

# Epidemiology trends and progress in breast cancer survival: earlier diagnosis, new therapeutics

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#### **Purpose of review**

In this review we will critically appraise the latest evidence on breast cancer (BC) survival trends and discuss how these may reflect breakthroughs in early diagnosis and treatment approaches. We will address the wide global inequalities in BC survival and review the ongoing initiatives aimed at improving cancer control worldwide.

#### **Recent findings**

BC outcomes have improved in high-income countries during the last decades, following the implementation of strategies for early detection and optimal multimodality treatment. Novel therapeutics, such as anti-HER2 targeted treatments, have also contributed to the progress in BC survival. However, BC mortality is still high in low-income countries, due to the lack of optimal healthcare infrastructures. In the context of marked inequities in BC management across world regions, international collaborations such as the Global Breast Cancer Initiative and the Global Initiative for Cancer Registry Development work to foster capacity-building in developing countries, tackle the burden of BC and deliver the Sustainable Development Goals by 2030.

#### Summary

Collection of robust, high-quality data from population-based cancer registries is crucial to drive and refine public health interventions. Population-based data are also the litmus paper to evaluate the real-world impact of clinical advances and monitor progress.

#### Keywords

breast cancer, early diagnosis, population-based survival, public health

#### INTRODUCTION

Cancer incidence and mortality have almost doubled in the last 20 years and keep rising, reflecting a shift in the age distribution in several low- and middle-income countries (LMICs) and the increasing prevalence of risk factors (Figs. 1 and 2) [1,2]. According to GLOBOCAN 2020, breast cancer (BC) ranked first for cancer-related mortality among women in 110 of the 185 countries, in 2020 [3]. In these countries, in 2020, BC surpassed lung cancer as the most common cancer type, accounting for 2.3 million estimated new cases, equal to 11.7% of all new diagnoses. In this review we will critically appraise the latest evidence on BC survival trends and discuss how these may reflect breakthroughs in early diagnosis and treatment. We will also address the wide global inequalities in BC survival and review the ongoing initiatives aimed at improving cancer control worldwide. Table 1 summarises the most relevant studies among those published during 2022-2023.

# BREAST CANCER SURVIVAL

Population-based cancer survival is a key indicator of the overall effectiveness of a healthcare system in managing cancer [2]. The CONCORD programme established global surveillance of cancer survival in 2015. In its third iteration (CONCORD-3), the study included patient-level, population-based data for six

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## **KEY POINTS**

- In the last 40 years, BC outcomes have improved in high-income countries, where five-year net survival exceeds 85%, but in low-income countries survival is still poor, around 60%.
- Early BC detection through cancer screening programmes is the basis for improving BC outcomes at population level, with an average 23% mortality risk reduction among invited women in highincome countries.
- The COVID-19 pandemic led to a sustained drop in breast cancer screening delivery in several countries, with a predicted excess in BC mortality.
- Integrated multimodality treatment for stage I-III breast cancer, including surgery, radiotherapy and optimal systemic treatments, is also key to improving BC outcomes, with the largest survival gains seen for patients with HER2-positive BC.
- In the framework of the United Nations' Agenda for Sustainable Development, the Global Breast Cancer Initiative and the Global Initiative for Cancer Registry Development represent pivotal international collaborations to tackle international inequalities in BC control.

million women diagnosed with BC in 66 countries. During 2010–2014, age-standardised five-year net survival for BC varied widely globally, ranging from 70% to 90%. Survival was 85% or more in 25 countries in Europe, North America and Oceania [2]. A recent study from the SURVCAN-3 collaboration, using similar methods, included 32 countries across Africa, Central and South America and Asia. Threeyear net survival for women with BC was 80% or more in Central and South America, while it varied between 62% in Zimbabwe and 88% in Kenya for Africa, and between 56% in Iran and 94% in South Korea for Asia [4<sup>••</sup>].

