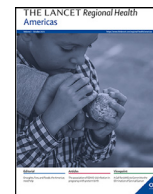




Contents lists available at ScienceDirect

The Lancet Regional Health - Americas

journal homepage: www.elsevier.com/locate/lana

Health Policy

Practical considerations for expediting breast cancer treatment in Brazil ☆☆☆

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ARTICLE INFO

Article history:

Received 24 May 2021

Revised 11 July 2021

Accepted 12 July 2021

Available online 3 August 2021

Keywords:

Breast neoplasms

Early detection of cancer

Cancer prevention and control

Health policies

Women's health services

Primary health care

One-stop clinics

Patient navigation

ABSTRACT

Patients in Brazil continue to present with late-stage breast cancer. Notwithstanding these figures, policies and programs to overcome this long-lasting scenario have had limited results. We enlist the main barriers for advancing breast cancer diagnosis in Brazil, based on the available evidence, and we propose feasible strategies that may serve as a platform to address this major public health challenge.

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1. Introduction

Breast cancer is the most common type of cancer and the main cause of cancer-related death among women worldwide [1] and similar findings have been reported in Brazil. According to the Brazilian National Cancer Institute, the disease is the most common malignant neoplasm affecting women. Estimates for the 2020–2022 period indicate 66,280 new cases of breast cancer each year, with 18068 deaths being documented in 2019 [2,3]. About 40% of all breast cancer cases in Brazilian woman are diagnosed at advanced stages (III and IV), and these figures have remained unchanged overtime [4] despite the strategies that have been implemented, such as screening and educational campaigns [5].

In 1990, a public health system with universal coverage was established in Brazil (*Sistema Único de Saúde, SUS*). With successes and setbacks in the implementation of health programs and organization of its health system, Brazil has achieved nearly-universal access to health services [6]. Cancer treatment is performed in specialized care units, with different levels of complexity, ranging from units with medical oncology and radiation therapy only, to hospital complexes [7].

It is well known that starting treatment quickly improves breast cancer outcomes [8,9]. Once the treatment allocation units are in place, the bottleneck of breast cancer continuum of care in Brazil remains early diagnosis and access to treatment. The reduction of waiting time to start therapeutic procedures is one of the main issues for improvement of patient's quality of life and possibilities of cure [10].

Important advances in the breast cancer continuum of care have been made through mammography, advanced surgical procedures, and adjuvant therapies. Substantial improvements in survival in many countries occurred, however, even prior to these technological and diagnostic advances, suggesting important and less cumbersome opportunities for early detection and treatment that can be more readily incorporated in low- and middle-income countries (LMIC) [11]. Throughout the text we discuss the challenges and point potential solutions to mitigate the impact of

☆ Personal opinion may not reflect the Instituto Nacional de Câncer orientation

☆☆ **Search strategy and selection criteria:** References for this Health Policy were identified through searches of PubMed with the search terms “breast neoplasms”, “early detection of cancer”, “cancer prevention and control”, “health policies”, “women's health services”, “primary health care”, “one-stop clinics” and “patient navigation”. Articles were also identified through searches of the authors' own files. Only papers published in English and Portuguese were reviewed. The final reference list was generated on the basis of originality and relevance to the broad scope of this Review.

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breast cancer in Brazil, with special attention to improving early diagnosis and treatment initiation, rate-limiting steps to the entire process.

1.1. Screening programs for breast cancer

As most breast cancers are attributed to non-modifiable risk factors, breast cancer control efforts cannot rely uniquely on risk reduction [12]. The World Health Organization (WHO) has defined two distinct but related strategies to promote the early detection of cancer: screening, with identification of asymptomatic disease in a target population of apparently healthy individuals, and early diagnosis, which is the recognition of symptomatic cancer at an early stage [5].

Brazil is a country of continental dimensions with an estimated population of 212 million inhabitants [13]. Despite the existence of a publicly funded health care system offering universal coverage, the Unified Health System (SUS), there are still wide socio-economic and ethno-racial inequities in access to health care [14].

