

# Forty-Five Years of Research and Progress in Breast Cancer: Progress for Some, Disparities for Most

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## Gains in Breast Cancer Treatment Unavailable for Most

Impressive gains in breast cancer research and treatment have been made over the past 45 years in high-income countries. Many women are now cured with a simple lumpectomy, minimal lymph node surgery, and targeted or endocrine therapy.<sup>1</sup> However, this progress is in stark contrast to what exists in low- and middle-income countries (LMICs)<sup>2</sup> where women have a higher burden of breast cancer mortality and significantly poorer quality of life after breast cancer treatment.<sup>2,3</sup> Although the death rate from breast cancer has dropped by 40% between 1989 and 2015 across the United States,<sup>4</sup> breast cancer mortality has been steadily rising since 1999.<sup>5</sup> Wide global variation in breast cancer mortality again highlights that not all countries have achieved the same success.<sup>6</sup> In fact, most of the advances since the 1970s in the United States, such as screening mammography, radiotherapy, antihuman epidermal growth factor receptor 2 therapy, bone-directed therapy, and other targeted therapies,<sup>1</sup> are still not available for most women with breast cancer (Table 1, Fig 1). Breast reconstruction surgery, chemoprevention, and genomics<sup>1</sup> are similarly inaccessible. When mastectomy is the only option, there are many fears and misconceptions and little incentive for women to seek earlier medical care.<sup>7</sup> Since much of the improvement in mortality is now being credited to systemic therapies, it may be time to rethink the conventional wisdom where breast cancer treatment equals mastectomy or lumpectomy plus radiation.

## Care Patterns in Different Countries

By the time most women in low- or middle-resource settings pursue medical care, breast cancer is often locally advanced or metastatic.<sup>2</sup> Early detection is hindered by the lack of access to regular preventive primary care and the lack of awareness about early signs of breast cancer.<sup>8</sup> Mastectomy is unfortunately still the king in many places,<sup>1</sup> even when there is increasing access to systemic therapies such as aromatase inhibitors, tamoxifen, or chemotherapy, which can be used before surgery to try to avoid mastectomy.<sup>8</sup> In areas where there is limited access to radiation, treatment is the same regardless of the stage

and frequently includes mastectomy, chemotherapy, and hormone therapy, with all the toxicity, stigma, and disability associated with those treatments.<sup>7,9</sup> The African Breast Cancer—Disparities in Outcomes study, a multicountry prospective cohort study, found that mastectomies outnumbered breast-conserving surgery in all participating countries and that at least 30% of deaths were preventable through downstaging and improvements in treatment.<sup>7</sup> Similar situations can be found in Europe,<sup>6</sup> for example, in Kosovo, an upper-middle-income country<sup>10</sup> with a population of 1.8 million<sup>11</sup> located in Southeastern Europe. Although historically speaking breast cancer treatment started many years earlier, the first oncology clinic was established within the University Clinical Center of Kosovo at the end of 2010. There, patients with cancer start specific oncology treatment without having to leave the country.<sup>12</sup> In 2013, radiotherapy treatment began, which increases the opportunities for breast conservation or improved survival after mastectomy; however, even in 2019, 83% of women were still treated with mastectomy and only 17% had breast conservation.<sup>12</sup> All services at the oncology clinic for patients with cancer are government-subsidized and free of charge. Every year, around 400 new cases of breast cancer are diagnosed.<sup>13</sup> Late diagnosis and a large number of advanced cases at the time of diagnosis are still common. In 2019, 44% of women with breast cancer were diagnosed in stage III and IV and 56% in stage I and II of the disease.<sup>13</sup> Despite the fact that 56% of women are diagnosed in stage I and II, mastectomy is still performed in most of them.<sup>13</sup> Treatment with chemotherapy, human epidermal growth factor receptor 2–targeted therapy, or hormone therapy for breast cancer in Kosovo is available but remains challenging because of supply shortages.

The challenges in breast cancer treatment are not unique to a particular country, region, or continent. They are systemic throughout the globe. Many countries have been trying to address it in different ways. For example, in Rwanda, a low-income country of 12.5 million in East Africa, the Ministry of Health in collaboration with US institutions established the Butaro Cancer Center of Excellence (BCCOE), Rwanda's first public cancer facility in the country.<sup>14</sup> Breast cancer is the most common cancer treated there, with approximately 1,800 cases

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**TABLE 1.** Breast Cancer Treatment and Year

Treatment	United States	Rwanda	Kosovo
Breast-conserving surgery	1970	2014	2000
Sentinel node biopsy	1995	NA	NA
Breast reconstruction	2000	2015	2014
Tamoxifen	1970	2012	1990
Aromatase inhibitor	1990	2012	2000
Cobalt RT	1960	NA	NA
Linear accelerator	1980	2018	2012
Doxorubicin	1980	2012	2000
Cyclophosphamide	1960	2012	2000
Paclitaxel	1990	2012	2004
Trastuzumab	2000	2012 <sup>a</sup>	2008

Abbreviations: NA, not available; RT, radiotherapy.

