Current Breast Cancer Reports (2018) 10:179–186
https://doi.org/10.1007/s12609-018-0286-7

GLOBAL BREAST CANCER (BO ANDERSON AND C DUGGAN, SECTION EDITORS)

Breast Cancer Disparities Among Women in Low- and Middle-Income Countries

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Published online: 7 August 2018

Abstract

Purpose of Review The burden of breast cancer in low-income and middle-income countries transitioning to higher levels of human development is a public health crisis, set to increase dramatically in the coming decades. This paper provides an overview of the burden in human and economic terms, a summary of the costs, and cost-effective analyses for breast cancer interventions and suggests a way forward through research to better inform national, regional, and global policies for breast cancer control.

Recent Findings Inequitable access to effective health services for breast cancer is striking between and within countries, where much of the costs are shouldered through out-of-pocket expenditures. A variety of factors can influence opportunities for women with breast symptoms to seek care and to access effective and affordable early detection and treatment services.

Summary Research into disparities and solutions to overcome these, including an evidence-informed investment case for breast cancer control, can help to garner the necessary political will and sustained commitments to ensure adequate and sustainable resources are available to reduce disparities in breast cancer survival.

Keywords Breast cancer · Cancer disparities · Health systems · Cost-effectiveness · Health economics

The Global Burden of Breast Cancer: Regional and National Differences in Incidence and Mortality

Globally, breast cancer is the most common cancer in women, accounting for 25% of all female cancers, which equates to over 1.6 million cases worldwide as of 2012 [1].

The global age-standardized incidence rate (ASR) is 43.1 cases per 100,000 women [2]. In contrast, the next most common cancer in women, colorectal cancer, has a rate of 14.3 cases per 100,000 women [2]. Although breast cancer is widely recognized as a significant public health concern in high-income countries, historically, low- and middle-income countries (LMICs) have had lower incidence rates of breast cancer than in HICs [3]. However, the rate of increase and the absolute burden of breast cancer is higher in less-developed regions, with projected estimates to over 1 million new cases per year in LMICs alone by 2020 [4]. The rising age-standardized incidence rates are attributed, in part, to changing patterns of reproductive risk factors such as earlier menarche, delayed childbearing, lower parity, and shortened duration of breastfeeding. Increasing life expectancy and exposures to so-called "Western lifestyle" factors such as less physical activity, more overweight and obesity, and greater consumption of alcohol are also contributing factors [5]. Since breast cancer is the most common cancer in women in almost all countries across the world, regardless of economic development, breast cancer control should be a global health priority. However, LMICs tend to focus their limited resources on interventions aimed at communicable diseases and maternal and child health,

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This article is part of the Topical Collection on *Global Breast Cancer*

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which is reflected by the fact that they account for only 5% of global spending on cancer [6].

In addition to the differences in incidence rates between developed and developing countries, there is enormous regional variability in incidence and mortality across low- and middle-income countries (Table 1). For example, the incidence of breast cancer in Africa is 36.2 cases per 100,000 women overall but ranges across the continent from as high as 64.2 in Mauritius to around 10 cases per 100,000 women in The Gambia, Lesotho, and Swaziland [2]. In South-Eastern Asia, where the overall incidence is 34.8, individual countries range from 40.3 in Indonesia to approximately 10 cases per 100,000 in some of the smaller countries [2]. Other large and rapidly growing countries that will contribute significantly to the future global burden of breast cancer include Brazil (59.5 cases per 100,000) and Nigeria (50.4 cases per 100,000) among others (Table 1). The strong correlation between increasing breast cancer incidence and a country's economic level or human development index (HDI) [7] also reflects the increased prevalence of risk factors generally associated with high-income countries [5].

Although the least developed countries may currently have lower rates of breast cancer compared to middle- and high-income countries, they generally suffer from the highest mortality rates (Table 1). Globally, the age-standardized mortality rate due to breast cancer is 12.9 cases per 100,000 women, which accounts for 15% of all cancer deaths in women [2]. However, mortality in Africa (17.3 cases per 100,000), Central and South America (12.8 cases per 100,000), and Southeast Asia (14.1 cases per 100,000) are all higher than this global average. Interestingly, India (12.7 cases per 100,000) is similar to the global rate, and China is far lower (5.4 cases per 100,000). Beyond potential biological differences, for example, the apparent high proportion of triple-negative tumor sub-type among specific populations, the disproportionately high mortality rates in many LMICs largely reflect barriers to early detection and diagnosis of breast cancer resulting in late stage at presentation, as well as scarcity of resources and programs for optimal treatment [8–10]. For example, in Africa where a recent meta-analysis estimated a median of 75% of cases that were diagnosed at stage III/IV [11], the 5-year survival of breast cancer is half of that in the USA: 50% compared to 89% [12–14].