2. Breast cancer late diagnosis in Brazil

Mammographic screening, the most widely accepted procedure with proven efficacy to promote early breast cancer diagnosis and improve survival [15], was introduced in Brazil as a public policy back in 2004 [16]. The coverage, however, could be higher, especially among women within the public system estimated to be at 60% of the target population and the repeated mammogram at follow-up within 24 months at 30% [17]. AMAZONA III, a recent prospective breast cancer registry in Brazil with 2950 patients with newly diagnosed stages I to IV breast cancer (63% being from the public sector), showed that only 34% were diagnosed through screening, while 66% were symptomatic at the time of diagnosis [18]. The distribution of breast cancer stage at diagnosis was: I (26%), II (42%), III (27%) and IV (5%). The incidence of women with late-stage diagnosis, i.e., stages III and IV has remained as high as 40% for more than a decade, a level more than twice the one in Norway, even before the introduction of mammographic screening in that country [4,5]. The current proportion with stages III and IV disease at presentation in developed countries remains much lower, ranging from 8% to 22% [19].

A nationwide hospital based-cancer registry network in Brazil estimated that a mammographic screening program with 80% coverage could have averted 2500 breast cancer deaths in 2012. In contrast, in the same year, if 80% of patients who were diagnosed five years earlier at stages III were diagnosed at stage II, 7500 deaths could have been prevented. Clinical stage change by early detection would have a greater effect than mammographic screening on breast cancer deaths for settings in which women present with late-stage disease. Therefore, the focus should be on timely diagnosis of symptomatic breast cancer rather than on screening for asymptomatic disease [5,20].

A recently published large randomized trial in India that compared clinical breast examination (CBE) screening with no screening showed that biennial CBE performed by trained female primary health workers significantly accelerated breast cancer diagnosis by 16 months, and also led to a shift at disease presentation with fewer stage III or IV cancers in screened women [21]. Overall, CBE led to a non-significant 15% reduction in breast cancer mortality; however, a post-hoc analysis demonstrated a significant reduction of nearly 30% in women aged 50 and older.

2.1. Access to treatment: the patients' journey

The finding of a breast abnormality can represent the initial step in a patient's breast cancer journey. At this point, access to

health care system is vital in reducing time to diagnosis. After history taking and clinical examination, imaging studies are due. Ultrasound is portable and can be used beyond breast imaging, making it more widely available than mammography in LMICs [22]. It is the preferred imaging tool for palpable lesions, it is less affected by breast density, in particular for younger women (over-represented in LMICs) who more commonly have dense breast tissue and it can provide ultrasound-guided breast biopsy [23]. Once a breast cancer diagnosis with its according subtyping is available and the results are conveyed, the patient may be transferred to a facility where appropriate treatment will start. Treatment varies according to the stage of the disease as well as the breast cancer subtype, consisting mainly of surgery or drug treatment as the first procedure.

In the Unified Health System (SUS), according to the Brazilian Health Ministry policy, once there is suspicion of breast cancer at primary care, women are referred to a named medium complexity unit for diagnostic investigation. After breast cancer is confirmed, treatment is administered at a hospital unit. Appointments must be made through a centralized regulatory system which organizes access to services by means of the appropriate referral in a timely fashion [24].

According to the WHO [25], early diagnosis programs are comparatively easier to implement, since they cover symptomatic patients only and they are less expensive when compared to screening procedures that target entire populations. There are three main steps to early diagnosis: awareness of cancer symptoms and getting medical care (access interval); clinical evaluation, diagnosis and staging (diagnostic interval); and transition to treatment (treatment interval) (Figure 1). Strategies focused on reducing delays between the detection of first sign or symptom and treatment initiation should address the delays in all these steps.

