Compendium report on global challenges and opportunities to improve the care of women with triple-negative breast cancer

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Foreword

Breast cancer is the most common cancer type in women worldwide. Of the different subtypes of breast cancer, triple-negative breast cancer (TNBC) is the most challenging to treat. TNBC is more aggressive than most other subtypes and has the worst prognosis. In contrast to other subtypes, innovations in the medical treatment of TNBC have been absent for many years. However, the recent introduction of immunotherapy and targeted therapy might be the beginning of a new era for TNBC patients.

This report provides a global perspective on TNBC. It primarily compiles key statistics, conclusions, and recommendations from earlier IHE reports on TNBC in Asia-Pacific, Europe/Northern America, and Latin America. It also adds information of a recent IHE report on breast cancer in the Middle East and Africa.

The responsibility for the analysis and conclusions in this report lies solely with the authors.

Lund, June 2024

Peter Lindgren
Managing Director, IHE

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Summary

Breast cancer is a critical and growing public health challenge. On the global level, breast cancer is the most commonly diagnosed cancer type (25% of all new cancer cases) and the leading cause of cancer death (16% of all cancer deaths) in women. In 2022, an estimated 2.29 million new breast cancer cases were diagnosed and around 670,000 women died from the disease.

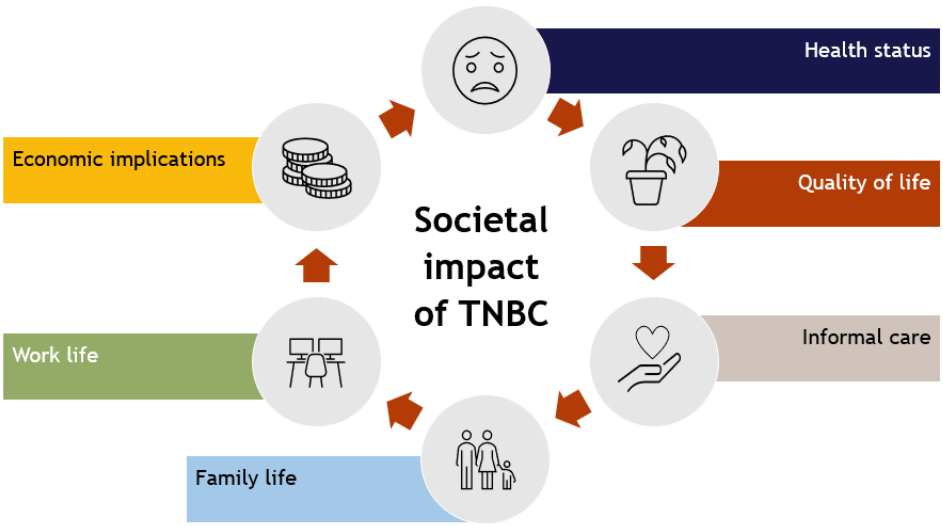
Triple-negative breast cancer (TNBC) is a subtype of breast cancer that occurs in around 10–20% of newly diagnosed cases. TNBC tends to be more aggressive and used to be more difficult to treat successfully compared with other subtypes. Until recently, the limited number of treatment options (only chemotherapy alongside surgery and radiation therapy) contributed to TNBC having the poorest prognosis of all breast cancer subtypes. In the United States, the 5-year survival rate of TNBC cases was 77% compared with 91% of all breast cancer cases in the diagnosis period 2012–2018. Because of its relatively low survival, TNBC accounts for around 30–40% of all breast cancer deaths.

TNBC carries a significant economic burden, with substantially greater costs associated with increasing disease severity. Medical costs of treating metastatic patients (stage IV) are around 3–5 times higher than of early-stage patients (stage I–III) in high-income countries. Productivity losses of the economy from sick leave and premature mortality also increase with disease stage.

Societal effects of improved TNBC care

Multiple actions from various stakeholders are needed to improve the early detection, diagnostics, and treatment of TNBC. Indeed, the Global Breast Cancer Initiative by the World Health Organization emphasizes the joint efforts required to improve access to resource-appropriate and quality services for women around the world. This would help to reduce the future disease burden of TNBC.

Enhancing the quality of care of TNBC patients will not just improve their survival and quality of life. It would also have positive implications for the need for informal care, patients' families, and patients' work lives. All of this has economic implications for the patient, her family, the health care system, and the economy.



Recommendation 1: Raise health literacy to facilitate early detection

TNBC has a much worse prognosis when diagnosed at a late stage. The 5-year survival rate of TNBC ranges from 91% in cases diagnosed in stage I down to 12% in cases diagnosed in stage IV in the United States. It is also considerably more costly to treat a case in stage IV than in stage I. This gradient in survival and costs makes early detection of the tumor – through self-detection and/or screening – particularly crucial.

