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RESEARCH ARTICLE

Disrupting the Status Quo in Late Diagnosis of Breast Cancers in the Resource Limited Settings

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ABSTRACT

Breast cancer tops the list of female cancers both in incidence and mortality. Eastern and south Asian countries have seen a very significant 86%-89% rise in age standardized incidence. Currently 5-year survival of breast cancer in low- and middle-income countries is only 40-60%. There is an urgent need to reduce delays in diagnosis of breast cancer and establish effective referral pathways to improve the observed low survival. Existing literature describes reasons for such delays in breast cancer management extensively, yet does not propose solutions to disrupt this status quo.

Pre-diagnostic delays and diagnostic delays are interdependent due to overlapping socioeconomic and cultural barriers to seeking health, and accessing and accepting care. Non-availability of diagnostic tests or trained human resource and out of pocket expenditure complicate these delays. Present article highlights probable solutions to mitigate these problems with an emphasis on resource limited settings.

Early diagnosis of breast cancer essentially involves reducing the delays in triple assessment of symptomatic patients in the context of limited resources. Clinical breast examination, use of ultrasonography and fine needle aspiration biopsy which are possible to organize at secondary level can mitigate some of the delays. Newer technologies like portable ultrasound devices, use of artificial intelligence, cartridge based real time receptor assay can further reduce the diagnostic delay. Many pilot studies and interventions using newer point of care tests are in progress to establish their role against gold standard investigations in clinical practice.

Delay in diagnosis cannot be mitigated by providing standalone solutions. Robust pathways with provision of green corridor for referrals, task shifting of patient navigation to various grassroot level health care workers, developing contextual practice guidelines, recognising challenges and weaknesses of cancer control system, and realizing importance of equitable distribution of health resources can strengthen the cancer control strategies and mitigate the delays in breast cancer diagnosis.

Introduction:

Breast cancer tops the list of female cancers both in incidence (accounting for 24.5% of all cancers) and mortality (accounting for 15.5% of all cancer deaths) across the globe[1]. The incidence of breast cancers, though lower at present in the low- and middle-income countries (LMICs) compared to the high-income countries (HICs), is rapidly rising due to demographic transitions and lifestyle changes[2]. While Eastern and South Asian countries have seen a very significant 86%-89% rise in age standardized incidence rates (ASR) of breast cancer between 1990 and 2017, a rise of 30%-35% in ASR has been documented in African countries during the same period[3]. The LMICs due to rising incidences and being some of the most populous countries in the world, account for a large share of global breast cancer burden. Farley et al predicted that 60% of breast cancer cases and 70% of breast cancer related deaths annually will happen in LMICs by 2040[4]. The inequalities in access to early detection services and stage-appropriate treatment between the higher and limited resourced countries account for the difference in 5-year survival of breast cancer patients, which may be as high as 90% in many HICs and only 40-60% in the LMICs. This not only leads to premature loss of lives, but also catastrophic health expenditure adding to poverty and social disruption[5]. The usual plight of the breast cancer patients was highlighted by an oncology hospital based study in India that reported breast cancer patients to be travelling a median 150 Kms (IQR: 80-255) to reach the oncology center and get a confirmed diagnosis, and having a median interval of 203 days (IQR: 110-401) between symptom onset and treatment initiation[6]. As expected, 65% of them presented at stage III or IV. The World Health Organization (WHO) brought the issue of delays in the management of breast cancer in LMICs to the global agenda through the Global Breast Cancer Initiative (GBCI) in 2022 and recommended early detection through health promotion and timely breast diagnostics as the key strategies for reducing pre-diagnostic and diagnostic delays respectively. Pre-diagnostic interval defined as the '*interval between women noticing the symptom and presenting to the healthcare provider'* and diagnostic interval defined as the '*interval between patient's first contact with the healthcare provider till the confirmation of diagnosis'* are dependent on several social, cultural and health system related factors. Most of the available literature focuses on discussing the factors responsible for prolongation of these intervals (delays) but falls short of providing solutions. Our current commentary addresses the issues of pre-diagnostic and diagnostic delays in breast cancer management in LMICs and discusses some of the possible context-appropriate solutions to reduce delays in the pathway of care to eventually reduce the mortality from breast cancers in these countries.