The 2019 Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), estimated the global cancer burden using mortality-to-incidence ratios (MIRs) instead of survival as the reference metrics, using a combination of vital statistics data from multiple sources and modelling for countries where these data were not available. In this report, MIRs were complemented by other outcome measures such as years of life lost (YLLs), years lived with disability (YLDs) and disability-adjusted life-years lost (DALYs). BC was the leading cause of cancerrelated DALYs, deaths and YLLs among women. It accounted for 20.6 million absolute DALYs, equal to 8.2% of all cancer-related DALYs, ranking fourth after lung, colorectal and gastric cancer [5<sup>••</sup>]. While these estimates may prove informative in terms of morbidity and mortality contributions to total cancer burden over the lifetime, there is concern for the possible methodological flaws of MIRs models, which may not be a robust surrogate for population-based survival data [14].



**FIGURE 1.** World maps for breast cancer age-standardised incidence rates. Estimated, age-standardised incidence rates for breast cancer globally, in 2020. Data from GLOBOCAN 2020, International Agency for Research on Cancer 2023.



**FIGURE 2.** World maps for breast cancer age-standardised mortality rates. Estimated age-standardised mortality rates for breast cancer globally, in 2020. Data from GLOBOCAN 2020, International Agency for Research on Cancer 2023.

In Europe, BC mortality decreased by 2–4% per year between 1990 and 2017 [15]. Similarly, in the US BC mortality declined by 43% between 1989 and 2020, and further subsided by 1.3% per year during 2011–2020 [6"]. Five-year relative survival in the US rose from 75% in 1970s to 90% in 2017 [16"]. Notably, in the US, mortality rates for Black women have been higher than in White women since 1980, reflecting possible disparities in access to adequate BC screening and care [6"].

In sub-Saharan Africa, 77% of women present with a late-stage disease at diagnosis [4<sup>••</sup>]. Here, fiveyear age-standardised relative survival was in the range 20–60% during 2008–2015, comparable to values observed in the US or in Norway in the 1940s, possibly reflecting the combined effect of rising incidence and suboptimal access to care [17].

Currently, more than two thirds of BC deaths occur in LMICs, where mortality trends are still on the rise [3,18<sup>•</sup>]. In high-human development index (HDI) countries, 90% of BC deaths occur at 50 years of age or more, with half of these deaths occurring in women 70 years of age or older [6<sup>•</sup>,19]. Conversely, in low-HDI countries, less than 50% of BC deaths occur in women older than 50 years of age, with 70% of BC deaths in LMICs considered premature [19,20<sup>•</sup>].

#### **EARLY DETECTION**

Cancer early detection programmes aim to attain a reduction in cancer-specific death rates and gains in

quality-adjusted life years (QALYs). According to the World Health Organization (WHO), the strategies for timely cancer detection at population level may vary between countries, depending on cost-effectiveness assessments and on the available resources. For instance, settings with limited resources may prioritise access to clinical breast examination in presence of symptomatic lesions, which can lead to an earlier-stage diagnosis even if a mammographic screening programme is not in place [21,22].

Based on several randomised trials showing an estimated 20–30% reduction in mortality with active surveillance for women at high-risk of developing BC, in the 1980s and 1990s many Western countries implemented population-based mammography screening programmes [23–27]. Screening mammographies are usually offered every 1 to 3 years to women aged 40–74 years, with timing and age windows varying between countries [28]. In LMICs screening is mainly promoted by advocacy groups, except for Latin America, where most countries recommend BC screening in national cancer control plans [29].

The effect measure of a screening programme is the reduction in BC mortality [27]. The effectiveness of BC screening is still under debate, and the real magnitude of its impact on mortality is still not well defined [21,24,26,30,31]. Such assessment is technically complex as it is hampered by the low statistical power of the population-based studies published to date [26,32<sup>•</sup>]. Several observational