Global challenges for early detection include a lack of breast health awareness among women and reluctance to consult health care services upon noticing symptoms as well as low involvement of primary care in early detection. Many countries lack an organized population-based screening program. Countries with a screening program may have a narrow target age group and a low participation in the program due to individual reasons such as the misbelief that "breast cancer it is not going to happen to me" or due to various accessibility barriers in the form of costs, time, and geography.

Recommendation 2: Ensure optimal care delivery

Timely and comprehensive breast diagnostics followed by appropriate treatment are vital to increase the survival prospect of TNBC patients.

Challenges that hamper the provision of optimal care to TNBC patients around the world include slow referral from primary care to specialized care and poor coordination of diagnostic and treatment service providers, low quality and shortages of breast cancer imaging and pathology services, shortages of pathologists, radiologists, and oncologists, incomplete pathological assessment and biomarker testing before treatment start, high copayments for medical services, and lack of patient involvement in decision-making along the care pathway.

Recommendation 3: Consider adoption of innovation in clinical practice

The development of novel medical treatment options in oncology has grown over the past two decades, but patient access differs greatly across the world. For TNBC patients, new medical treatment options have only started to emerge since 2018. They include immunotherapy and targeted therapy for patients with BRCA mutations. These new treatment options might help to close the survival gap between TNBC and other subtypes of breast cancer, where novel options have been available for longer (HER2-targeted therapies for HER2-positive breast cancer, and CDK4/6 inhibitors for hormone receptor-positive breast cancer).

Global challenges for the adoption of new treatments in clinical practice include lack of comprehensive biomarker testing, outdated local clinical guidelines, hesitant adoption of new treatment approaches by clinical staff, and lack of availability of new treatments, especially in the public sector in middle-income and low-income countries.

List of abbreviations

AI	Artificial intelligence
ASCO	American Society of Clinical Oncology
BRCA1/2	Breast cancer gene 1/2
CBE	Clinical breast examination
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
HER2	Human epidermal growth factor receptor 2
HR	Hormone receptor
IARC	International Agency for Research on Cancer
KPI	Key performance indicator
NCCN	National Comprehensive Cancer Network
PD-L1	Programmed death-ligand 1
PR	Progesterone receptor
SEER	Surveillance, Epidemiology, and End Results
TNBC	Triple-negative breast cancer
US FDA	Food and Drug Administration in the United States
WHO	World Health Organization

1. Breast cancer and TNBC

This report focuses on triple-negative breast cancer (TNBC). It describes patient characteristics (chapter 1), the disease and economic burden to society (chapter 2), global challenges in TNBC care (chapter 3), and recommendations for improved care (chapter 4).

The report mainly compiles information from previously published IHE reports on TNBC in Asia-Pacific (focusing on Australia, Hong Kong, South Korea, Taiwan, Thailand) (1), Europe and Northern America (2), and Latin America (focusing on Argentina, Brazil, Chile, Dominican Republic, Colombia, Mexico, Panama, Peru) (3), supplemented with additional information from a recent IHE report on breast cancer in the Middle East and Africa (focusing on Algeria, Egypt, Jordan, Israel, Morocco, Saudi Arabia, South Africa, Türkiye, and United Arab Emirates) (4). The former reports employed a pragmatic review of publicly available literature, including scientific articles and grey literature, to bring together evidence on the landscape of breast cancer and TNBC across the included geographies.

1.1 Breast cancer

Breast cancer is the most commonly diagnosed cancer type and the leading cause of cancer death in women[1] globally (6). Breast cancer occurs in every country of the world in women at any age after puberty, but with increasing likelihood later in life (7). In 2022, an estimated 2.29 million new breast cancer cases were diagnosed and around 670,000 women died from the disease. Breast cancer is responsible for 25% of all new cancer cases in women and 16% of all cancer deaths in women worldwide; see Figure 1. The estimated average lifetime risk for a woman to get breast cancer (before the age of 85) is close to 7% (1 in 14 women) globally. The lifetime risk is highest in Northern America at 14% and lowest in Asia at 5% (6).

