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GLOBAL BREAST CANCER (AB CHAGPAR, SECTION EDITOR)

Late Presentation of Breast Cancer in Lower- and Middle-Income Countries

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Abstract

Purpose of Review Breast cancer incidence and mortality in low- and medium-income countries has increased and is predicted to rise. Late presentation, associated with poor prognosis, is unfortunately common to most of these countries. This review discusses recent studies and offers recommendations to address pertinent issues raised.

Recent Findings Late presentation continues to prevail in many LMICs, worse in sub-Saharan Africa. Socioeconomic and demographic factors play a significant role. The fear of mastectomy is a prominent cause of reluctance to seek treatment. Increasing awareness, clinical breast examination and opportunistic mammographic screening have a role to play in addressing the issue. The provision of health infrastructure and creating access may overcome some of the other factors that sometimes seem unsurmountable.

Summary Late presentation of breast cancer in LMICs must be addressed through implementation research and the institution of tailored and innovative approaches.

Keywords Late presentation · Breast cancer · Low- and middle-income countries · Mastectomy

Introduction

Breast cancer is the leading female cancer worldwide, with nearly 2.1 million new cases expected in 2018 [1••]. Worldwide incidence varies across countries and regions; it is relatively higher in the high-income countries, with age-standardised rate of 92/100,000 in western Europe compared to 29.9/100,000 in East Africa (Globocan 2018) [1••] The lower incidence in low- and middle-income countries (LMICs) may be due to absence of screening programmes and a dearth of risk factors for the disease. Breast cancer incidence in the high development index (HDI) countries increased in the late 1980s and 1990s. Since then, mortality rate for breast cancer continues to decline in high-income countries (HICs) whereas lower- and middle-income countries (LMICs) document higher mortality incidence ratios [1••, 2•]. The reduction in mortality in HICs has been attributed to two main factors: the detection of early disease and effective accessible treatment and research [2•, 3].

There is an increasing incidence of breast cancer in LMICs attributable to an ageing population, changes in lifestyle (diet, lack of physical activity and obesity), reproductive factors (early menarche, delayed and fewer childbearing, shorter periods of breastfeeding), increased awareness and better reporting [1••, 4–6]. These nations with fewer resources and weak health systems are unprepared to handle the anticipated increase in incidence and may thus result in disproportionately higher mortality [1••].

Many LMICs in Africa, Asia and Latin America continue to document high breast cancer mortality rates [4, 7, 8]. The CONCORD-2 study from 279 population-based registries in 67 countries showed that 5-year survival in patients diagnosed between 2005 and 2009 was 80% in HICs, compared to LMICs like India (60%), South Africa (53%) and the Gambia (11.9%) [9, 10•].

The mortality rate from breast cancer in LMICs remains high for many reasons. It competes with other communicable and non-communicable diseases for a stake in meagre health

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spending budgets in many of these countries. Poor health infrastructure and governance structures are directly linked to lack of economic prosperity, resulting in hampered early detection strategies by the absence of effective screening programmes [11]. Not surprisingly, one of the main reasons for late treatment is the patient delay in accessing treatment [12]. Limited access to timely and effective interventions following detection and diagnosis of breast cancer is a major hindrance to improving outcomes.

Existing health infrastructure, geography, cultural and genetic build up are factors influencing the health care needs of a society. However, the implementation of broad evidence-based strategies to improve health outcomes is heavily dependent on available socioeconomic elements. Here, we look at the various factors in LMICs influencing late presentation of breast cancer and evaluate current recommendations to improve the situation.

Difference Between Breast Cancer in HICs and LMICs

Breast cancer in LMICs differs from HICs in that they occur in relatively younger age groups (about 10 years earlier than in HICs); most cases seen are in the 40- to 49-year group [10•, 13–18]. The median/mean age at diagnosis is between 44 and 49 years in most LMICs [14, 17, 19–26]. This could be a result of the population structure (majority being young) in those countries.

Additionally, breast cancers in many LMICs have poor prognostic factors such as higher grade and hormone receptor negative tumours [21, 25–27].

Delay in Presentation and Treatment of Breast Cancer in LMICs

Patient and systemic factors are significant contributors to profound treatment delays in LMICs [27].

Patient delay is "the time it takes for a woman to seek help once she has discovered a breast symptom" [28].
System delay is "the time it takes for a woman to be evaluated, diagnosed, and treated once she has sought help" [28].
Patient delay may be influenced by the inaccessibility of health facilities; system delay may also be influenced by patient factors, e.g. patients may be reluctant to proceed with treatment following diagnosis, choosing to consult other practitioners of alternate medicine. In our experience, a significant number of patients in West Africa abscond following diagnosis [29, 30].