When comparing these global cancer statistics, it is important to also note the striking differences in the availability and quality of population-level cancer data. At the time of the GLOBOCAN 2012 report, only about 10% of the populations in Africa, Asia, and Central/South America were covered by high-quality cancer registries [15]. The new CONCORD-3 results now provide cancer statistics through 2014 and captures 75% of the global cancer burden by combining 322 population-based cancer registries, across 71 countries [16].

Table 1 Incidence and mortality rates by country income level and human development index (HDI) from GLOBOCAN 2012 [2]

	Incidence rate per 100,000 women (range)	Mortality rate per 100,000 women (range)
By development		
More developed overall	74.1	14.9
Less developed overall	31.3	11.5
By human development index		
Low HDI	32.6	17.0
Medium HDI	26.5	9.8
High HDI	45.2	14.6
Very high HDI	78.2	14.1
Major low- to middle-income regions		
Central and South America	47.3 (71.2–11.9)	12.8 (22.7–5.0)
Africa	36.2 (64.2–~10)	17.3 (25.9–~5)
Southeast Asia	34.8 (40.3–~10)	14.1 (18.9–~9.3)
Asia	29.1 (80.5–4.6)	10.2 (25.2–1.8)
Large and growing populations		
China	22.1	5.4
India	25.8	12.7
Indonesia	40.3	16.6
Nigeria	50.4	25.9
Brazil	59.5	14.3
South Africa	41.5	16.5
Russia	45.6	17.2

These data highlight the range in global breast cancer survival and the trend of increasing survival rates from 2000 to 2014 in most countries worldwide. However, population-based data from LMICs are still limited. Only 3.5% of the African population, for example, are covered by data contributing to CONCORD-3. Accurate and timely data are essential to understand global cancer disparities, monitor the impact of cancer prevention programs, and advocate for and appropriately use resources to reduce cancer morbidity. Current projections estimate up to 3.2 million cases of breast cancer per year by 2030 [5]. With over half of all new breast cancer cases and over 60% of breast cancer deaths occurring in developing countries [17], LMICs will be hit hardest in the coming years especially as many of these populations experience rapid growth and aging.

The Breast Cancer Survival Gap: Barriers to Early Diagnosis and Timely, Effective, and Affordable Treatment

In breast cancer patients, a delay of more than 3 months before diagnosis has been shown to result in increased morbidity and mortality [18]. In many developing countries, the time from symptom recognition to diagnosis far exceeds this time. For instance, data from North and sub-Saharan African countries suggest average times of between 4 and 15 months [9]. Even after diagnosis, many patients frequently do not have access to affordable, effective treatment and those who do commence treatment may not complete their full course due to financial constraints, distance, time away from work, and family responsibilities, among other factors.

The reasons behind these delays are multifactorial and involve the complex interplay of financial, system, provider, and patient-related factors [9, 19–21]. Financial factors are frequently tied to the fact that many patients have to pay out of pocket for their health care [22]. Moreover, few LMIC have comprehensive national insurance funds that include coverage for cancer diagnosis and treatment. In comparison to developed nations, the percentage of GDP invested in health is roughly half of that seen in high-income countries [22]. This issue is explored in the sections that follow.

System factors include a lack of access to high-quality diagnostic services and treatment facilities, and to a skilled health care workforce [18, 23, 24]. The greatest health worker deficits exist in LMICs, and in a number of countries, the initial access to health care is through a community health worker or a nurse at a rural facility/health center [20]. High health worker deficits exist in these countries, and these deficits are further amplified when it relates to all oncology personnel including clinicians, nurses, physicists, and biomedical staff. There is a marked paucity of trained oncologists in many countries. In a recent survey, out of 93 countries assessed, eight countries in LMICs had no clinical oncologist to manage cancers. In addition, in 27 countries (29%), a single oncologist would provide care for greater than 1000 incident cancers. Of these countries, 25 were in Africa and 2 were in Asia, reflecting the challenges of delivering effective cancer are in these regions [25].

Diagnostic instruments, devices, and services including pathology services are also profoundly limited in most low- and many middle-income countries. The shortage of skilled laboratory staff and materials to process specimens in a timely fashion, compounded by the lack of well-trained pathologists to accurately interpret biopsy results, all serve to compound treatment delays [24]. In addition, many countries lack the infrastructure to deliver comprehensive oncology care and there is limited access to many oncology services such as chemotherapy or radiation oncology services [25]. As of 2013, only 23 out of 52 countries in sub-Saharan Africa had access to radiation facilities [26, 27].