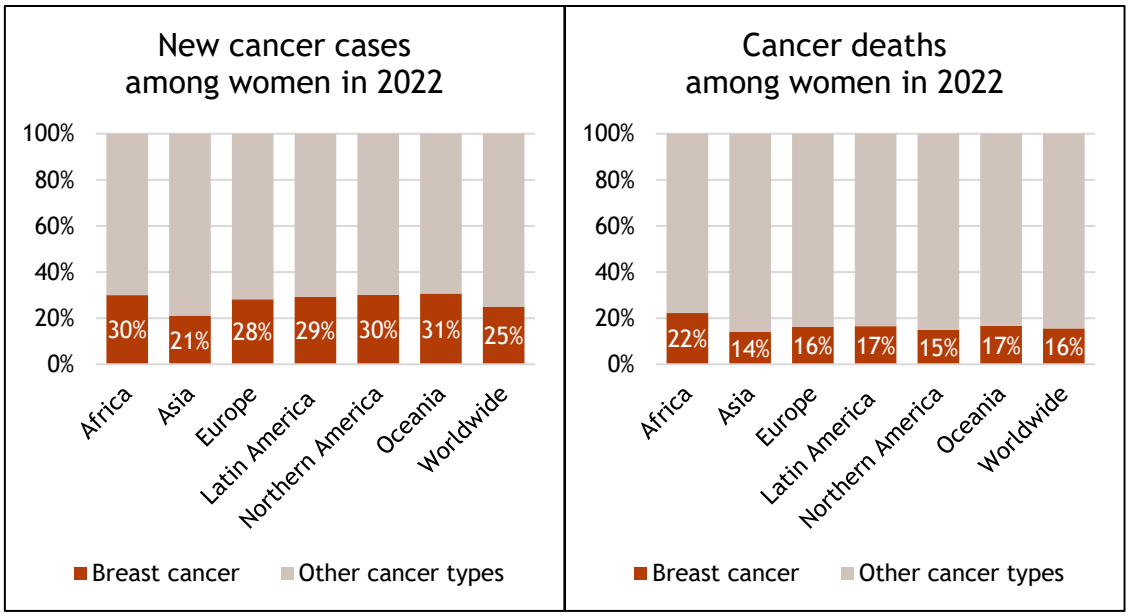


Figure 1: Proportion of new breast cancer cases and deaths among women by world region in 2022.

Notes: Cancer refers to all types excluding non-melanoma skin cancer. Source: Estimates by IARC (6).

[1] Men can also get breast cancer, but it is rare. Only about 1 out of every 100 breast cancer cases diagnosed in the United States is found in men (5). This report focuses on women with breast cancer.

1.2 What is TNBC?

Breast cancer consists of several distinct subtypes that differ in their biological characteristics. The standard classification of the subtypes is based on the presence of three receptors in the tumor cells; two hormone receptors (HR) called estrogen receptor (ER) and progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2). Four subtypes based on the tumor's expression of ER, PR, and HER2 are typically defined (8, 9); see Table 1. The most common subtype is luminal A, which is hormone-receptor positive (i.e., ER and PR positive) and HER2-negative. TNBC is a subtype of breast cancer in which neither ER, PR, nor HER2 are overexpressed. The word "negative" in TNBC simply refers to the lack of expression of the three receptors.

Table 1: Subtypes of breast cancer

Subtype	Expression of receptors	Prevalence in the United States
Luminal A	ER-positive, PR-positive, HER2-negative	68%
Luminal B	ER-positive, PR-any-level, HER2-positive	10%
HER2+	ER-negative, PR-negative, HER2-positive	4%
TNBC	ER-negative, PR-negative, HER2-negative	10%

Notes: Percentages do not sum up to 100% as "unknown" cases are excluded. Source: SEER (10).

The treatment of TNBC usually involves a mix of surgery, radiation therapy, and systemic therapy (i.e., cancer medicines). Systemic therapy options depend on tumor characteristics and differ therefore between breast cancer subtypes. The lack of expression of the three main receptors in TNBC tumors has hampered the development of effective cancer medicines (11). Systemic therapy options for TNBC used to be restrained to chemotherapy (12), which kills/damages fast-growing tumor cells but also fast-growing healthy cells in the body.

TNBC accounts for around 10–20% of all newly diagnosed breast cancer cases globally (13). Figure 2 shows the minimum and maximum proportion of TNBC in selected locations in different world regions, ranging from 9% in France and Taiwan to 21% in Algeria and Brazil.