Publication	Data Source	Country	Study time-frame	Outcome Measure	Main Finding
Soerjomataram <i>et al.</i> [4 <sup>•••</sup> ]	Population-based cancer registries	32 Countries in Africa, Central and South America, Asia	2008 - 2012	1-year, 3-year and 5-year net survival for 15 major cancer types	3-year net survival ranging from 54.6% to 96.8%, during 2008-2012
Global Burden of Disease 2019 Cancer Collaboration [5 <sup>•••</sup> ]	Vital registration systems, cancer registries, verbal autopsy reports	204 Countries and Territories across the five continents	2010 - 2019	Mortality-to-incidence ratios, YLLs, YLDs, DALYs	10 million deaths and 250 million DALYs due to cancer, in 2019
Giaquinto <i>et al.</i> [6 <sup>•</sup> ]	SEER, National Program of Cancer Registries	US	1975 - 2022	Incidence, mortality, survival	Rise in BC incidence rates, decline in BC mortality rates, persisting racial disparities in mortality, during 1975-2022
Ding et al. [7 <sup>■</sup> ]	Cancer registries and health insurances	Flanders (Belgium)	2001 - 2018	OR for MBC risk stratified by level of BC screening uptake	Five-fold increase in the risk of MBC for women not attending screening
Doan <i>et al.</i> [8 <sup>■</sup> ]	Sample of Medicare fee-for-service enrollees	US	2016 - 2022	Proportions of BC screening uptake during the COVID-19 pandemic	Decrease in BC screening uptake by 24% during the pandemic
Xiang <i>et al.</i> [9 <sup>■</sup> ]	SEER	US	1990 - 2016	BCSS after breast- conserving surgery plus RT versus mastectomy plus RT in resectable BC	Improvement in BCSS by 18% with BCS plus RT (HR = 0.820 (CI 0.746- 0.901))
Ellegard <i>et al.</i> [10 <sup>∎</sup> ]	Medical records from the Southeast Healthcare Region	Sweden	2006 - 2014	BCSS and local/distant RFS with or without trastuzumab for patients with early BC	5-year BCSS of 93.4% for patients receiving trastuzumab, compared to 87.4% for those not receiving trastuzumab
Palmieri <i>et al.</i> [11 <sup>®</sup> ]	English Hospital Episode Statistics database	England	2016 - 2021	Prevalence of MBC in the population of England	Steep rise in prevalence of MBC, from 38350 patients in 2016 to 57215 in 2020
Courtinard <i>et al.</i> [12 <sup>∎</sup> ]	ESME database	France	2008 - 2017	OS by BC subtype, using real-world data	OS ranging from 14.7 months for patients with TNBC to 39.5 months for patients with HR+/ HER2-positive MBC, during 2008-2017
Goyal <i>et al.</i> [13 <sup>∎</sup> ]	SEER	US	2015 - 2017	OS with endocrine therapy ±CDK4/6i in elderly MBC patients	3-year OS of 73.0% for patients receiving CDK4/6i versus 49.1% for patients not receiving CDK4/6i

BCSS, breast cancer-specific survival; CI, confidence interval; HR, hazard ratio; OR, odds ratio; RFS, relapse-free survival; TNBC, triple-negative breast cancer.

studies in developed countries suggest an average reduction in BC mortality by 23% among women invited to participate and by 40% among women actually attending the screening [27,29]. A Dutch study reports an almost six-fold higher risk of latestage presentation for women never attending a screening programme compared to women attending a screening programme [7<sup>•</sup>]. A population-based study, matching GLOBOCAN 2020 age-standardised mortality rates for BC to a broad panel of standardised national health system indicators for 148 countries, found that countries attaining a sustained decrease in mortality rates had at least 60% of newly diagnosed BC patients presenting with stage I or II disease, highlighting the impact of early diagnosis on mortality rates [33].

The net effect of screening on mortality can be confounded by overdiagnosis – the diagnosis of

indolent tumors that would not cause harm if they remained undetected - and by the 'healthy user effect', the attitude of patients attending prevention programmes to also engage in other healthy behaviours [25,32<sup>•</sup>]. The impact of overdiagnosis is also difficult to measure, with estimates varying widely between reports, in the range 0-55% of all detected cases [34–36]. To address these concerns, the European Collaborative on Personalized Early Detection and Prevention of Breast Cancer (ENVISION), a network of international research consortia, launched a series of initiatives aimed at defining a personalised approach to BC prevention and early detection [28]. Two of these initiatives, the two short-term trials WIS-DOM and MyPeBS, are evaluating the effectiveness of a risk-stratified approach to BC screening [28], paving the way to improvements in efficacy and cost-effectiveness.