Health workers are the gatekeepers of access to care. In addition to the shortages in trained personnel in many LMIC [28, 29], poor knowledge among health workers can cause further delays, for example, through misdiagnosis, with false reassurance of patients and sometimes inappropriate treatment, such as antibiotics for presumed mastitis. In addition, dysfunctional referral pathways in fragmented health systems contribute to patients presenting at oncology centers with advanced cancers [11]. In one study, breast cancer patients in Cameroon had an average of four health worker interactions before being referred to definitive oncology services [30].

Patient-mediated barriers to health care seeking include socioeconomic factors such as educational level, health literacy, and employment status which can influence knowledge and awareness of breast health and symptoms and signs of breast cancer [9–11, 18, 30–32]. For instance, a survey of knowledge of breast cancer among 225 women attending hospitals in East Africa (Tanzania) found that only 30% of risk factors and 51% of breast cancer symptoms were identified correctly [33].

Sociocultural factors may play a significant role in influencing the health-seeking behavior including women who discover an enlarging breast mass and know that this could represent cancer [34]. A woman's health beliefs, the beliefs of the community around her, and the support she receives from those around her are all fundamental in determining her agency, and therefore, her access to health care. Fatalism, social stigma, collectivism, fear, and myths around breast cancer and use of alternative treatments all play a role as potential barriers to care [30–38].

A variety of myths around cancer in general and breast cancer in particular are also predominant in many cultures on different continents. Qualitative research has described

community perceptions of patients with breast cancer, as being "promiscuous" or of "dubious character" [35]. Cancer may be considered contagious resulting in avoidance of the individual [34, 36]. In a Tanzanian study, 33 most women subscribed to at least one or two myths about breast cancer, such as belief that putting money under the brassiere causes breast cancer (82.2%) or that breast cancer is the "will of god" (70.2%); one third believed that breast cancer represented an "attack from the enemy." It is not difficult to imagine how the myths and other beliefs about breast cancer briefly summarized here can lead to stigma, and to patients fearful of being isolated or ostracized in their communities. As a result, many women are less likely to disclose when they develop a breast problem [34, 37].

In many societies, women are often not the primary decision-makers for health. For example, married women might need to get permission from their partner, or as in the case of many communities in South Asia, their mothers-in-law, before they can attend a clinic or hospital. In this regard, spouses and other relatives may act as a potential barrier, as their endorsement is required to access health services and to adhere to treatment recommendations [32, 34]. In addition, in many societies, there is a prevailing sense of collectivism rather than individualism. Health care decisions may thus be collective and largely determined by the opinions of greater family/clan or community rather than by the individual. Patients may have their treatment prescribed by the community and this may result in additional delays, especially if the decision is to first try homeopathy or other traditional approaches over conventional treatment modalities [34].

Social conservatism and patriarchal norms may also play a role in communities where the breast as a "sexual organ" is not discussed in public, further exacerbating stigma and secrecy around breast cancer [34, 38]. In addition, women and their spouses may be reluctant to have a male health care provider examine them, leading to avoidance of the health care system for a breast symptom [34, 38, 39].

The factors briefly described here can act individually or in concert, contributing to delays in presentation and diagnosis for women with breast cancer in LMIC. In sub-Saharan Africa, for instance, three quarters of breast cancer patients are diagnosed with advanced disease.

Breast Cancer Control Interventions: Costs, Cost-Effectiveness, and Affordability

Box 1 provides a summary of the current evidence base on cost-effectiveness of clinical breast exams (CBEs) and mammography to screen for breast cancers based on results from modeling studies.

Box 1 Selected studies on cost-effectiveness of breast cancer screening approaches

Interventions are reported as cost-effective when the cost is less than three times per capita income per unit of benefit.