Factors responsible for the delays in the diagnostic pathway of breast cancer:

Large body of literature and systematic reviews of Asian and African studies have documented several factors affecting pre-diagnostic and diagnostic intervals in LMICs[7-9]. Pre-diagnostic delays ranging between two and six months and diagnostic delays up to

nine months were noted from Sub Saharan Africa[7]. A systematic review of 26 studies from Asian countries observed that diagnostic delays in breast cancer patients were more commonly associated with factors related to 'health care delivery' and 'health workforce' rather than those related to the patients per se (Table 1)[7-9]. There is a complex interplay and overlap between the patient and provider level delays in diagnosis of breast cancer. For example, lack of awareness and fear about cancer in the community compounds the existing diagnostic delay when combined with lack of provider level empathy and improper guidance. Similarly, non-availability of cost effective and accessible screening and diagnostic services further adds to patient and system level barriers to early diagnosis.

Table 1 Summary of Factors Responsible for Pre-diagnostic and Diagnostic Delays

	Factors at patient/community level	Factors at health system levels
Pre-diagnostic delay (late presentation after symptom onset)	• Lack of education and/or health literacy • Limited awareness to identify early symptoms • Low socio-economic status of the woman and her family • Unrealistic health beliefs and myths about cancer • Fear and stigma of being diagnosed as a 'cancer patient' • Social and cultural factors like family size and type, family dynamics and patriarchy • Lack of women's autonomy to make health related decisions	• Lack of access to affordable primary care services of appropriate quality • Nonavailability of organized screening program • Lack of female providers for breast examination/screening • Requirement of out-of-pocket expenditure for screening and/or diagnostic tests
Diagnostic delay (after patient has reached or contacted the health system)	• Lack of awareness that early diagnosis can cure cancer, especially when cancer is asymptomatic • Fear of biopsy and other complex procedures • Fear/stigma associated with getting a cancer diagnosis • Faith in traditional healers and other complementary medicinal practices • Dependence on family members to be able to access and/or pay for services • Lack of support from family members	• Lack of diagnostic facilities within accessible distance • Lack of adequate number of health professionals trained to provide appropriate diagnostic services • Cost of diagnostic services • No health insurance or the services are not covered by such insurance • Loss of wages if travel is needed for diagnosis • Inability to navigate through screening and referral pathways • Poor attitude of healthcare workers towards patients • Timings of services are inconvenient • Misdiagnosis, inability to interpret imaging or pathology findings

Reducing the pre diagnostic interval:

Based on the observation by Duggan et al.[10], countries having at least 60% of invasive breast cancer patients presenting at stage I or II were able to achieve a sustained annual mean reduction in age-standardised mortality rate of at least 2%, the GBCI identified detection of more than 60% of invasive cancers at stage I or II as a key indicator to monitor pre-diagnostic delays.[11] Increasing cancer awareness in the community and educating the frontline health professionals to be able to recognize the early symptoms and signs of breast cancer and perform a good quality clinical breast assessment should be the key strategies to achieve downstaging in LMIC settings with limited capabilities to roll out population screening. Raising public awareness through community nurses using educational resources tailored to the needs of local population and training the health staff in rural clinics and hospitals to be able to perform appropriate assessment of symptomatic women were instrumental in achieving a significant reduction in advanced stage breast cancers (from 60% to 35%) in Sarawak province of Malaysia[12].

Implementation of community awareness programme requires a structured plan prepared in consultation with all relevant stakeholders and adequate budget allocation. The communication strategies and the messages need to be contextualized based on local cultures, ethos, literacy level of the target audience and practices. DESH (Detect Early and Save her/ him) program implemented in a rural community in India documented that up to 57% of the adults participating in a survey reported cancer stigma to have long-term effects on their personal lives[13]. Cancer awareness and early diagnosis programs need to be integrated into the existing health systems involving frontline health providers like community health workers (CHWs), general practitioners, nurses and clinicians at PHCs. Such a programme has to recognize the faith of the community on traditional and complementary medicines and spiritual practices and educate the practitioners of alternative medicine[14]. Lessons can be learnt from the successful involvement of practitioners of traditional and complementary medicines in HIV control programmes in resource-limited countries[15]. Their communication skills, ready availability and acceptance in the community need to be leveraged.[10] CHWs have been traditionally seen as health promoters and educators for communicable diseases and maternal and child health. As the LMICs see a gradual but definite epidemiological transition from communicable to non-communicable diseases (NCDs), the CHWs need to be trained for their additional role in NCD control[16]. Highly visible campaigns using multi-pronged strategies (using brand ambassadors, billboards, media advertisements etc) focused on raising breast cancer awareness has been proved to improve breast cancer screening participation in Morocco[17]. In an urban community covered under employees health scheme in Mumbai, India women aged 30-69 were informed about the early symptoms of breast cancer and the benefits of early detection through letters sent to their home addresses once a year. In parallel, a breast clinic with comprehensive diagnostic facilities was established to evaluate the symptomatic