2.2. Strategies to mitigate late diagnosis and promote access to care

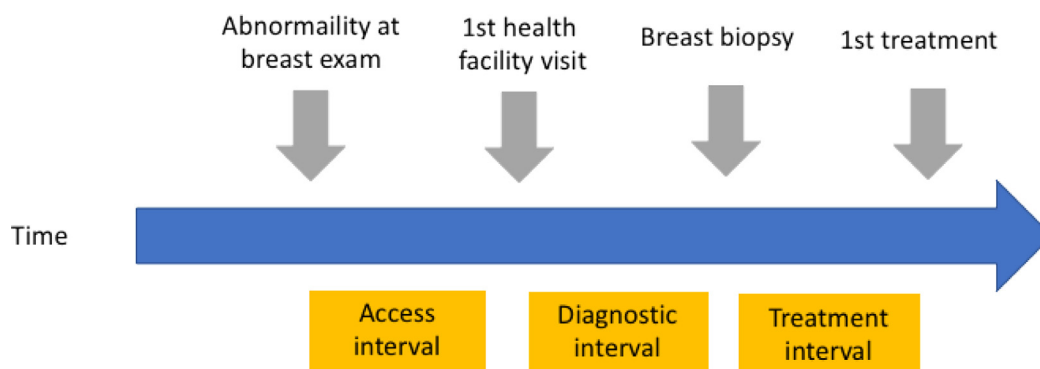
It is well known that starting treatment quickly improves breast cancer outcomes [8,9]. An ordinary law from 2012 defined the limit of 60 days from diagnosis to the beginning of cancer treatment in Brazil. Almost 40% of the patients experienced a delay in beginning their treatment for more than 60 days, being longer in SUS when compared to the supplementary health system [26]. More recent data showed that only 51% of patients started their treatment within 60 days from the date of diagnosis [24]. One may argue that in Brazil the main barrier resides in providing breast cancer diagnosis, the named second step. Inaccurate clinical assessment and delays due to inaccessible diagnostic testing, pathology and staging as well as the transition to treatment may be the resultant from poor coordination of services.

Policies and programs to overcome these barriers should focus on expediting the flow from early diagnosis to treatment initiation, as shortening delays in care may have significant impact in improving outcomes. We enlist potential strategies that encompass procedures and locations to attain these goals and provide existing local data when available (Figure 2).

2.3. Procedures

2.3.1. Clinical breast examination

Strategies to achieve earlier diagnosis of palpable lesions are quite different from formal screening programs. They aim to identify signs or symptoms, accelerate access to first diagnostic procedures and initiate treatment promptly. Prioritizing the reduction of the time intervals may constitute an affordable way of reaching greater impact in the outcomes of women with palpable disease [27]. Although clinical breast examination (CBE) has not been recommended as a primary screening modality due to its limited



Modified after WHO

Figure 1. Timelines to breast cancer early diagnosis and treatment initiation

evidence of benefit, there is emerging data signaling that women presenting with a new diagnosis of breast cancer are more likely to be diagnosed at an earlier stage of the disease if they report having had a previous CBE (unrelated to current diagnosis). In a population in which most breast cancers are self-detected, previous clinical breast examination was associated with shorter patient delay and earlier stage at diagnosis. In regions of the world that lack mammographic screening, the routine use of clinical breast examination may provide a resource-appropriate strategy for improving early diagnosis [28].

Brazil has one of the largest community health worker (CHW) programs in the world—238000 community health workers that serve as a bridge to the health system for nearly 160 million people, comprising 75 percent of the Brazilian population [29]. Evidence suggests that CHWs can play a number of important roles in breast cancer early detection initiatives in LMICs [30]: breast cancer awareness and community education, history taking and even performing breast examination that may be comparable to a physician's exam [31]. The implementation of systematic breast examination by trained teams in the primary care facilities, within a program that is already available in SUS and covers a large territory, could decrease the time from symptomatic disease to diagnosis.

2.3.2. Breast biopsy

Although breast ultrasound (US) is inappropriate as a stand-alone screening method, US is an established tool for suspected cancers. For patients with symptoms or signs suspicious for breast cancer, which typically comprise palpable lumps (but also, nipple inversion, localized skin retraction or other modifications) US is the method of choice at all ages including those under 40 [23].