Late presentation is rife in most LMICs [26, 31]. Most patients (33–90%) present more than 3 months after noticing changes in the breast [21, 24, 32–34]. Mean and median delays are as high as 10 months (Ghana [median]), 10.3 months (Cameroon [mean]), 13 months (Uganda [median]) and 18 months (Ethiopia [mean]) [24, 29, 32, 34]. Socioeconomic and racial factors could explain why in North America, African-Americans present relatively late compared to their Caucasian counterparts [35, 36]. These findings were echoed in another study in which the odds of late-stage breast cancer presentation among African-American women were higher compared to their white counterparts (OR 1.433; 95% CI, 1.316, 1.560) [37••]. In Canada (British Columbia and Ontario), immigrant women were significantly less likely to have screen-detected breast cancer (adjusted RR 0.88 [0.79–0.96] in British Columbia, 0.88 [0.84–0.93] in Ontario) than long-term residents, in spite of equal access to health facilities. Significantly longer median diagnostic interval (2 [0.2–3.8] days in British Columbia, 5.5 [4.4–6.6] days in Ontario) was documented in the immigrant women. [38].

Disparities in late breast cancer presentation among racial/ethnic groups are seen within LMICs and in societies with people of diverse racial origins like South Africa (blacks have a lower incidence but present late with more advanced disease) and Malaysia (late disease commoner in Malays than Indians) [25, 39]. The reasons have not been clearly elucidated but may be due to socio-economic factors.

Between 50 and 80% of breast cancer patients in LMICs present with stage III/IV disease [35, 40–46] (Table 1).

Although there is marked heterogeneity between populations, the general trend portrays a high number of stage III/IV cancers in LMICs. The variation reported from countries within this cohort is illustrated in Table 1.

The large proportion of advanced stage disease is reflected in the treatment practices of breast cancer management in these populations: high rates of neoadjuvant chemotherapy (an attempt to make locally advanced tumours operable), no surgery at all (on account of metastatic disease) and high mastectomy rates with low rates of breast conservation [22, 33]. The lack of radiotherapy facilities in these countries may be contributory to the low breast conservation practices as well [47].

Reasons for Late Presentation

The reasons for late presentation are complex and multiple, but there are common threads such as low level of awareness, failure to recognise the symptoms and denial [48]. Others include fear and misconceptions [4].

Cultural practices, religious and other beliefs compound the problem and may be population-specific.

Table 1 Breast cancer stage at presentation in LMICs with emphasis on stage III and IV (per cent)

Country	Stage I	Stage II	Stage III	Stage IV	Stages III and IV
Rwanda [19]	24		52	24	76
Ghana [40]	14.5	17	47.2	5.2	*52.4*
S Africa [43]	17.3	21.9	27.8	32.9	*60.7*
S Africa [44]	5	41	45.7	8.3	*54*
Cambodia [14]	1.6	20.6	53.6	24.3	*77.9*
Pakistan [20]	2.7	33	52.1	12.3	*64.4*
Pakistan [31]	5	25	38.3	31.6	*69.9*
Malaysia [42]	7.7	32.7	17.3	42.3	*59.6*
Uganda [45]	8	17	65	10	*75*
Nigeria [23]	11.7	26.2	46.6	15.5	*62.1*
Ethiopia [24]	3	27.3	57.4	12.2	*69.6*
India [46]	46		54		*54*
Cameroon [35]	29.2		70.8		*70.8*

Patient Level Factors

Socioeconomic and Demographic Factors

Ali et al. in South India showed that some socioeconomic and demographic factors had a bearing on late presentation. In a multivariate analysis, being divorced or widowed $p = 0.045$ (95% CI 0.89–2.37) and being illiterate $p = 0.045$ (95% CI 1.06–7.03) were independent predictive factors of late presentation [49]. Brinton et al. drew identical conclusions in a large population-based case-control study of breast cancer in two cities in Ghana [50••]. A meta-analysis of 10 studies from the middle east suggested that older age and poor educational level are associated with late presentation [51]. A retrospective analysis of 170,757 patients in hospital-based cancer registries in Brazil showed that the odds of presenting with advanced disease reduced with increasing education: primary (incomplete), primary (complete), secondary and higher education [52].

