resource adapted programs should be designed and implemented with participation of local authorities, local experts and engaged physicians. In this regard, international collaboration and guidance by a number of institutions should be both very feasible and cheap. Public campaigns raising attention to women's health in general and particularly to the need to identify new breast nodules are extremely important starting points. At the same time, education and training of the healthcare workforce are vital aspects to consider. Proper identification and prompt referral of patients to the appropriate diagnostic procedures is mandatory for any successful program. Early detection programs should be implemented in a context-conscious manner and carefully weighing each country's health system capabilities.

A second important step to consider is the access to healthcare, particularly primary care, that remains an important impediment compromising outcomes. Patient education and enabling access to healthcare should be the focus of new strategies among which emerging social media tactics and telemedicine will probably will be both effective and feasible. Some lessons learned with the COVID-19 pandemic could be applicable to this discussion. The massive worldwide communication efforts addressing the pandemic are certainly unparalleled even by the AIDS crisis in the 1980's. Furthermore, and importantly, telemedicine and the ability to reach almost all individuals instantly through a cell phone, raises both challenges and opportunities that can revolutionize health education in the coming years.

A third step requiring specific attention and demanding organization, resources and training is the quality of the initial diagnostic and staging procedures. Besides timely care, accuracy should be one of the main objectives of all programs. Adequate biopsy procedures, proper handling of the obtained material, availability of basic pathology and immunohistochemistry and effective communication of the diagnosis throughout the whole process, are essential.

Importantly, evidence indicates that the greatest delays in diagnosis may not be related to patient health-literacy or cancer related cultural stigmas but related to healthcare disparities such as access and quality of the service delivered [17]. Unquestionably, early diagnosis based on patient awareness and adequate access to diagnostic procedures is the most effective initial strategy to achieve breast cancer control in limited resource scenarios.

Finally, multidisciplinary care and personalized medicine have been proposed as the best approaches to manage breast cancer patients [18]. However, we should be very conscious that although these approaches may be easily applicable in HIC, worldwide, most patient cases will not be discussed in a weekly multidisciplinary meeting. Nevertheless, the basic principle of discussing management strategies among the specialists remains important. A careful analysis identifies two basic premises that once recognized should facilitate implementation of multidisciplinary care across different healthcare scenarios. The first is navigation. Helping patients through the complex geographical, organizational and logistical intricacies should have a significant impact in the timing of care and therefore on outcomes. The second is what we call an attitude of communication. We do not necessarily need a weekly in-person meeting to implement multidisciplinary care, what we need is a clear disposition towards discussing patient management addressing the different areas involved. A phone call involving the oncologist, the surgeon and the radiotherapist (and other areas as well) should be an adequate and almost ideal solution with undeniable impact on results. This is another area where new communication technology strategies implemented and popularized during the COVID-19 pandemic, can have a profound impact.

Ultimately, it is critical to consider that while addressing discrepancies, different scenarios and a great deal of heterogeneity among LMIC and LIC makes this process extremely challenging. One worthwhile attempt to guide all of these initiatives has been proposed by the Breast Health Global Initiative suggesting stratification levels that help addressing each step of the process according to specific resource levels. Independent of the economic level, all underserved populations will face the increasing burden of breast cancer and will need to develop and adapt strategies to allocate their limited resources in the best possible and effective way [19].

3. Timely access to cancer management

The impressive outcomes seen in breast cancer mortality in HIC are probably the result of combined earlier detection and adequate treatment leading to higher cure rates. Still, while basic curative interventions for breast cancer are available to some degree in many settings, countries have very different cancer treatment capabilities.

After a diagnosis has been made, access to surgery and radiation therapy remain important goals of any strategy to improve outcomes. Delays after an initial consultation, particularly in the most aggressive forms of the disease, clearly compromise outcomes and should be identified and avoided [12,17]. Adequate access to surgery, radiation and systemic therapy should be implemented. Early detection will have an impact on outcomes as long as follow up care is available. Delays in the availability of surgery, radiotherapy and systemic therapies are frequent in low resource scenarios and for a long time, have been known to compromise outcomes [20].

This is a fundamental step in the management of breast cancer patients that requires involvement of multiple stakeholders and most importantly context dependent implementation. A clear definition of what can be offered in each scenario is mandatory [19]. The very complicated and painfull resource allocation discussion with prioritization of healthcare issues is critical in this situation. Limited resources imply in making choices. Therefore, investing in the most cost-effective approaches that address the most prevalent disparities should be the main focus of cancer control programs across LMIC.

Geographical distribution of qualified human resources and specialized cancer facilities do represent a particular obstacle in many regions [21,22]. Programs reaching to underserved and rural populations should be established as have been proposed in many regions [21,22].