women. This resulted in an increase in the percentage of women with early breast cancer from74% to 81 % and node negative cancers increased 39 to 53%.

Population-based well-organized breast cancer screening can be highly effective in reducing pre-diagnostic delays. Mammography is the only screening modality that has demonstrated significant mortality reduction among 45- to 74-year-old women. Due to availability, sustainability and feasibility concerns, mammography cannot be advocated as a screening tool uniformly across LMICs. Though the International Agency for Research in Cancer (IARC) has accepted that '*sufficient*' evidence exists for screening with Clinical Breast Examination (CBE) to clinically downstage breast cancer at presentation, 14 years follow up of the randomized controlled trial conducted in Trivandrum, India comparing three-yearly CBE to no screening failed to show any mortality benefit[18,19].

In absence of a feasible and affordable screening modality, the priority for the LMICs would be early diagnosis of the cancer in symptomatic women, for which building capacity of the frontline health professionals to be able to suspect the cancer and perform a proper clinical breast assessment (of which CBE is a key component) is the key.

Reducing the diagnostic interval:

Reducing the diagnostic interval essentially involves reducing delay in triple assessment (clinical evaluation, radiological investigation, tissue diagnosis) of women presenting with breast related symptoms. Ensuring availability of accessible, acceptable, and affordable ways to clinical breast assessment, imaging, and tissue sampling to reach a confirmed diagnosis can remove the present bottleneck for health systems in limited resource settings[20].

IMPROVING CLINICAL BREAST ASSESSMENT

Every woman presenting with symptoms suspected of breast cancer at primary care needs appropriate clinical breast assessment that includes taking history, performing CBE including palpation of axillary and supraclavicular lymph nodes, documenting and interpreting the findings and referring the positive cases for radiological assessment without delay. The women without any abnormal findings need to be reassured. The numbers needing imaging and pathology services can thus be reduced to prevent overload on the diagnostic services at secondary and tertiary care hospitals. Training of healthcare workers and medical practitioners to perform an effective breast assessment would reduce misinterpretation of findings and false reassurance[8,21]. A systematic review addressing CBE documented that there was inconsistency in performance of CBE by various healthcare workers and training would improve their performance[22]. Though there is no consensus on the content and duration of a structured training programme that is required to build competencies in performing CBE, various randomized controlled trials evaluating CBE have trained various cadres of health providers (CHWs, midwives, nurses, clinicians) over up to three weeks[23]. IARC has an online resource available to correctly perform CBE, identify abnormalities and facilitate referral for imaging and pathology services[24-27]. Newer modalities of optical and microwave imaging to aid the clinical breast examination are not yet ready to be incorporated for use at the

healthcare facilities. These devices have wide variations in sensitivity, specificity and suffer from common problems like high scatter and low spatial resolution[28].

IMPROVING RADIOLOGY SERVICES

Breast imaging is an integral part of triple assessment for the symptomatic women as well as for women positive on CBE screening and can reduce many unnecessary biopsies and tissue samplings. Nonavailability of radiological investigations and the work force trained to perform these procedures at secondary level of care is a major challenge in LMICs and the patients do not have any option other than to attend the overcrowded and often far away tertiary care centers for these investigations. Diagnostic mammography has been the gold standard to confirm or rule out breast cancers. However, limited number of mammography facilities available in the LMICs are of variable quality and unevenly distributed with fewer numbers been installed in the semi-urban and rural areas. For example, India with more than 1.2 billion population has only 2700 mammography machines available, which is less than five percent of the mammography units installed in the US. Even if the number of machines available is adequate in some of the emerging economies, the capacity utilization is poor (e.g., only 30% in Brazil) due to lack of manpower, machine maintenance etc.[29] Newer advances in mammography including Digital Breast Tomosynthesis (DBT) and Contrast Enhanced Mammography (CEM) improve the efficacy of diagnostic mammography and are mostly unaffordable in diagnostic services in the LMICs[30].