CBE **Summary: CBEs are generally cost-effective in LMICs**

- Biennial CBE for women ages 40–69 years in Ghana (US$1299 per DALY) [40]
- Single lifetime CBE at age 50 in India (Int $794 per LYS) [41]
- Annual CBE for women ages 40–55 years in Vietnam (US $995 per LYS) [42]
- Biennial CBE screening ages 40–70 in Costa Rica (US$5964 per DALY) [43]

Mammogram Summary: mixed evidence on the cost-effectiveness of mammography in LMICs

Cost-effective:

- 2-year interval for women ages 50–57 in Africa and Asia (Int $2500–$4500 per DALY) [44, 45]
- 2-year interval for women aged 48 and older, or between ages 40 and 49 in Mexico (Int $10,027–$15,508 per LYS [46, 47]
- Triennial combining fixed and mobile mammography screening from ages 45 to 69 in Peru (US $4125 per DALY averted) [48]

Not cost-effective:

- Multiple scenarios in India, Ghana, and Egypt [40, 41, 49]

We have listed the most cost-effective intervention identified in each study with a focus on lower-, lower-middle-, and upper-middle-income countries. *US$* US dollar, *Int $* international dollar, *DALY* disability-adjusted life years, *LYS* life years saved

Economic assessments play a key role in the selection of interventions and policies to improve breast cancer care and reduce the burden of this disease. As the majority of breast cancers in LMIC settings are diagnosed at stages III/IV, when treatment options are limited and less effective, there is growing recognition of the importance of early detection of these cancers to reduce mortality and to decrease the economic burden [9, 16, 19]. Cost-effective interventions are defined here as those that cost less than three times per capita income per unit of benefit (such as quality-adjusted life years). Modeling studies indicate cost-effectiveness in some settings but not in others [40–50].

Although screening mammograms have shown to reduce breast cancer mortality in high-income settings, there is general acknowledgement that mammography screening may not be feasible in low-income settings because of the high cost and infrastructure requirements. It should be noted that WHO cautions against population-based screening mammography in the absence of systems elements including recall mechanisms and strong referral pathways are in place, in addition to quality assurance at every step, and to rigorous monitoring and evaluation [51]. However, a phased approach to first improve access to early diagnosis and treatment is encouraged [19]. There is mixed evidence on the efficacy of CBE and mammography in LMIC [52–54], reviewed in the International Agency for Research on Cancer's latest volume

on breast screening [55]. There is more consistent evidence from modeling studies that CBE can be a cost-effective option in LMICs [40–43]. However, studies conducted in the real-world setting to date have not consistently shown CBE to be an effective screening modality to reduce breast cancer mortality [55]. While preliminary results from a large study in India demonstrated clinical downstaging, as occurrence of advanced-stage breast cancer was lower in the screened group compared to the unscreened group [52], final results on breast cancer mortality impacts are not yet available.

The World Health Organization has identified a list of "best buys" that categorize cost-effective interventions to address non-communicable diseases [56]. Several interventions for breast cancer screening and management are considered to be on average cost-effective, defined as a ratio ≤ I$ 100/disability-adjusted life year in LMIC; that is, the interventions may be cost-effective given specific country context. These recommended interventions include the following:

- Screening with mammography (once every 2 years for women aged 50–69 years) linked with timely diagnosis and treatment of breast cancer;
- Treatment of breast cancer stages I and II with surgery and systemic therapy, when required; and
- Basic palliative care for cancer, home-based and hospital care with multi-disciplinary team and access to opiates and essential supportive medicine.

However, these strategies must be considered also in terms of feasibility, acceptability, quality, and overall cost to the health system in terms of resources required to make such a program effective enough to reduce breast cancer mortality. For example, while mammography as a breast screening modality can be considered cost-effective per WHO's best buys, as previously stated, it is not recommended by WHO for most settings outside those of a high-income setting with a robust health system that can meet a long list of criteria [51].

In limited resource settings, it is essential first to build capacity to ensure equitable access to timely, effective, and affordable diagnosis and treatment services, and that these can be implemented on a large scale. This is aligned with the Breast Health Initiative paradigm, of a phased approach to implementation for breast cancer control [57]. Therefore, it is critical to identify not only the most cost-effective interventions but also ones that are affordable and are feasible given the existing implementation capacity. This issue is now widely acknowledged and there are ongoing efforts to identify interventions and develop treatment guidelines based on resource availability [58, 59].

Effective screening programs require substantial supportive infrastructure, including the availability of diagnostic and treatment services. Access to diagnostic mammograms and other procedures is a key barrier in the low-income setting as they are often only available in a few public facilities and the cost in the private sector is generally unaffordable for most individuals. In a recent study on the cost of cancer services in Kenya, the authors found that the average cost of breast cancer diagnosis in the public sector was about $400 compared to about $1200 in the private sector [60]. Furthermore, treatment cost in Kenya for stage III curative breast cancer was $1543 in public hospitals and $11,862 in private hospitals. Similarly, in India, the average out-of-pocket spending on inpatient cancer care in private facilities is about three times that of public facilities [61]. The overall high cost of cancer diagnosis and treatment can lead to disparities between those in higher versus lower socioeconomic strata in LMICs.