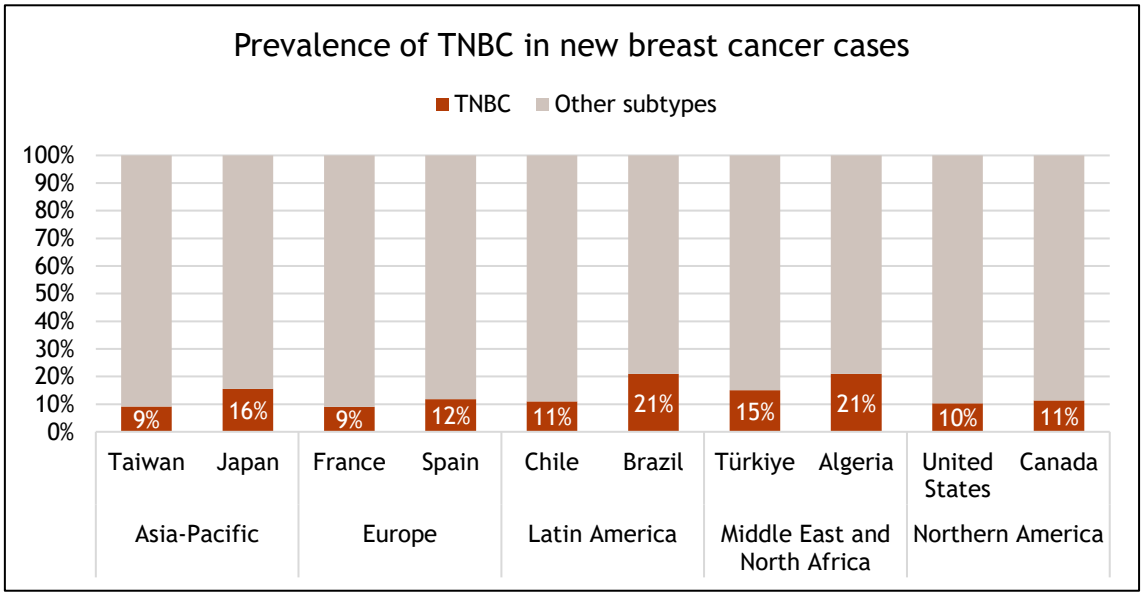


Figure 2: Prevalence of TNBC in new breast cancer cases in selected countries per region.
Source: (10, 14-23).

1.3 Risk factors

Many potential risk factors for developing breast cancer have been identified with varying levels of supporting evidence (24). However, not all risk factors have been linked specifically to TNBC. In general, risk factors can be divided into non-modifiable and modifiable risk factors; see Table 2. According to the WHO, up to 30% of all breast cancer cases are theoretically preventable as they are caused by modifiable risk factors (7).

Table 2: Risk factors of breast cancer and TNBC

Non-modifiable risk factors	Modifiable risk factors
Age: The risk increases with age **(25)**, although TNBC tends to be more common in younger ages. The risk for women under 40 years to get TNBC is estimated to be twice that of the next most frequent subtype (HER2+) **(25)**.	**Obesity and overweight:** The risk increases with higher body mass index (26). The link seems to be stronger in postmenopausal women than in premenopausal women (26). A link with TNBC has been established (27).
Family history: Around 5–10% of all breast cancers have a hereditary background **(28)**. Women who carry BRCA1/2 mutations are at an increased risk to develop breast cancer and especially TNBC **(29)**. One third of TNBC patients in the United States have a BRCA1 mutation **(30)**. In Austria and Germany, 21% of TNBC patients have BRCA1/2 mutations **(31)**, while in South Korea it is present in 13–14% of TNBC patients **(32)**, and in Australia in 9% of TNBC patients **(33)**.	**Physical inactivity:** A sedentary lifestyle increases the risk (34). The link between physical inactivity and TNBC is stronger than in other subtypes (34).
Ethnicity: Caucasian women have the highest risk to develop breast cancer in the United States **(35)**. Black women followed by Hispanic women are at a higher risk of developing TNBC compared with Caucasian women while Asian women are at a lower risk **(36-38)**.	**No breastfeeding:** Women who never breastfed their babies have a higher risk to get breast cancer (39). A link with TNBC has been established (39).
Breast density: A greater breast density increases the risk **(40)**. The link between breast density and developing TNBC is stronger in premenopausal women than in postmenopausal women **(41)**.	**No child births:*** Having given birth to children is associated with a lower risk of HR-positive breast cancer, but it does not seem to affect the risk of TNBC (42).
	Alcohol consumption:* The risk for breast cancer increases with more consumption (43), but the link with TNBC is less clear (44).
	Cigarette smoking:* The risk for breast cancer is increased compared with not smoking (45), but the link with TNBC is not clearly established (44).
	Use of postmenopausal hormone replacement therapy to treat menopausal symptoms:* The use increases the risk for breast cancer (46), but the link with TNBC is not clearly established (47).
	Use of oral contraceptives:* The use does not seem to increase the risk to get breast cancer or TNBC although some studies found a (weak) link of an increased risk (44, 48).

Notes: * No clear link of this risk factor to TNBC has been established.

1.4 Signs and symptoms

Signs and symptoms of TNBC generally resemble those of other breast cancer subtypes. The most common symptom is a new lump in either breast that was not there before. Common symptoms are summarized in Figure 3.