Ultrasonography of the breast has emerged as the most frequently used tool in the diagnosis of breast cancers in limited resourced settings where almost all breast cancers are detected among symptomatic women[31]. Ultrasonography is generally available at secondary levels of care in LMICs and is a less expensive modality for diagnosis of palpable breast masses. Ultrasonography forms a useful diagnostic tool in characterizing these masses and helps in directing core biopsies[32]. Technological advances with high resolution ultrasound equipment and linear array transducers improved the lesion characterisation on ultrasound from cystic versus solid lesions to more detailing of benign and malignant masses. A meta-analysis involving 26 studies & 76,000 patients (recruited between 2000 and 2018) reported a pooled sensitivity of 89.2% to detect histopathology proved breast cancers with ultrasound in the LMICs, with a pooled specificity of 99.7%[33]. Majority of these assessments were performed on symptomatic women and ultrasound performance was superior to mammography in most studies.

In low-resource conditions, the poor facilities and unstable power grid make it difficult to install and use high- or middle-end ultrasonography machines. Hand-held smartphone/tablet-sized, battery-powered portable ultrasound devices (PUD) are available at a much lower cost. IARC is conducting a multi-centric study to evaluate the technology to triage women positive on CBE screening in settings where such screening programmes exist (NCT06056843)[34]. PUD has the same sensitivity and specificity as that of the conventional ultrasound examination of breast and is expected to reduce the high false positivity of CBE in a cost-effective manner. In the IARC study in

India, evaluation of CBE positive women with PUD is done by non-radiologist physicians or nurses, trained by certified radiologists, and the CBE positive women with obviously benign lesions (pure cystic lesions, fibroadenosis, fibroadenoma etc.) are reassured and rest of the women are advised standard triple assessment. The wi-fi enabled PUD allows sharing of images real-time to get an expert opinion. The study outcomes are expected by 2024 and will establish the value of PUD to triage CBE positive women in limited resourced settings. The same equipment can also be used by radiologists to direct core biopsies or fine needle aspiration biopsies (FNAB). Though ultrasound is emerging as a realistic and feasible solution for improving diagnostic intervals in LMICs, the technique suffers from subjectivity, operator dependence and high training need[35]. Efforts are ongoing to develop artificial intelligence algorithms for localization and classification of lesions, especially using hand-held ultrasound devices[36].

Artificial Intelligence based diagnostic technologies have a potential to revolutionize the scenario for breast cancer imaging for diagnosis as well as screening. 'Mammo Assist' has been developed as a new AI-powered tool that detects early-stage breast cancer and has been proved in trials to increase a radiologist's efficiency and output by over 50%, as well as providing a standard interface for communicating with healthcare systems such as Radiology Information System-Picture Archiving and Communications System (RIS-PACS) and "Electronic Medical Records". Similarly, teleradiology and teleconsultation of specialists for confirming the lesion and its malignant potential can overcome the lack of trained workforce in LMICs. Improving oncology services at secondary care centers by task shifting, use of teleradiology and standardization of reporting in sonography and other operator dependent procedures can improve capacity of secondary and tertiary care centers to accommodate the increased patient volumes created by early detection programs as done in Kenya.

IMPROVING PATHOLOGY SERVICES

Tissue sampling and pathological evaluation are integral part of triple assessment to establish the diagnosis of breast cancer. Limited availability of pathologists and pathology services is a major challenge in most LMICs, especially in rural areas. Average number of pathologists per head of population in Africa is less than 1/1,000,000; the number being 50-70-fold lower than that reported from the Unites States of America or the United Kingdom. Few pathologists working in public health system are only available in major cities[37]. The use of immunohistochemistry (IHC) to detect various molecular markers has become an essential component of breast pathology, but has further added to the cost and complexities of establishing, and sustaining pathology facilities leading to increased affordability challenges in low resource setting[38]. Lack of equipment, consumables, trained pathologists and technicians has compounded the problem of access to pathology services at secondary care hospitals where most of the breast cancers are expected to be diagnosed. In reality, the patients suspected to have breast cancer in most limited resourced settings have to visit the city-based tertiary care facilities for diagnostic confirmation. These centers being overburdened with

volumes of tests resulting in diagnostic delays and increased cost to the patients. The advantages of a centralized pathology service with standardized reporting and stringent quality control need to be balanced with decentralized and more affordable services closer to the community. Centralizing pathology tests creates bottlenecks difficult enough for many women to overcome and force many of them to drop out of the care pathway. Global breast cancer initiative recognized this critical need and recommended decentralization of pathology services.