Low level of literacy (i.e. less than 8 years of education) was a barrier to early presentation of breast cancer in many reports from LMICs [19, 21, 39, 41, 50••, 53] (Table 2).

Breast Cancer Awareness

Ignorance about the cause, symptoms and treatment of breast cancer have been found in majority of surveys from LMICs [54–56]. Misconceptions about the cause of the disease are not uncommon. In Uganda, misconceptions included beliefs that money in the brassiere caused breast cancer (82% of 401 respondents) [57•].

Many expect breast cancer would be painful. The absence of pain has thus led to significant delays [58]. This belief is not limited to LMICs. In a publication from Singapore, 71% of respondents believed that breast cancer was always painful [59]. In our experience, the expectation that breast cancer would be painful can be a major barrier to early presentation. Other patients simply do not recognise the symptoms of breast cancer and thus report late [4, 5, 19, 28, 43, 60].

In a survey of 401 Ugandan women, Scheel et al. found only 19% of respondents thought that breast cancer could be treated successfully [57•]. In our own interaction with women, many are unaware that breast cancer can be treated successfully, and this is one of the reasons they give for delay in reporting to hospital or absconding after diagnosis.

Fear is recognised as an important cause of late presentation [29, 39, 43, 55, 59, 61]. The fear is invariably of mastectomy and chemotherapy [62]. The breast is an object of femininity, beauty and a powerful symbol of maternity in many cultures [63]. The fear of losing the breast often causes delay resulting in inoperable locally advanced cancer or metastatic disease. But, breast conservation could have been done if they had reported earlier. In some countries, the fear of losing the breast is because of stigma and misconceptions. The stigma has led to many patients waiting for months before seeking help [55].

Some have argued that poor knowledge about breast cancer is associated with a reluctance to be screened [57•, 64], and lack of breast awareness and knowledge about early detection methods has also been cited as a barrier [53]. Joffe et al. in South Africa, for example, showed that greater knowledge of breast cancer was related with lower stage at diagnosis [39]. However, others have found that knowledge about breast screening, symptoms of cancer and its treatment does not always necessarily translate to early presentation [65]. In their review paper of 51 studies from Nigeria that included 19,500 respondents, the authors found that knowledge about breast cancer in that country was relatively high in spite of late presentation. They concluded that "low awareness of breast cancer may not be the direct and foremost driver of persistent late presentation in Nigeria" [65]. Other factors, like deeply held cultural beliefs, may take precedence in times of vulnerability [66].

Table 2 Socioeconomic and demographic (SED) determinants of late disease, LMICs

Publication (country)	Sample size	SED factor	OR or *p*	95% CI
Brinton L et al. (Ghana) [50••]	1184	Poorly educated	OR 1.96	1.32–2.9
		Separated/divorced	OR 1.75	1.18–2.6
		Widowed	OR 2.25	1.43–3.55
Ghazali et al. (Malaysia) [33]	236	Divorced/widowed	OR 2.67	1.3–5.5
		Never performed BSE	OR 2.19	.09–4.38
Odongo J (Uganda) [32]	162	No social support from spouse or family	OR 7.1 $p = 0.001$	2.4–21.5
Gulzar et al. (Pakistan) [21]	125	Poorly educated Rural dwelling	$P < 0.001$ $P = 0.005$	
Ali et al. (South India) [49]	522	Divorced or widowed	$p = 0.045$	0.89–2.37
		Poorly educated	$p = 0.045$	1.06–7.03
Čačala et al. (S Africa) [43]	172	Less electricity in homes Poorly educated	$p < 0.05$ $p < 0.05$	

Cultural Issues

In many LMICs, there is a widespread belief that breast cancer is a spiritual disease and often leads to patient delay as they sometimes seek the help of spiritualists, or simply believe it is not a disease for orthodox medicine, thereby turning to alternative medicine [21]. Ancestral and spiritual beliefs, lack of health literacy and mistrust of the health system are compounding factors towards poor health-seeking behaviours [67]. Many patients prefer the use of alternative medicine and only report to the hospitals when the disease becomes inoperable. In Rwanda, many patients reported late because they consulted a traditional healer first [19, 61]. There are similar reports of delays attributable to the use of herbal and other alternative medicines in other LMICs [21, 34, 58]. In our own experience, we have known many knowledgeable people, including health professionals, who have resorted to their cultural and spiritual beliefs when they had breast cancer, and avoided hospital treatment until the tumours became locally advanced or metastatic.