Several modelling studies predicted an excess of BC-related mortality due to disruptions in healthcare provision during the COVID-19 pandemic, including interruption of cancer screening and deferral of diagnostic work-ups in many countries [37–39]. US studies based on data from Medicare, private health insurances or larger analytics databases, showed a sustained drop in BC screening attendance during the pandemic, ranging from a 40-60% reduction in the second quarter of 2020 to 6–17% in 2021, compared to prepandemic levels [8<sup>•</sup>,40,41<sup>•</sup>,42]. A similar trend was observed in Italy, where pandemic-related delays in screening activities widened the preexisting geographical inequalities [43<sup>•</sup>]. Conversely, minimal fluctuations were reported for the Netherlands and the Flanders, with prompter return to the prepandemic screening performance [44,45]. Long-term data are awaited, to understand the full impact of the pandemic on BC diagnosis, management and outcomes.

### **NEW TREATMENTS**

Together with early detection and prompt diagnosis, the third WHO pillar for achieving a BC mortality reduction is a timely access to integrated multimodality treatment for stage I-III disease, including optimal surgery, radiotherapy and systemic antineoplastic agents [20<sup>••</sup>].

A prospective cohort for women attending eight hospitals across five sub-Saharan African countries with a suspicion of BC, suggested that the main survival determinants were early detection and diagnosis, enabling a shift in the stage distribution at diagnosis, but also access to adequate treatment. Each of these factors independently accounted for an up to 12% reduction in BC deaths [46].

Surgery has historically been the mainstay of BC treatment, with breast-conserving surgery (BCS) followed by adjuvant radiotherapy (RT) becoming established as the standard treatment protocol in the 2000 s, based on landmark trials assessing the noninferiority of BCS to mastectomy [47–50]. Several population-based studies suggested that BCS plus RT yielded better overall survival (OS) compared to mastectomy with or without RT for most subsets of BC [51–54]. Based on data from the Surveillance, Epidemiology, and End Results (SEER) Program, 10-year survival was 60% for patients receiving BCS plus RT, compared to 54% for those receiving mastectomy plus RT [9<sup>•</sup>].

The evidence on the impact of systemic, adjuvant therapies is mainly for anti-HER2 or endocrine treatments. Studies from Canada and Sweden using data from the real-world setting found that anti-HER2 targeted agents led to survival improvements for women with HER2-positive early BC, with 5-year BC-specific survival of 93% versus 87% for patients receiving or not receiving adjuvant trastuzumab in 2006–2014, respectively [10<sup>•</sup>,55].

Vast evidence on the efficacy of endocrine therapy has been obtained from randomized clinical trials (RCTs), but robust real-world data are currently not available. The validity of such data may also be flawed by the uptake of the endocrine therapy in the general population, with up to 23% of patients showing suboptimal adherence [56,57].

Remarkable advances in the therapeutic options for metastatic BC (MBC) in the last decades led to improved efficacy and tolerability, mainly for patients with HER2-positive MBC or hormonereceptor positive (HR+)/HER2-negative MBC [58-60]. While efficacy data from clinical trials are robust, the real-world or population-based benefit of novel therapeutics is still hard to grasp, mainly because most countries do not collect MBC prevalence and survival data. In the US, around 4% of the four million BC survivors, some 160,000 people, are estimated to live with metastatic disease [6<sup>•</sup>], with an expected increase by more than 50% by 2030 [61,62]. An English study using the English Hospital Episode Statistics database, estimated that the number of patients living with MBC rose from 38350 in 2016 to 57215 in 2021 [11<sup>•</sup>].

The Epidemiological Strategy and Medical Economics (ESME) Research Programme in France is a nationwide, observational cohort study collecting electronic health records (EHRs) data for all consecutive, new MBC patients from 18 French Cancer Centers, since 2008 [63]. During 2008-2017, the median OS in the whole cohort was 39.5 months (95% CI 38.7-40.5), ranging from 14.7 months for patients with triple-negative MBC to 56.7 months for patients with HR+/HER2-positive MBC [12<sup>•</sup>]. In a breakdown by year of diagnosis, OS dramatically improved over time for patients with HER2-positive MBC, with a nearly 50% reduction of the probability of dying for women starting their treatment in 2016 compared to 2008. Conversely, survival remained substantially unchanged for patients with triple-negative or HR+/HER2-negative MBC [63]. Similarly, population-based studies from Canada, Denmark, Sweden and Australia showed that median OS, for patients receiving double anti-HER2 blockade, rose from 21.8 during 2006–2014 to 39.2 months during 2012-2017, compared to 14 months for patients diagnosed during 1985-2000 who did not receive trastuzumab [64-67].