Use of appropriate tissue sampling as per available resources can greatly help reduce the diagnostic delays resulting from patient movement and referrals, direct and indirect costs involved and possible drop out of patients during these stages. Currently, the two main modalities of obtaining a preoperative diagnosis of breast cancer are FNAB or core needle biopsy (CNB). FNAB from breast has a high diagnostic accuracy, is safe, economical and provides a rapid diagnosis and continues to be used in several parts of the world. The disadvantages of FNAB are its inability to diagnose tissue invasion, a slightly higher non-diagnostic rate and inability to reliably discriminate between invasive ductal and lobular carcinomas; limitations not applicable to CNB[39]. CNB additionally provides material for IHC-based molecular typing.

However, while assessing their clinical utilities these two techniques must be viewed in the context of 'palpable' or 'non-palpable screen-detected lesions', the former being much more common in symptomatic women. The accuracy of FNAB for non-palpable lesions is understandably low[39,40] with high inadequacy rates and this coupled with its inability to identify invasion has led to CNB being the preferred method for diagnosing non-palpable breast lesions[39,41-43]. On the other hand, for palpable lesions, FNAB or CNB have almost similar rates of sensitivity, specificity, and accuracy (Oyama, 2004). A systematic review and meta-analysis involving 46 studies and 16,642 patients with palpable breast lump reported pooled sensitivity of 93% and pooled specificity of 95% to detect breast cancers[44]. Same meta-analysis has shown that the risk of missing breast cancer is less than 1% when FNAB is included in triple assessment for palpable tumours[45]. Using a cytology prognostic scoring based on cellular morphology & arrangement, nuclear character, number of mitosis, and background features it is possible to comment on tumour type and grade[45]. Due to rapidity of the procedure and reporting, low cost, low training needs and less patient discomfort FNAB has high relevance in LMICs, the setting of prevalent diagnostic delays[46]. Rapid onsite evaluation (ROSE) of breast FNABs may provide immediate results to the patients and can be supported by tele-consultation in settings where pathologist is not available on site. PUDs can be used to improve the quality and adequacy of aspiration[47,48].

With the advent of neoadjuvant therapy, inability of immunostaining on FNA smears became a limitation of FNAB. This challenge can be overcome through preparation of cell blocks from the aspirated material that act as micro-biopsies[49]. Published reports from LMICs confirmed the reliability of FNA cell blocks for evaluation of hormone receptor and HER2 expression by IHC with excellent concordance with IHC staining of CNBs[50-53].

Immunohistochemistry to detect various breast cancer markers is a subjective assessment with high training need. A new cartridge based real-time reverse transcriptase polymerase chain reaction assay (Xpert® Breast Cancer STRAT4; Cepheid, Sunnyvale, USA) can quantitate the mRNA transcripts of estrogen receptors (ER), progesterone receptors (PR), human epidermal growth factor receptor 2 (HER2) and Ki67 in a closed system. Initial reports have shown a high concordance with IHC for ER, PR and HER2 with agreement of 98%, 93% and 90% respectively[54-56]. A cost-comparison analysis in Rwanda by Erfani et al revealed that per patient cost of STRAT4 assay was nearly half the cost of IHC. The test is objective, requires few pre-processing steps, can be completed in approximately one hour and the test platform is widely available in LMICs for detection of multi-drug resistant tuberculosis. Though the test is currently recommended to be performed using tissue sections from formalin-fixed paraffin-embedded breast cancer, IARC is conducting studies to evaluate alternative samples like sections from paraffin-embedded cell blocks or the cell smear sample scraped from the glass slides. A combination of FNAB to confirm diagnosis of cancer and molecular categorization of tumours using STRAT4 assay on either cell block slices or scrapes from FNA slides will provide all the information required to plan and initiate treatment and may be a solution to complete diagnostic evaluation in secondary care in LMICs.