Another well described and discussed barrier is access to innovation and new drugs. While not all of the advances are related to innovations, these certainly occupy center stage in many discussions [23]. Available information indicates 90% of new and potentially more effective medicines released into the market in the last 5 years are bought exclusively by three markets: United States (64%), European Union (18%) and Japan (7%). The rest of the world shares the remaining 10% [24]. Itself, a very clear discrepancy.

However, and very importantly, we should recognize that not all new medicines have categorical impact in outcomes and may not represent the main priority for all countries. Addressing the complex issue of technology incorporation, we have recently suggested a framework that could have applicability across different healthcare system scenarios [25].

For example, even though trastuzumab has been associated with improved cure rates in patients with HER2 positive early breast cancer and that has been included in the WHO list of essential medicines, sometimes we forget to recognize that chemotherapy, without anti-HER2 treatment, cures more than 60% of patients in the same scenario [26–29]. In these lines, in many low resource scenarios, the push should not necessarily be for the latest antibody, but for having adequate surgery, access to radiation therapy and standard adjuvant or neo-adjuvant chemotherapy. Results will improve and eventually, further advances and technology incorporation will be possible and implemented in a much more organized and efficient care system.

Table 1
Select Potential Interventions that could positively impact Breast Cancer control in LMIC.

Interventions addressing the Health Care System as a whole.
- Improve health systems by offering Universal Healthcare coverage in all countries.
- Prioritize resource allocation and discuss alternative strategies for financing health care.
- Guarantee the existence of National Cancer Care Plans that should assure access to the basic diagnostic and treatment procedures.
- Stimulate the creation and qualification of Population Based Cancer Registries.

Interventions addressing education of the population (Health Awareness) and training the workforce
- Develop culturally-adapted Breast Cancer awareness campaigns directed to the populations at risk.
- Guarantee adequate numbers and training of health care professionals.
- Implement technology-based strategies with proven ability to ease access and facilitate the patient's journey in complex and fragmented health systems (navigation and telemedicine).

Interventions addressing causes of Breast Cancer, prevention strategies and early detection programs
- Organize cancer awareness programs (directed at risk factor identification) associated with early detection programs in line with cultural characteristics of the population and with participation of advocacy groups.
- Secure access to diagnostic and initial cancer treatment procedures (biopsy, pathology, and basic systemic therapy such as endocrine therapy and basic chemotherapy).
- Guarantee adequate numbers of radiotherapy equipment and personnel

Other Interventions
- Stimulate the performance of clinical research addressing all the barriers that limit access to clinical trials.
- Stimulate virtual multidisciplinary forums that should improve management decisions and ultimately improve outcomes of patients managed outside tertiary cancer centers.

Ultimately, the same concepts apply to other aspects of the patient's journey and require attention as well. Palliative interventions throughout the whole process, rehabilitation services after treatment and end-of-life care to minimize suffering improve quality of life and should be integral part of all cancer control programs.

As a final comment, addressing and improving breast cancer control should have a wider and positive impact in LMIC healthcare systems. Available information suggests that healthier women do take better care of their children and contribute to a better society. Investing in women's health does have an impact in the education and productivity of their children and families. Societies that prioritize women's health should be expected to have a better outlook in future generations [30]. Furthermore, attention to breast cancer care should lead to improvements in healthcare in general and in parallel, result in strengthening of healthcare systems overall [12].

Finally, although recognition of inequities is important, much more important is what we can do about them. In that regard, we recently addressed the cancer control situation in Latin America and the Caribbean updating progress and remaining challenges particularly after the COVID pandemic that certainly negatively impacted efforts of diagnosis and complicated patient access to health care systems not only in LMIC but all over the world [31]. Acknowledging the significant complexities of cancer control in general and of breast cancer in particular we offer a few practical suggestions to guide efforts to improve outcomes in low resource scenarios (Table 1). These proposals are far from completely addressing all important issues but just serve as an initial road map. Collaboration of all involved stakeholders with local experts is required. Close interaction and guidance form international partner institutions should be sought as will aid in the local adaptation of each suggestion and help in the process to evolve to more detailed plans.

4. Conclusions

Breast cancer represents a significant global challenge. While identifying discrepancies is imperative, much more important, is what we do

about them. Moving away from silent indifference to proactive involvement is essential. The broad landscape of possible alternatives requiring study should be more than enough stimulus to engage all of us with passionate commitment. If we want effective, sustainable and longstanding solutions for these complex problems, all stakeholders should be invited and encouraged to actively participate.

Major global disparities in distribution and access to optimal care, compromise outcomes in a substantial proportion of patients with breast cancer and this should be a priority on the agenda of all countries. The main priority objectives should be provision of an early diagnosis and appropriate timely breast cancer treatment. Available evidence indicates these goals are feasible and can be implemented according to locally available resources.

Statement

This manuscript has not been previously published and is not under consideration for publication elsewhere.

Declaration of competing interest

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