When a suspicious lesion is identifiable on US, US is the preferred image guidance technique for percutaneous needle biopsy. Besides providing histologic diagnosis of a breast mass, immunohistochemistry (IHC) can successfully be done on the paraffin block obtained. Handheld US-guided breast biopsy has many advantages including being a fast procedure, associated with low costs, allowing for the use of smaller needles, being minimally uncomfortable for the patient and not exposing the patient to radiation [23]. According to European medical societies recommendations regarding the essential requirements for quality cancer care, 50 breast guided procedures a year represent the minimum caseload of a breast center [32].

Little data is available regarding core needle biopsy for breast cancer diagnosis in LMIC. A retrospective analysis of almost 900 core biopsies performed as an outpatient procedure at a regional center in India showed a high sensitivity (97%) and specificity (100%) for cancer diagnosis, associated with a low cost [33].

2.3.3. Accurate pathology

Currently, even after the breast lesion is biopsied, there may be long delays for a definitive breast cancer diagnosis. Pathology has been a bottleneck in the provision of appropriate clinical care in resource-constrained settings. Innovative approaches to breast cancer diagnostics are needed at the point of care in the absence of adequate tissue processing facilities, trained technicians to run those facilities, and pathologists [30].

Observational studies suggest that the median time from presentation to diagnosis in Brazil may go up to 72–185 days [34]. The percentage of women with more than 90 days from presentation to diagnosis may reach up to 68% [35]. Private health services are often utilized in an attempt to shorten these time intervals. Up to 43% of the biopsy results and 21% among patients in the public sector obtained their diagnosis in private services [36]. Improvement of the capacity of the regulatory system to recognize and to give appropriate pursuance of breast cancer cases, especially for the women that live far away from the diagnostic facility is critical in promoting early diagnosis [37].

Breast cancer is no longer considered as a single disease entity as the breast cancer subtypes behave differently, and therefore deserve to be treated accordingly. Tumor factors such as tumor size, nodal status, tumor grade, estrogen receptor, as well as HER2 status are key elements in providing optimal local and systemic treatments [38]. The concordance in the results between a reference laboratory and close to 150 local laboratories in Brazil was compared. Among 500 invasive breast carcinomas reviewed, there was a concordance in 89% and 85% of the results for estrogen and progesterone receptors, respectively and a much lower concordance of 34% regarding HER2 receptor testing, between local and reference laboratories [39,40].

A treatment delay of more than 61 days to chemotherapy administration before surgery (neoadjuvant chemotherapy) among patients with HER2-positive tumors may increase the risk of death [41]. In the adjuvant setting, similar findings were observed in the triple negative breast cancer subset (tumors that lack both hormone receptors and HER2) [42]. Expedite and accurate pathol-