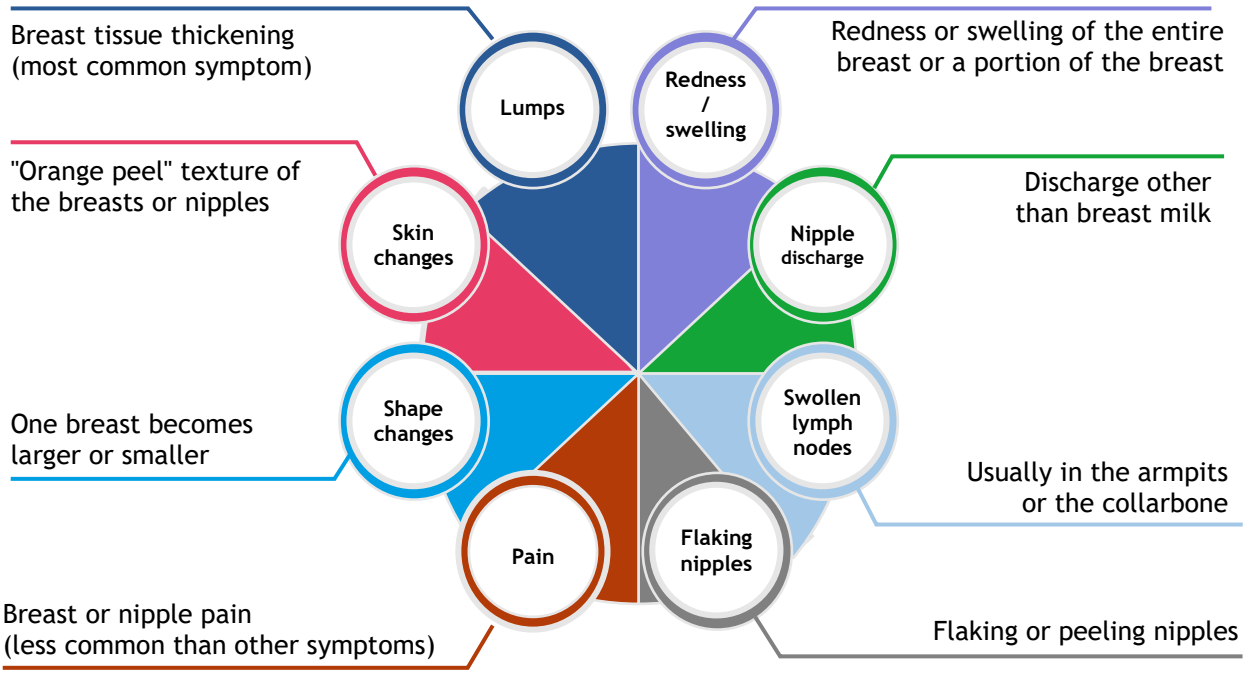


Figure 3: Common signs and symptoms of TNBC.

Source: (49).

1.5 Age at diagnosis

The likelihood of developing breast cancer increases with age (25). TNBC tends to be slightly overrepresented in younger women compared with the average breast cancer patient; see Figure 4 for age patterns in selected countries. For instance, around 24% of all TNBC cases in the United States are diagnosed in women under 50 years, compared with 19% of all breast cancer cases (10). The younger age of TNBC patients has consequences for various aspects of their quality of life and family life, including risk of infertility, premature menopause, and worse bone health (50, 51). Many women are still of working age when diagnosed with TNBC. The diagnosis and treatment of TNBC has negative implications for their work life, which in turn affects the size of the economic burden of TNBC (see section 2.2).

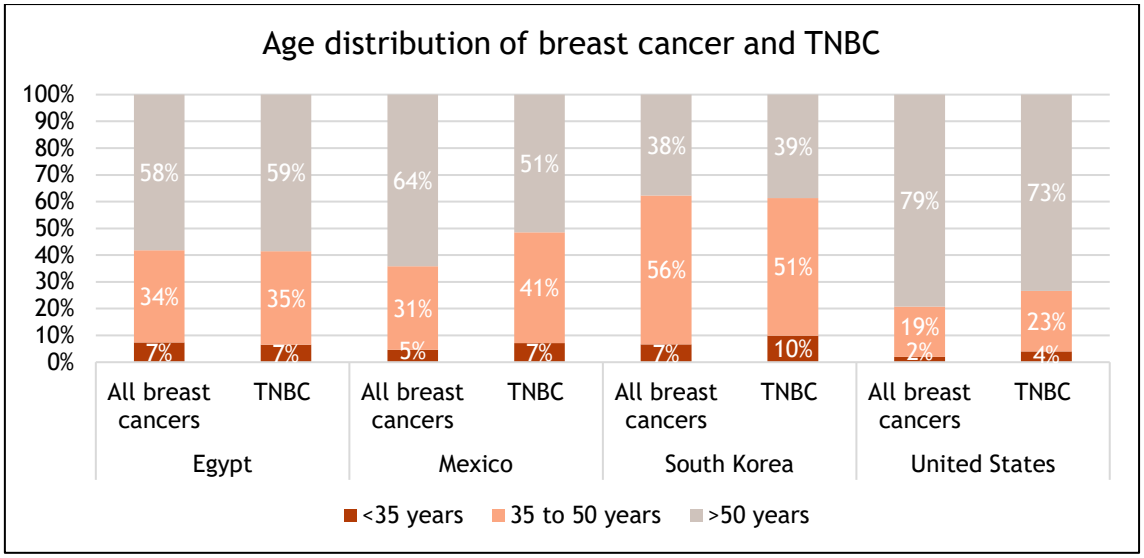


Figure 4: Breast cancer incidence by age group in selected countries.

Notes: For Mexico and the United States, the underlying data for the age groups 31–40 years and 50–54 years, respectively, were split proportionally to fit the age cut-offs shown. Source: (10, 52-54).