Adequate financing of educational and awareness programs for the public and health care providers, and for diagnosis and treatment facilities including a well-trained health workforce at primary, secondary, and tertiary care, is essential to ensure that core cancer services are accessible to all those in need. Affordability of services along the continuum of care is key to reduce the burden from breast cancer as insurance coverage for treatment alone, although important, will not reduce the overall burden. Essential services as briefly described here should be covered by health insurers, and countries that are considering universal health coverage should include them as essential interventions in their minimum package of health services.

The Economic Impact of Breast Cancer in LMICs

In addition to understanding the health burden of breast cancer, there are two powerful economic arguments that can be made to further appreciate its impact. Firstly, quantifying the full economic consequences that breast cancer places on society as a whole, focuses attention on the magnitude and distribution of costs associated with its morbidity and mortality [62]. The second perspective quantifies the returns of investing in breast cancer research and care to highlight how prioritizing breast cancer care can be "money well spent" [63].

The economic impact of breast cancer encompasses both a micro- and macro-economic perspective. At the micro-economic level, breast cancer can have profound effects on women, their families, individual health services and businesses, and government departments. In addition to the individual impact on women who are diagnosed with, or die from, breast cancer, their families are likely to face large, often catastrophic, medical, and non-medical costs, forced to sell assets and accrue debts [64–66].

At the macro-economic level, cancer impacts the national economy and society at large through increased health expenditure, labor and productivity losses, and reduced investment in human and physical capital formation. For example,

employment-related complications due to breast cancer include decreased productivity, job loss, dismissal, and reduction of work-related benefits. When aggregated, these can have a damaging impact on the labor supply and the functioning of an economy. To further complicate matters, much of the work undertaken by women is not associated with monetary transactions. Therefore, for any macro-economic analysis of breast cancer to truly capture productivity and welfare loss, calculations should also reflect non-income-generating work, such as gathering water and firewood, preparing food, tending to livestock, and caring for children [67].

To date, quantifying the negative impact of breast cancer on the wider economy has been made almost exclusively in high-income settings [68–70] with narratives about the economic impact in LMICs [71] but little in the way of actual figures [72]. While there have been recent estimates on the return on investment for other NCDs in LMIC settings [73, 74], there is little evidence on the macro-economic benefits (or returns) to be made from investments in breast cancer care [5]. A recent return on investment analysis undertaken in Egypt, on closer inspection, was more akin to a micro-economic intervention-specific cost-effectiveness analysis [75]. The growing body of evidence on the costs and cost-effectiveness of different strategies for breast cancer treatment and diagnoses is essential; however, there remains a critical need for more evidence on the wider economic impact of breast cancers.

Conclusions and Future Directions: the Case for Research

In terms of the human costs and the economic impact, the burden of breast cancer in countries transitioning to higher levels of human development is no longer "becoming" an important health issue; it is already a public health crisis, set to increase dramatically in the coming decades. It is important that the drivers of this increasing breast cancer risk and potential mitigating factors to reduce risk are further elucidated, for example, through epidemiological and prevention research. At the same time, all countries should strive to develop high-quality, population-based cancer registries. This rich source of data is essential to understand and monitor the national burden, discern regional differences, and project incidence and mortality trends to inform national policies and cancer control programs. Equally important are efforts to better understand locally relevant barriers to improving outcomes in resource-constrained settings, and to develop and test potential solutions to overcome these, for example, through implementation research.

Given the complex range and interplay of the barriers briefly reviewed here, a way forward to reduce health inequities for women with breast cancer globally, regionally, and nationally must comprise a multi-pronged strategy that takes into consideration the local contexts (i.e., societal, cultural), as well as the logistical challenges (i.e., health systems, referral pathways, financing for health). WHO outlines such an approach to address solutions to multi-level barriers to early diagnosis and treatment in their 2017 Guide to Cancer Early Diagnosis [19].

Finally, an evidence-informed investment case for breast cancer control can help to garner the necessary political will and sustained commitments (nationally, regionally, and globally) to ensure that adequate and sustainable resources are available to reduce disparities in breast cancer survival.

Compliance with Ethical Standards

Conflict of Interest E. Paskett has received grants from Merck Foundation and is a stockholder with Pfizer. O. Ginsburg, A.F. Rositch, L. Conteh, M. Mutebi, and S. Subramanian declare that they have no competing interests.

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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