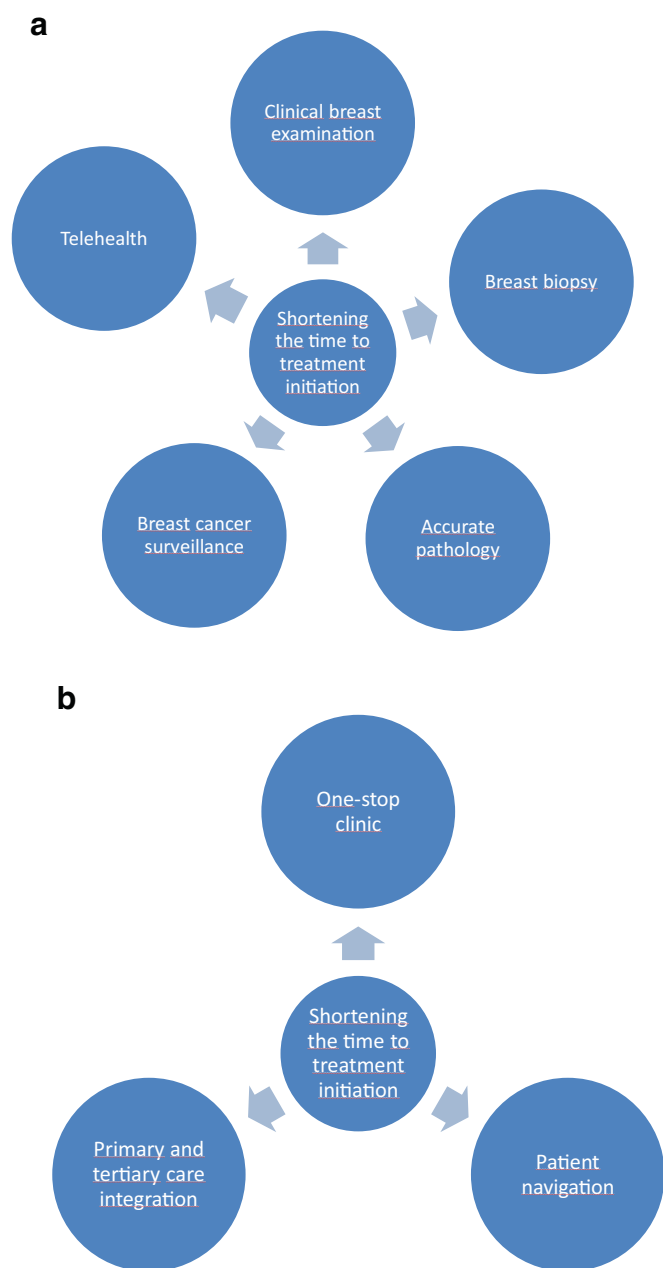


Figure 2. Shortening the time to treatment initiation. a: Procedures. b: Locations

ogy results can potentially set treatment prioritization for specific breast cancer subgroups in limited resources settings.

High-quality immunohistochemistry is the standard of care for hormone receptors and HER2 assessments but remains a challenge in LMIC hospitals. Initiatives such as telepathology aligned by main medical centers and platforms for performing quantitative reverse transcription polymerase chain reaction that is already widely distributed in LMIC for a variety of tests, including rapid diagnosis of tuberculosis, using a simple dedicated cartridge, should be entertained and could provide alternative options to speed up the process without demanding long time to implementation [43]. In Brazil, since most of the clinical pathology resources are allocated in high income regions and/or in the most populous urban centers, the centralization of pathologic studies in diagnostic centers, supported by telemedicine resources and direct communication lines with the point of care team could lead to a quick improvement

in the quality of the process, while requiring low investments in structure and personnel [44].

2.3.4. Breast cancer surveillance

Identifying a set of indicators to monitor and to evaluate in a breast cancer early detection program is essential for its program improvement and progress along a defined resource-stratified pathway [45]. Besides patient's age and the temporal trend in stage at diagnosis, metrics to be monitored include: the interval between onset of symptoms and healthcare evaluation, healthcare first visit and diagnosis, and between diagnosis and treatment initiation, mirroring the 3 steps previously described (Table 1).

Many high-income countries have comprehensive population-based cancer registries since the mid of 20th century [46]. The systematic gathering of data including all cases of cancer that occur in a specific area is crucial in determining the priorities for public policies. In Brazil, however, population-based cancer registries are decentralized at the municipal level and few of them provide reliable high-quality information. The Information System for the Control of Breast Cancer (known as SISMAMA) was created in 2009, but it remains mainly dedicated to mammography information [47].

Data regarding the incidence of invasive disease, late-stage diagnosis and cause specific mortality are other potential indicators to evaluate the effectiveness of a health care system in cancer control [4]. Along with survival information obtained from comprehensive population-based cancer registries, data are paramount in guiding and monitoring the results of the initiatives proposed to accelerate breast cancer diagnosis and treatment [48].













2.3.5. Telehealth

Due to the recent COVID-19 pandemic, there has been a delay in breast cancer diagnosis worldwide. Significant disruptions occurred to breast imaging, including deferred screening mammography, triaging diagnostic breast imaging, and changes in breast cancer care algorithms [49]. In Brazil, a similar trend took place. According to a cross-sectional study, based on the number of mammograms performed by the Brazilian public health services, provided by DATASUS, an open access database, the number of mammograms performed in 2020 declined by 42% when compared to the previous year [50]. This was accompanied by an increase in the proportion of palpable lumps.