1.6 Quality of life

TNBC has a negative impact on many aspects of patients' quality of life as well as their families. Previous studies have pointed to a multitude of factors that may affect quality of life negatively; see Table 3.

Table 3: Aspects of quality of life affected with TNBC

Aspect	Description
Physical health	TNBC patients face the lowest survival chances of all breast cancer subtypes; see section 0. TNBC patients report lower functional well-being as well as sleep quality than patients with other breast cancer subtypes (55, 56).
Mental health	TNBC patients report more depression, anxiety, fear, intrusive thoughts, stress, and feelings of inadequacy than patients with other breast cancer subtypes (56, 57). Women who undergo mastectomies (removal of the entire breast) can experience long-lasting negative effects on self-esteem and body image (58).
Informal care	Partners of breast cancer patients have to cope with new roles and responsibilities as informal caregivers. This includes practical support in the household (i.e., responsibility for additional household chores) and taking care of children and/or elderly family members in multigenerational households. Time for family caregiving for breast cancer patients averaged 6.4 hours per day in the US (59). This may affect the partner's ability to continue to work or productivity at work (60).
Family life	Breast cancer may lead to negative effects on the dynamics of the relationship with one's partner in terms of emotional support, sexuality, and intimacy (61). Treatment with chemotherapy, which used to be the cornerstone treatment in TNBC, can temporarily or permanently cause infertility (62), and thereby affect family planning. Children may also be greatly affected, both emotionally because of fear of their mother dying and practically if they need to support their mother with different tasks (63).
Work life	Breast cancer patients of working age commonly worry about losing their jobs during and after treatment, facing workplace discrimination, financial instability, and long-term unemployment (64, 65).

Aspect	Description
Household finances	The household income of breast cancer patients may be affected in multiple ways. For working-age patients, the high symptom burden may force them to be on extended sick leave or permanently quit their jobs. For breast cancer patients, a systematic review showed that the likelihood of returning to work varies from 43% to 93% within one year of diagnosis across high-income countries (66). In addition, studies of caregivers to cancer patients have indicated a productivity loss due to absenteeism/presenteeism in the range of 21–27% (67). Families also have to cope with out-of-pocket expenditure for transportation to and from health care facilities and for medical services (co-payments or full payment).

1.7 Survival

TNBC is a subtype of breast cancer that is more aggressive than the hormone-receptor positive subtypes (luminal A and B) (68). TNBC tumors are associated with higher metastatic potential, a higher tendency of recurrence after initial treatment, and overall poorer prognosis (68). The limited number of medical treatment options (only chemotherapy) in the past contributed to TNBC having the poorest prognosis of all breast cancer subtypes (12); see Figure 5 for a comparison of survival rates in selected countries. For instance, the 5-year relative survival rate of TNBC cases was 77% compared with 91% of all breast cancer cases in the diagnosis period 2012–2018 in the United States.

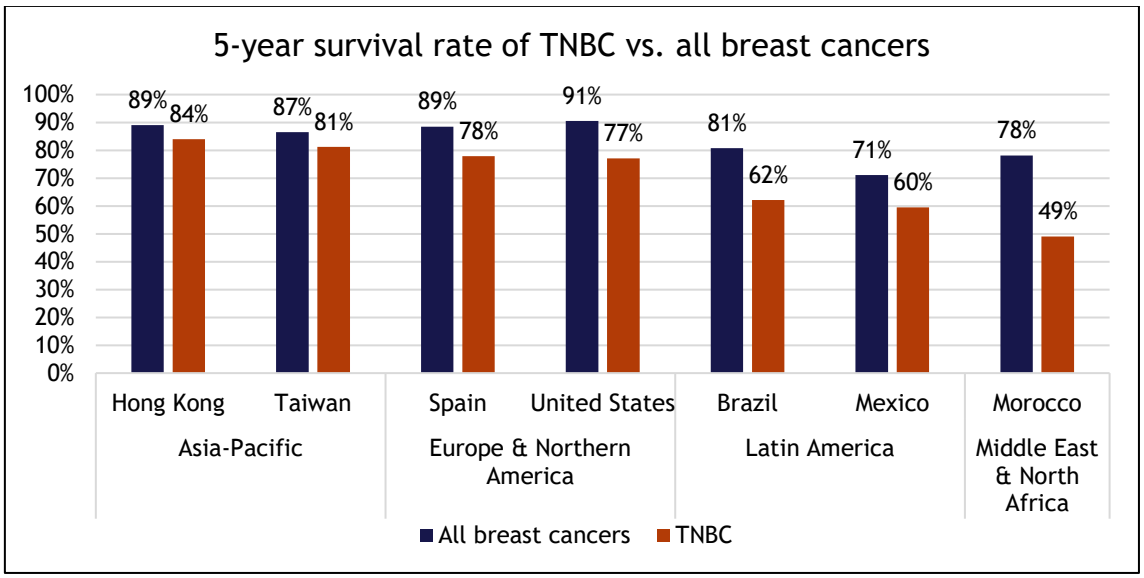


Figure 5: 5-year relative survival rates of TNBC and all breast cancers in selected countries per region.