Similar to radiology services, application of artificial intelligence and telemedicine have potentials to create access to expert opinion and improve diagnostic accuracy at centers with less experience. A virtual slide telepathology program was described as early as 2009[57]. Recently, The Kyabirwa Surgical Center in Jinja, Uganda, established a telepathology service in collaboration with an academic institution in New York City, demonstrating the feasibility of implementing a telepathology model[58]. Thus choosing an appropriate test as per available resources, decentralization of services, use of telepathology and cohousing of radiology and pathology services in the health facility can reduce the diagnostic delays in breast cancer.

Patient navigation to facilitate cancer early detection:

Patient navigation aims to reduce delays in cancer care access by helping patients overcome individual as well as health system level barriers and follows each patient till she/he attains a predefined end-point (e.g., definitive diagnosis). Navigation has been evaluated in several studies to improve participation in breast cancer screening and compliance of screen-positive women to further assessment. A systematic review of such studies reported 33.6% to 45.5% increase in breast cancer screening participation with the help of patient navigation compared to usual care[59]. Patient navigation has also been proved to improve access to timely diagnosis and treatment and treatment adherence among socio-economically disadvantaged populations[60]. Most of the patient navigation services in cancer care have been reported from the high income countries and they range from coordinating provider appointments to ensure timely diagnostic and treatment services to facilitating financial support[61]. A scoping review of patient navigation for cancer care services in the LMICs focusing predominantly on breast and cervical cancers

documented that the most common navigational services included counselling of patients to assist them understand their signs and symptoms, supporting them to avail follow-up services and coordinating appointments for diagnostic workup and treatment[61]. The scoping review also observed that most of the services were being provided at the tertiary care facilities that defeated the purpose to supporting patients to minimize the structural barriers they face in navigating the fragmented primary and secondary healthcare.

A patient navigation programme has to define the objectives and the target populations and determine the points of intervention across cancer care continuum based on the objectives and population characteristics. Understanding the barriers faced by the target population to access services and their needs through sample surveys among the population and cancer patients will help design the navigation services. Background and qualification of the patient navigators and their responsibilities will very much depend on the services they are expected to provide. The navigation approaches are highly variable and may include counselling and information sharing through help-lines, having a nurse, counsellor or cancer survivor in the facility to provide assistance, CHWs providing services at home etc. Training of the navigators and periodic evaluation of the impact of such services are essential for effective navigation.

Improving breast cancer care in the broader perspective of cancer control policies:

Primary care is the first level of contact of a symptomatic woman with the health system and secondary level of care is the first level of referral where her disease is to be confirmed and some of the therapeutic interventions (e.g. breast conservation surgery, first line chemotherapy) can be performed. Table 2 summarizes the different strategies that can be adopted at primary and secondary levels of care (the weakest link in the care pathway in most LMICs) to improve breast cancer early detection. More efforts and resources need to be invested to conduct implementation research in various settings to get better insights into how these strategies can be best adapted to different health system contexts. We have advocated for reinstituting FNAB as the final tissue diagnostic procedure as detection of expression of the receptors and HER2 and Ki67 is now feasible. One valid concern about using FNAB as the final diagnostic measure is its inability to differentiate between in-situ and invasive cancers. However, the proportion of in-situ cancers among women presenting with palpable masses in the LMICs is extremely low. In the IARC led Indian randomized trial evaluating CBE a total of 6122 CBE-positive cases were detected in 53,418 asymptomatic women[19]. Among them only four cases of carcinoma in-situ were detected among total 119 breast cancers detected at baseline. The proportion is likely to be even lower in symptomatic women.