The requirements for social and physical isolation required during the COVID-19 pandemic engendered a stimulus and enormous opportunity for further telehealth use, becoming a safer method to deliver health care to patients [51].

Brazil is a country of unique settings for telemedicine development and applications. Its broad territory, with isolated and difficult-to-access places, and an unequal distribution of quality medical resources, indicate there is huge potential for the expansion of telemedicine in the country [52]. Breast cancer diagnosis can be much facilitated by telehealth strategies such as health education (taking into consideration cultural barriers as well as public awareness), triage and on-line consultations, patient navigation, imaging and telepathology. One may take advantage of programs already in place. The Brazilian Ministry of Health established in 2007, the National Telehealth Program, focused on primary care, which was further expanded in 2011, and named Programa Nacional Telessaúde Brasil Redes. With a goal of training Family Health Strategy (ESF) teams, the Program is currently operating in 23 states of Brazil, with 8097 service units in total serving more than 3000 cities [52]. Overcoming barriers such as maintenance costs as well as restrictions imposed by health-care professionals, this plan may be adjusted to a wide range of diseases including early cancer diagnosis.

Table 1
Essential breast cancer journey data points

Metrics	From	To		
Time I		1st sign or symptom		Health care evaluation
Time II		Health care evaluation		Breast imaging
Time III		Breast imaging		Breast biopsy
Time IV		Breast biopsy		Pathology result
Time V		Pathology result		Treatment facility consultation
Time VI		Consultation		Treatment initiation (surgery or systemic treatment)

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2.4. Locations

2.4.1. Patient navigation

In most locations, where the care is fragmented, patients face enormous challenges moving through the sequential stations in complex health care systems. Patient navigation (PN) program is a coordinated process of patient-centered assistance that aims to overcome barriers in accessing timely quality care and treatment. Trained health care workers, volunteers and even patients advocates may be enrolled as patients navigators working through the different steps, ultimately shortening the time to breast cancer treatment initiation [53].

Alerta Rosa, a breast cancer navigating program in Mexico, has reported encouraging results. In their initial report after a one-year enrollment, they showed a median time from alert activation to treatment initiation of 33 days [54]. Further on, this program also developed a prioritization system based on patients more common symptom presentation and was able to identify women with different probabilities of having breast cancer.

A systematic review identified 113 published articles that assessed PN and cancer care [55]. Most publications focused on the effectiveness of PN in screening (50%) and diagnosis (27%) along the continuum of cancer care, with 52% of them related to breast cancer. Although unanswered questions remain, cost-effectiveness studies showed that PN programs yielded financial benefits.

Although not yet validated in low and middle-income countries, PN has great potential to alleviate the barriers faced by patients in the complex and fragmented health care delivery systems, improving outcomes of women with breast cancer in Brazil [56].

2.4.2. One-stop clinic

The facility where a clinical diagnosis is made may be different from where the biopsy is obtained, pathology reviewed and/or staging performed [57]. The greater the number of facilities that patients need to visit for cancer diagnosis and treatment, the greater the burden placed on individuals and families to overcome financial and geographic barriers and the greater the risk of duplicated services.

One-stop clinics are equipped and staffed so that patients may undergo a range of tests carried out at the same location, have their results reviewed by specialists, receive a diagnosis and, in some cases, have treatment in the same place without referral back to the general practitioner. A systematic review of twenty-nine studies reported on the use and outcomes of one-stop clinics in primary care patients for symptoms that could be indicative of cancer. One-stop clinics were associated with reduced time from referral to testing (15 versus 75 days), increased same day diagnoses (79% versus 25%), and were also associated with a very high acceptability by patients [58]. Symptomatic breast cancer patients being diagnosed at a dedicated breast assessment unit as compared to usual care had decreased time to diagnosis with lower costs [59]. One-stop clinic may shorten the time to treatment initiation, especially in more developed regions of the country, taking advantage of resources already in place.