Notes: Data for Hong Kong, Taiwan, Brazil are absolute rates and "All breast cancers" exclude TNBC cases. Data for Mexico are absolute rates and for Morocco 3-year absolute rates. Source: (69-75).

The survival chances of breast cancer patients depend critically on the stage at diagnosis. For TNBC, the 5-year relative survival rate was 91% in patients with localized disease (stage I) but only 12% in patients diagnosed with distant disease (stage IV) in the diagnosis period 2012–2018 in the United States; see Figure 6. This underlines the paramount importance of early detection of breast cancer and TNBC.

In addition, TNBC used to have lower survival rates in every single stage at diagnosis than the other breast cancer subtypes in the United States; see Figure 6. This situation indicates that

treatment modalities used in TNBC in 2012–2018 were less effective than treatments used for other subtypes. This survival gap between TNBC and other subtypes of breast cancer highlights the need for more effective treatments in TNBC.

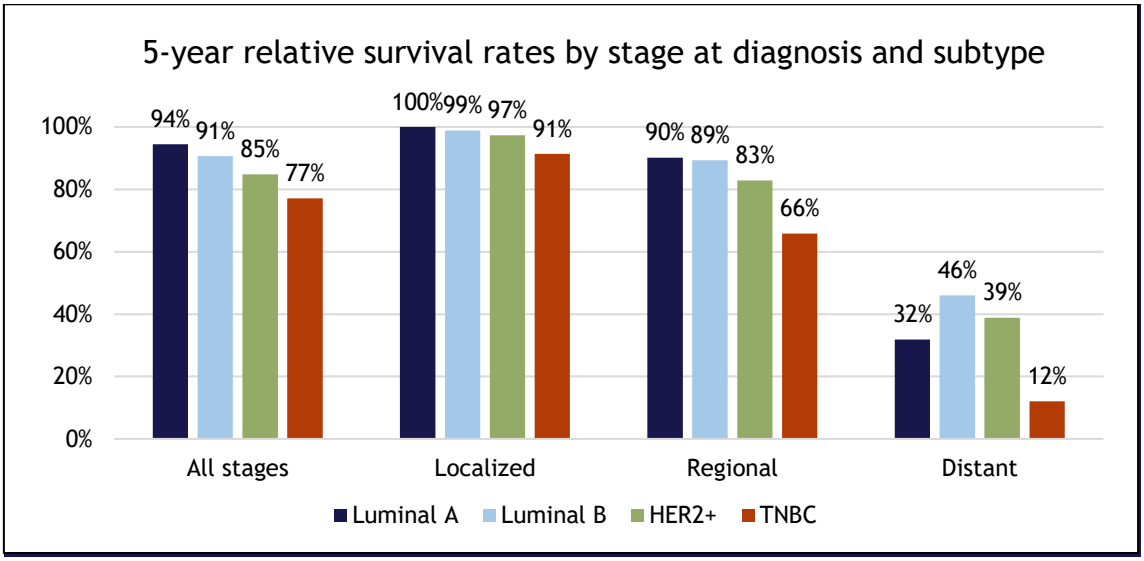


Figure 6: 5-year relative survival rates by stage at diagnosis and breast cancer subtype in the United Sates (diagnosis period 2012-2018).

Source: SEER (74).

2. Disease and economic burden of TNBC

2.1 Incidence and mortality

The annual numbers of newly diagnosed cancer cases (i.e., incidence) and cancer deaths (i.e., mortality) are key parameters to measure the disease burden of breast cancer to health care systems and to society. Previous analyses have indicated that TNBC accounts for 10–20% of all new cases of breast cancer but 30–40% of all breast cancer deaths because of its low survival compared with other breast cancer subtypes (76, 77).

Information on time trends in the incidence and mortality of TNBC is generally limited, because cancer registries only began routinely measuring the current standard set of molecular markers (i.e., ER, PR, HER2) in recent years (78). Therefore, Figure 7 only shows past and future trends of breast cancer incidence and mortality. In the past, incidence rates were highest in Europe and Northern America and lowest in the Middle East and North Africa. All regions recorded increasing trends in incidence over time, e.g., from 115 to 164 cases per 100,000 women (+43%) in Europe and Northern America between 1995 and 2022, and from 33 to 72 cases per 100,000 women (+120%) in Latin America.