<sup>a</sup>Private pay only.

Source: Hortobagyi<sup>1</sup> and personal correspondence (G. Uwizeye and D. Ademi, June 2020).

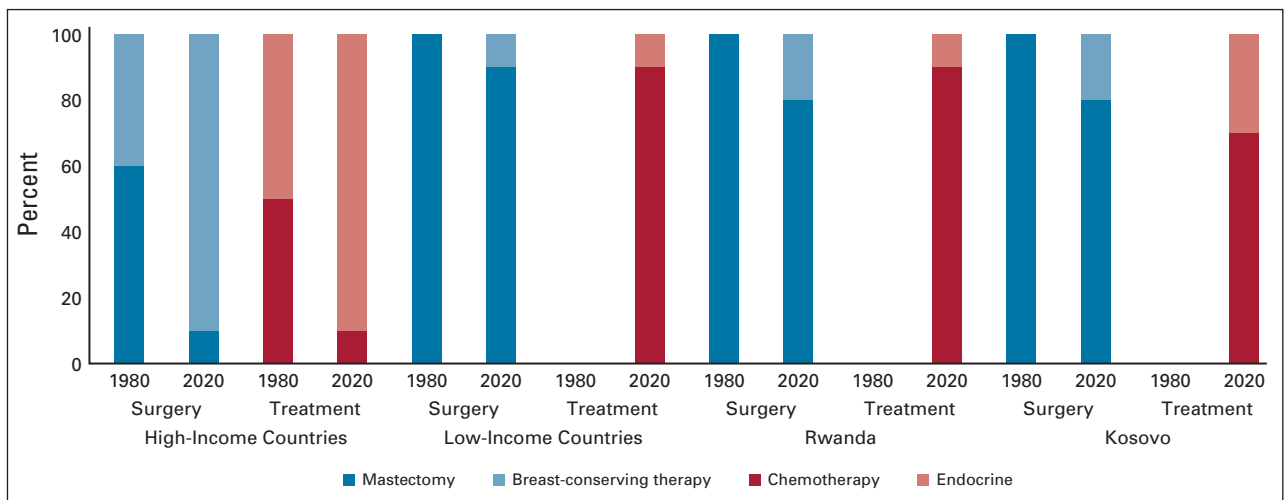
treated between 2012 and 2019. The services are covered by a national health insurance program and subsidized through charitable contributions.<sup>14,15</sup> Over 7 years, 35% of early-stage patients received surgery within 60 days of biopsy or completion of neoadjuvant chemotherapy, and 68% of early-stage patients received chemotherapy, whereas 99% had indications for chemotherapy on the basis of national protocols.<sup>15</sup> No one received radiation despite 44% of cancer being locally advanced and most meeting criteria for post-mastectomy radiation.<sup>15</sup> Rwanda has also initiated programs to improve early detection. The training of community health workers in breast cancer screening is one such effort that has been shown to increase the rate of early-stage cancer diagnoses,<sup>14</sup> and increasing availability of radiation may improve options for breast conservation to further incentivize women to present earlier.

In Honduras, breast cancer is the most common cancer of women and a common cause of death. Although data are scarce, some reports suggest that 78% of breast cancers diagnosed there are stage III or IV.<sup>16</sup> There is limited access to cancer education, screening, and treatment in general, but community-based educational programs and opportunistic screening campaigns have improved cancer knowledge in cervical and breast cancers. Community participation in these programs is especially high when they are advertised by local community leaders, with food and transportation to a central village provided.<sup>17,18</sup> To conclude, the situation in dealing with breast cancer treatment is similar in many other LMIC countries although details and circumstances vary widely.

**What Else Can be Done?**

Health care depends on funding and resources, but funding levels in LMIC countries are unlikely to change soon and in many places, are subject to political changes in government. The challenge is what can be done with the current resources and funding. Resource-stratified guidelines are increasingly available and are a great first step in trying to address this issue.<sup>19</sup> Such guidelines provide an opportunity to learn and use state-of-the-art comprehensive guidelines while considering real-time resources available in the social context and needs of the country. The National Comprehensive Cancer Network (NCCN) framework and Breast Health Global Initiative 2005 guidelines<sup>20,21</sup> are among noted examples that should be given consideration.