Financial Constraints

Aside from cancer awareness and cultural issues, many patients report late because of financial constraints or the belief that treatment will be unaffordable [19, 21, 68, 69•]. Although some countries have national health insurance schemes, patients nonetheless often bear direct and indirect costs.

System-Level Factors

Access to care is a challenge in many countries with limited resources. Lower resourced countries in Europe continue to report significantly worse breast cancer outcomes than better resourced countries, often due to their weaker health systems. This may lead to a more advanced stage of breast cancer at diagnosis in these countries. For example, Eastern Europe reports local advanced breast cancer presentation of 65–85% compared to 9% in northern Europe [64].

Many LMICs lack the infrastructure and the ability to sustain an effective mammographic breast screening programme; and even where there is access to this, uptake may be low [64] as there are other physical and psychological barriers that prevent women in LMICs from breast cancer screening, including domestic responsibilities, pain and embarrassment [70]. In many LMICs, organised mammographic screening is simply impractical due to lack of infrastructure and capacity to provide downstream care for non-palpable tumours, and clinical breast examination and ultrasound are often considered a more cost-effective option to downstaging breast cancer [71•]. In Peru, women who had undergone previous clinical breast examination (CBE) were more likely to have early stage disease on presentation (OR 2.44, 95% CI 1.01–5.95) [72•]. Despite this, unfortunately, LMICs are less likely to promote breast cancer screening and early detection strategies in their national cancer control programmes due to competing needs [73].

Diagnostic facilities and services (radiology and pathology) as well as treatment facilities (oncology centres with radiotherapy machines and even surgical services) are not accessible to majority of the people [10•, 47]. Patients often are dissuaded from seeking treatment due to long travel distances to access healthcare. For example, in Rwanda, patients in the same district as the main health facility were found to have less delay than those who lived in other districts [19]. Still, poor access to quality cancer surgery in LMICs is a major bottle neck to improving outcomes especially for locally advanced breast cancer [74].

Thus, inadequate healthcare infrastructure is a major contributor to patient delay [20]. Greater than 3-month delay from symptom onset to treatment is associated with poorer survival [75], and sadly, palliative care is not well developed in the majority of LMICs where morphine is often unavailable [76].

Impact of Late Presentation

Globally, advanced stage breast cancer as a result of late presentation results in poor outcomes and is a major drain on resources [77]. Indeed, stage at presentation is the most important single determinant of breast cancer survival and a major contributor to disparities in outcomes worldwide [78, 79].

Late presentation manifests in larger tumour size and axillary nodal involvement, both known to adversely affect survival [40]. In HICs, age-standardised net survival rates for breast cancer is over 85%, compared to sub-Saharan African countries reporting as low as 53.4% (95% CI: 35.5–71.3) in South Africa and 11.9% (95% CI: 0–24.7) in Gambia [9, 10•].

Recent publications from Ethiopia, Uganda, Ghana and South Africa [Soweto] demonstrate that, even with limited resources, survival of patients with early stage disease is high, with 5-year survival rates of stage 0 and stage I breast tumours almost comparable to those in advanced countries [40, 80–82]. It would therefore appear that the poor overall survival rates of breast cancer patients in these countries could be attributed to the larger proportion of advanced disease cases seen at presentation [40].

Late presentation is associated with locally advanced and metastatic disease putting a strain on the meagre financial resources and underdeveloped palliative care services. A good number of patients present with de novo metastatic disease requiring expensive and often complex medical and surgical interventions to maintain a good quality of life. For example, brain metastases will require a CT scan and radiotherapy, pleural effusions will require thoracostomy, bone metastases will require bone modifying agents such as bisphosphates, radiotherapy and complex surgery to fix pathologic fractures. Metastatic disease often requires several lines of expensive systemic therapies, and still may not be associated with disease resolution. In the absence of some form of public health insurance, this situation often results in catastrophic spending [83]. Death is inevitable within a short time from diagnosis of metastases, often following a drastic drain on family finances, affecting the morale of patients and care givers, worsening stigma associated with a cancer diagnosis and higher reliance on unorthodox health practices [84].

These tumours tend to be large, often associated with peau d'orange and or ulceration with offensive discharge and bleeding. The patients are shunned by loved ones and society further worsening the stigma and helplessness. They may also often present with lymphedema, a difficult condition to treat and associated with disability, unproductiveness and low quality of life [85]. Long-term survivors of advanced disease having gone through countless medical procedures, treatments and psychological hiccups are at higher risk of significant consequential health problems compared to survivors following early cancer treatment [86]. The management of such tumours poses a challenge to under-resourced countries with inadequate numbers of oncology specialists, radiotherapy equipment, palliative care service and primary care physicians. The cost effectiveness of many evidence-based treatment guidelines developed in HICs may not be applicable in these group of patients requiring further investment in implementation science [87].