Table 2: Reducing the diagnostic delays

Levels of care	Current challenges in LMICs	Strategies for Mitigation of delay
Primary care	• Patients with symptoms have to attend a specialized care facility for consultation and diagnosis that may be far away from home, over-crowded and do not have comprehensive diagnostic facilities	• Competencies developed of general practitioners, clinicians and nurses at primary care in clinical breast assessment • Practitioners of traditional and complementary medicines are integrated in routine care • Services are free of user charges or covered by insurance
	• Women hide symptoms or do not attend CBE screening (where available) due to myths, misconceptions, fear and stigma associated with cancer diagnosis	• A programme with adequate budget for contextually appropriate, structured and sustained health communication in the community and/or primary care • Availability of women health providers • Navigation through CHWs, helpline etc.
	• Screening for breast cancer with CBE exists but sending large number of screen-positive women to higher facility is a challenge	• Use of handheld portable ultrasound devices (PUD) to rule out obviously benign conditions or normal breasts by trained medical officers or nurses. Same may be applicable for symptomatic women also. A practice guideline and a training curriculum incorporating the new strategies to be developed
Secondary care	• Lack of specialists and trained workforce and infrastructure to perform triple assessment of the women with suspected breast lesions either on clinical breast assessment of CBE screening	• Having a policy and plan to build/improve capacity at secondary level of care to complete diagnostic workup within a stipulated duration • Building capacity to perform breast ultrasound (and also diagnostic mammography, if available) • Use of PUD to reduce the load on routine ultrasound service that is usually engaged in antenatal checkups and other routine assessments • Training of specialists (surgeon, gynecologist, radiologist) and non-specialist clinicians to be able to perform FNAB (with or without ultrasound guidance) • Building capacity at the hospitals to stain and read FNAB slides, prepare cell blocks and perform IHC on cell blocks • Co-housing radiology and pathology services will improve coordination • Possibility of introducing STRAT4 tests using an existing test platform in the hospital to be explored • Relevant practice guidelines to be developed involving all stakeholders • Regular monitoring of the time taken to complete the diagnostic process after registration of the hospital
Referral pathways	• Patients get lost in the diagnostic workflow at busy secondary hospitals that results in delays and often dropouts	• Better coordination between and primary and secondary level of care and also among various departments within the hospitals • Having a contextually appropriate and feasible system of navigating the patients across the flow of services (including getting appointments) • Extending Role of community health workers as navigators
	• Lack of knowledge about government schemes for financing investigations and treatment at higher centers when such services are not available for free of charges	• The entitlement of the patients in the insurance schemes to be well advertised • The navigators as well as the service providers need to be well aware of these schemes • A dedicated office at the hospitals to support patients getting more information and submit claims for reimbursement

As emphasized by the GBCI of WHO, improving breast cancer diagnosis and treatment through reduction of pre-diagnostic, diagnostic and treatment delays cannot be considered in isolation. Integration of breast cancer control program in existing healthcare systems is essential to maximize the use of resources and make services more efficient and effective. Many LMICs can be cited as models for this integration and best practices in cancer control.

Zambia built their breast cancer program on the existing cervical cancer and HIV control programs without significant additional investment in infrastructure or workforce[62]. It also recognized fragmented efforts by multiple organizations and initiatives and made an effort to bring them under a single consortium. A robust SWOT (strength, weakness, opportunities and threats) analysis of the existing services followed by capacity building among radiographers, nurses, general surgeons led to integration of services by utilizing existing human resources and services.

Brazil has prioritized use of strong health technology assessment before investing in health interventions including cancer care. The country has implemented extension of universal health care, decentralization of diagnostic services to smaller cities and incentivization of the registered referral centers to mitigate inequity in cancer care[63]. Cancer patients in Brazil have the legal right to initiate treatment within 60 days from the pathological diagnosis of cancer and effort is ongoing to apply the 'sixty-day law' to diagnostic interval.[64]

Countries have successfully established a 'green corridor' within the system to facilitate further investigation of the women with abnormal findings on clinical breast assessment without unnecessary delay[65]. Such an approach requires a documented protocol for referral and a benchmark for completing all the investigations within a stipulated period.

National health insurance (NHI) also plays a big role in reducing affordability issues and subsequent inequity and delays in breast cancer diagnosis. In Most LMICs in sub-Saharan Africa, the health systems are gearing up towards NHI, but coverage is variable[63]. Partnerships with HICs and Various international bodies like IAEA, IARC and WHO can handhold the LMICs during this phase of integrating their breast cancer program with comprehensive cancer control activities within existing health systems. IAEA through its Program of Action for Cancer Therapy (PACT) provides evaluations and training and guidance resources for improving cancer control including breast cancer early detection and treatment[66].

Conclusion:

A united global effort with guidelines based on resource stratification, use of newer affordable technologies, decentralization of services and task shifting, more investment in human resource development and health systems integration approach can reduce the diagnostic and pre-diagnostic delays in breast cancer diagnosis. It is important to highlight the fact to policy-makers and all stakeholders that a delay exceeding 90 days between breast cancer symptom onset and treatment initiation can increase the odds of death by 47% (95%CI 42% to 53%) compared to those having shorter delays[67].

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