2.4.3. Integration of primary and tertiary care

Initiatives to tackle cancer are frequently performed by specialists, mostly centered on secondary and tertiary care. However, the primary care physicians (PCP) are vital in all aspects of cancer

Table 2
Main barriers and suggested strategies to expedite breast cancer diagnosis and treatment initiation

Main barriers	Suggested strategies	Commentaries
Late-stage presentation	Clinical breast examination	Performed by trained health care workers in order to provide earlier diagnosis
Lack of a well-defined strategy to address palpable lesions	Breast biopsy	Handheld US-guided breast biopsy availability and training
Long delays for accurate pathology reports	Accurate pathology	Centralized pathology and telepathology
Insufficient data availability	Breast cancer surveillance	Systematic gathering of data to evaluate current situation and guide future initiatives
Unequal spatial distribution of medical resources	Telehealth	Health education, triage and on-line consultations, patient navigation, imaging and telepathology
Fragmented care	Patient navigation	Agents to facilitate moving through the various steps
Fragmented care	One-stop clinic	Clinical exam, breast biopsy, pathology and staging in one single center
Primary care and cancer centers as stand-alone units	Integration of primary and tertiary care	Enhance communication with delineation of roles

care at the population level. Their role extends from early diagnosis through palliative care, providing a holistic medical care. Furthermore, the PCP may help to navigate an otherwise complex and confusing system, providing a critical contribution from the very beginning in reducing cancer diagnostic delay [60,61].

Breast symptoms are a common reason for encounter in primary care. Signs and symptoms associated with an increased probability of breast cancer include increasing age, presence of breast lumps, thickening of the breast, axillary lymphadenopathy, and tethering to the skin or chest wall.

A cross-sectional survey including 886 patients referred to four major public cancer hospitals in Mexico City suggested that policy should focus on strengthening the quality of public primary care services and improving referral routes to cancer care centers [62]. The Mexican scenario resembles the one faced in Brazil where patient may start their diagnostic workup in a private unit and go through many different health services before reaching the treatment location instead of before arrival at the treatment location.

The Brazilian Health Care Network (RAS - Rede de Atenção à Saúde) is defined as the organizational arrangements of actions and health services coordinated by primary health care. The main barriers identified in the Breast Cancer Care Network in São Paulo, Brazil included the first contact of users with the health service, the high turnover of primary care professionals, the lack of standardization of referral and the low cooperation between municipal and state health services [63].

Cancer centers and primary care centers cannot exist as stand-alone services that do not communicate with each other and a greater reliance on PCP could improve the quality of patient care. Better communication between the tertiary sector and PCP across the cancer phases would enable clear delineation of roles and potentially improve the current results [64].

3. Conclusion

Patients in Brazil continue to present with late-stage breast cancer. Policies and programs to overcome this long-lasting scenario should focus on expediting the flow from early diagnosis to treatment initiation and ultimately ameliorating patients' outcomes (Table 2). Strategies may encompass procedures such as enhancement of clinical breast examination, breast biopsy and accurate pathology as well as breast cancer surveillance and telehealth. These actions take place occasionally in one-stop clinic, although more often patients will be transferred through different locations. Therefore, patient navigation and integration of the primary and tertiary care settings are key components that deserve further improvement.

As no one treatment fits all breast cancer patients, individual strategies aiming to improve early diagnosis and treatment initia-

tion should also consider the local cultural characteristics as well as the infrastructure already in place. Some of the suggestions provided are complementary while others may be even contradictory. Expedite and accurate pathology is an integral part of all diagnostic sequences, but one-stop clinic and patient navigation are unlikely to be present in the same location. Implementation of these actions involves other essential stages that include, but are not limited to, the program financing and policy making that were not currently addressed.

Despite the enormous amount of work to be done in order to change an enduring breast cancer late-stage presentation, Brazil has unique characteristics that provide an opportunity for many of the barriers to be circumvented. Brazil has a universal health system (SUS), a large community health worker infrastructure and an established information system for the control of breast cancer. Engagement of the various stakeholders and communication between the parts are essential elements moving forward.

Contributors

All authors contributed equally for the article.

Declaration of interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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