In effect, the paradox is that for patients in LMICs with advanced disease, the treatment of breast cancer becomes relatively more expensive with unsustainable out of pocket payments. Thus, the result of late presentation is indeed very dire. Overstretched health systems and many patients in LMICs cannot afford the high cost of managing advanced disease. Patients and caregivers spend their last days in worsening poverty, pain and regret.

Recommendations

Education

Increased breast cancer awareness including addressing misconceptions and healthy lifestyle adjustments must be prioritised. Reports from many LMICs have confirmed that knowledge of breast cancer breast awareness is unacceptably low [57•, 88, 89]. This should be addressed through culturally sensitive educative programmes starting from basic community and primary care levels [43, 90, 91]. Educational materials must also be customised to each target group with consideration of the cultural and religious beliefs involving community opinion leaders and practitioners [91].

Screening

For many years, population mammographic breast screening was accoladed for reducing breast cancer mortality. Recently, the effectiveness of screening mammography in reducing breast cancer mortality has been questioned and continues to be debated [92]. Even so, there are challenges in instituting screening programmes in LMICs due to logistical issues and the relatively young population with dense breast who cannot be effectively screened with mammography. In studies from Switzerland, opportunistic and organised breast cancer screening yielded overall little difference in prognostic profile [72•, 93]. Teh et al., in a recent review, concluded "in a setting with resource constraints, targeted screening of high risk individuals will give a higher yield" [94]. It is a model worth considering as LMICs attempt to adopt a variety of measures to address the problem of late presentation. Clinical breast examination is a viable option to downstage tumours and reduce mortality and can be performed by nonskilled trained attendants [95]. Breast self-examination is recommended by many professionals, if only to create more breast awareness; it should be encouraged [96]. It is imperative that countries with

limited resources be encouraged to invest in cost-effective early breast cancer detection strategies to promote down staging [97].

Affordable and Accessible Care

The provision of affordable and accessible facilities for early detection and treatment may lead to early detection. Egypt, for example, started implementation of a programme in 1984 which included intensifying education about breast lumps, establishing interconnected referral pathways across all lines of comprehensive management, phased international and local training of skilled health care workers and improved accessibility to health interventions for all citizens free of charge. Their basic guiding principle was that "early detection programs would be frustrating for both patients and health authorities if patients were unable to afford timely and quality accessible treatment". With this programme, they reported a decline in advanced breast cancer cases from 1987 to 2008 [98]. Mean time from symptom to seeking advice also improved significantly: 18 months in 1987, 8 months in 1989 and 1 month in 2007 [98]. In a review of breast cancer in sub-Saharan Africa, Pace et al. also stated that "even without systematic early detection efforts, the availability of affordable treatment can lead to earlier detection of breast cancer in a population" [47]. Shouldering the cost of cancer care and increasing accessibility to resource stratified recommended health care interventions should be high on the agenda of LMICs.

Use of Innovative, Culturally Sensitive Means of Tackling Causes for Delays

Reasons for late presentation are often complex and multifactorial and vary across different cultures and regions. A coordinated multidisciplinary effort with investment in local research must be employed and tailored to local country health needs. Success stories from Egypt, Zambia and Iran are examples to be emulated [98, 99]. Community, voluntary or primary care workers have effectively played an important role improving health care outcomes through navigation. Patient navigation is a cost effective, culturally sensitive intervention with proven evidence of down staging breast tumours in disadvantaged populations [100].

In implementing policies aimed at achieving lower rates of late reporting, solutions must be targeted, implementing culturally specific and acceptable measures [101]. For example, in Pakistan, where women did not want to be attended to by a male doctor, more female health providers need to be trained [21].

Conclusion

We believe that a combination of methods is required to address late presentation; these would differ from one country and region to another. A 'cut and paste' approach from HIC early breast cancer detection recommendations must be discouraged. Even within countries, ethnic and cultural diversities must be considered when formulating strategies to address the issues of late presentation of breast cancer. Ultimately, strengthening economies through global concerted efforts will translate into improved health systems, a prerequisite to improve cancer outcomes in LMICs.

Compliance with Ethical Standards

Conflict of Interest Joe-Nat Clegg-Lamptey, Verna Vanderpuye and Florence Dedey declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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