If optimal resources and infrastructure are not available to achieve significant improvements in mortality, then the focus should be on which interventions make the most impact with the least impact on quality of life. Quality of life may improve simply by improving involvement of patients in the clinical decision-making process using data to educate and inform. Since a large amount of breast cancer



**FIG 1.** Availability of surgery and treatment for breast cancer across countries.

treatment falls within the domain of preference-sensitive care,<sup>22</sup> ie, care where preferences of women are taken into account in clinical decisions, introducing shared medical decision making may be beneficial. Such tools would not involve substantial costs and would engage women in treatment decisions. Data from early breast cancer trials in the 1970s are still highly applicable to the resources available in many LMICs and could provide data to support a shared decision-making approach where a woman may choose lumpectomy rather than mastectomy even if radiation is not readily available. The data on lumpectomy and whole breast radiation versus lumpectomy alone from the Early Breast Cancer Trialists' Collaborative Group meta-analysis report a 16% reduction in risk of in-breast recurrence with radiation but only a 4% improvement in the 15-year risk of death for all participants.<sup>23,24</sup> For the node-positive group, a more likely scenario in LMICs, there was a 21.5% reduction in recurrence over 10 years because of radiation, but death from breast cancer is only reduced by 9%. Increasing access to modern systemic therapies throughout the developing countries could use current medication distribution infrastructure, and rates of recurrence and death would further improve with training for optimal delivery of systemic therapy. In countries where delays in seeking and completing care are common and delays more than 3 months have been shown to correlate with poor outcomes,<sup>7</sup> the absolute benefits of each modality of treatment are likely further reduced. A woman may choose treatment that results in a better short-term outcome with a higher long-term risk of recurrence if the risks and benefits are clearly explained and mastectomy and chemotherapy translate to significant psychosocial suffering such as abandonment, divorce, or financial and social destitution. The ABC-DO study found that the increased mortality in older women was entirely due to background mortality from other causes.<sup>7</sup> Shared clinical decision making may be an accessible, inexpensive intervention to aid women in making decisions about breast cancer. Improving women's understanding of the situation will improve the management and treatment of breast cancer.<sup>25</sup>

Another useful example from high-income countries derives from prediction tools such as UKPredict<sup>26</sup> that enables a shared decision-making conversation with patients. A 65-year-old postmenopausal woman in the United Kingdom with a 3-cm breast cancer and one positive lymph node has a 68% 10-year survival, compared with an 87% 10-year survival for the same woman without breast cancer. Survival can be improved by 6% with hormone therapy and 5% with chemotherapy, a reasonable incentive to proceed with hormone therapy and chemotherapy. To apply this tool, which was validated in a high-income country, to a LMIC requires many modifications. First and foremost, the 10-year life expectancy of a 65-year-old woman with or without breast cancer is much lower, as the average life expectancy

is 18 years shorter in LMICs compared with developed countries according to recent WHO updates. Second, if radiation is not available, survival with surgery alone is reduced especially when optimal management includes postmastectomy radiation, and the benefits from hormone therapy and chemotherapy may not only be increased when available but also be reduced by delays in care or drug shortages. Nomograms for estimating the benefit of radiation in the elderly with stage II and III breast cancer have been developed,<sup>27</sup> which also assist in showing the absolute benefits of radiation with respect to comorbidities and life expectancy. Increasingly, in the United States and other western countries, women over 65 years are opting for breast conservation without radiation when treated with hormone therapy.<sup>28-30</sup> Much of the improvement in mortality in high-income countries is attributed to targeted therapy and chemotherapy, and many of these drugs have been added to the WHO Essential Medicines List.<sup>31,32</sup> Drug availability is still suboptimal in low- and middle-income countries<sup>33,34</sup> but if available could have a significant impact on survival and quality of life. Nomograms for LMICs that take into account the emerging data on access and delays in care, therapy options, and life expectancy are urgently needed to assist with decision making. Such methods would help to prevent additional suffering until earlier detection and access to care can be improved. However, they should be adopted and validated to the LMIC setting.

The path to addressing breast cancer patient quality of life and mortality in each country is not a straightforward exercise, but rather an effort that needs to be constructed around the specifics and resources of each country. As breast cancer outcomes improve in some parts of the world, access to better therapies will vary, as illustrated in our examples from Rwanda and Kosovo. Tools to help determine and explain the relative impacts of each therapy in a prognostic and predictive format in real time will improve the quality of life of women with breast cancer around the world. Research to identify quality measures for breast cancer care is invaluable and must be incorporated into these models as countries grapple with the burden of cancer.<sup>14</sup> Such measures will vary by population and health care system and should be carefully weighed against cultural and quality of life factors associated with breast cancer treatment to improve outcomes. The resource-stratified treatment tables and process metrics developed by the Breast Health Global Initiative and others provide structures for a comprehensive approach to set priorities deliberately to establish a minimum standard of care with the rational and equitable use of existing resources.<sup>21</sup> The burden of breast cancer in LMICs needs a holistic approach that includes the development of oncologic infrastructure, screening, shared decision making and awareness among women and reduction of risk factors.<sup>35</sup>

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