Data on the survival impact of cyclin-dependent kinase 4/6 (CDK4/6) inhibitors or antibody-drug conjugates are still scanty, and large, up-todate, population-based studies are warranted. A multicenter German study on real-world exposure to CDK4/6 inhibitors for 448 patients, reported a median progression-free survival (PFS) of 17 months, but survival data were not available [68]. A population-based study, including 630 US women 65 years or older diagnosed with HR+/ HER2-negative MBC during 2015–2017, found that the addition of CDK4/6 inhibitors to first-line endocrine therapy was associated with a 41% reduction of the risk of dying compared to endocrine therapy alone [13<sup>•</sup>]. These findings, overall, are consistent with results from RCTs.

## CLOSING THE BREAST CANCER SURVIVAL GAP: A COLLECTIVE EFFORT

Overall, improvements in BC survival have been remarkable, but dramatic inequalities persist within countries and on a global scale. The highest risk of dying from noncommunicable diseases (NCDs), including cancer, is for populations living in LMICs, where one third of BC-related deaths occur [69,70<sup>•</sup>]. Only 25% of low-income countries have operational cancer surgery services, and access to systemic treatments is limited by lack of infrastructure or unaffordable drug costs [71,72]. Overcoming these disparities requires collective action on multiple levels.

In 2015, the United Nations (UN) released the Agenda for Sustainable Development, defining 17 Sustainable Development Goals (SDGs) for the years 2015–2030, in the economic, social and environmental domains [73]. Two of these goals are relevant to cancer control: SDG 3.4 aims at reducing premature mortality from NCDs by a third by 2030, relative to 2015 levels, while SDG 3.8 aims at attaining universal health coverage [73]. If SDG 3.4 was met, the largest gains in expected life-years lived between 30 and 70 years of age, attributable to cancer, would occur in low-income countries [72].

Since most BC diagnoses are not due to modifiable risk factors, for an improvement in BC outcomes to occur, scaling up of optimal disease management worldwide is needed [22]. The WHO and the UN recently launched the Global Breast Cancer Initiative (GBCI), which aims to establish a global collaboration to reduce BC mortality across the three pillars of health promotion and early detection, timely BC diagnosis, and comprehensive BC management [22]. The GBCI will unfold through three inter-related approaches: bringing together stakeholders to build action plans, providing operational guidance to governments, and supporting the implementation of cancer control strategies of proved success [22].

Health indicators must be systematically collected to allow international comparisons, to prioritise interventions and monitor their impact. Local data collection is vital to local action planning and refinement. However, vital statistics are often inconsistently collected in LMICs, especially in Africa or East Asia, hampering international comparisons based on robustly collected, population-based data [74,75]. In 2012, the International Agency for Research on Cancer and other key partners implemented the Global Initiative for Cancer Registry Development (GICR), to deliver capacity-building for population-based cancer registries [76]. With GICR's support, it is expected that high-quality cancer data will be available for at least 30 LMICs in the next few years [74]. Moreover, as the epidemiological landscape of BC changes and the number of women living after a BC diagnosis increases, new indicators focusing on quality of life and disability will need to be developed and validated on a global scale [70<sup>•</sup>].

Finally, in 2022 the Lancet Oncology Commission on Breast Cancer was launched, with the aim of presenting high-quality, evidence-based recommendations to influence global policy in reducing BC burden worldwide. These recommendations will span areas such as prevention and early detection, personalised BC management, and safe treatment de-escalation [77<sup>••</sup>].

## CONCLUSION

The epidemiological transition in LMICs, with a shift from communicable to noncommunicable diseases as the leading cause of deaths, has driven a rise in the burden of BC. In the last decades, large-scale implementation of programmes for BC early diagnosis and timely, multimodal management has led to remarkable improvements in BC survival. New systemic treatments also had a marked impact on outcomes, notably anti-HER2 agents. However, the toll taken by BC on patients still depends on where they live, with wide inequalities both globally and within countries. Large collective initiatives are in place, to tackle these disparities and ultimately, to improve lives of women diagnosed with BC. A high level of awareness in all the players, including clinicians working in the BC field, is the first step to contribute to the global challenge of improved BC control.

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## **Conflicts of interest**

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