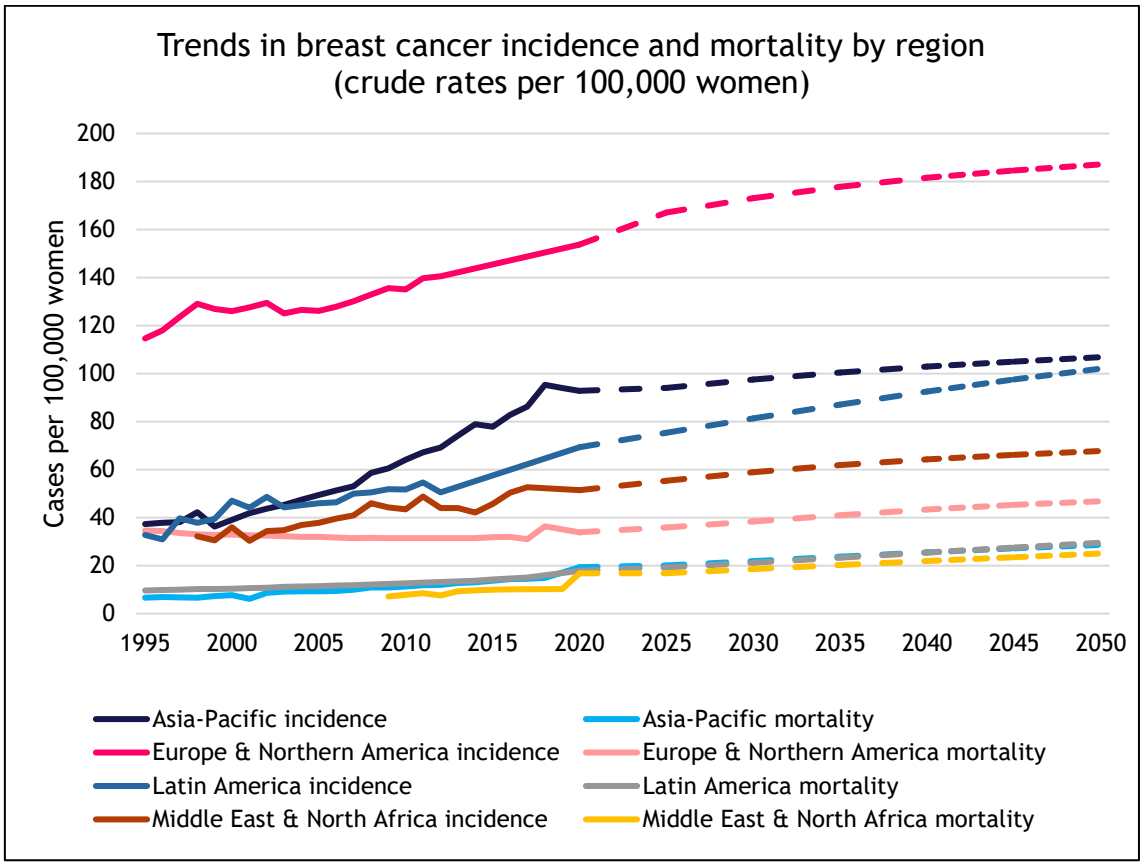


Figure 7: Estimated trends in breast cancer incidence and mortality crude rates per 100,000 women in selected regions, 1995-2040.

Notes: Asia-Pacific includes Australia, Hong Kong, South Korea, Thailand, and Taiwan, and numbers in 2020-2040 only include Australia, South Korea, and Thailand. Europe & Northern America include the 27 member states of the European Union, Canada, and the United States. Latin America includes Argentina, Brazil, Chile, Colombia, and Mexico. Middle East & North Africa includes Algeria, Saudi Arabia, and Türkiye. Numbers in 2020-2040 are predictions based on unchanged age-specific risks to get breast cancer. Source: IARC (79-81).

Several factors explain the past increases in the incidence rates of breast cancer. The most important factor are demographic changes, in particular population aging (82, 83). A higher share of adult and elderly women in the population leads to more breast cancer cases, because the risk to get breast cancer increases with age. Unfavorable developments in the prevalence of major modifiable risk factors, in particular obesity/overweight, also contributed to the overall increase. For instance, obesity rates in women in the United States have increased from 13% in 1975 to 37% in 2016, and in South Korea from 1% to 5% (2). In addition, the implementation of breast cancer screening programs since the 1980s might have led to an overdiagnosis of slow-growing tumors with low-risk profile (84).

Between 2022 and 2050, the number of new breast cancer cases is expected to continue to increase in all regions – between 14% in Europe and Northern America and 42% in Latin America – solely due to population aging.[2] The future increases might be augmented by the continued rise in obesity and physical inactivity as well as more screening around the world.

By contrast, breast cancer mortality rates remained in 35 deaths per 100,000 women (0%) in Europe and Northern America, while these rates increased less than incidence in Latin America (+91% vs. +120%) between 1995 and 2022; see Figure 7. The decoupling of trends in mortality from incidence in recent decades has also been documented elsewhere (82, 83). The growing gap between breast cancer incidence and mortality reflects the progress made in improving the survival of breast cancer patients.

2.2 Economic burden

The burden of TNBC on society can be measured in monetary terms. The societal costs of TNBC include direct costs (costs for medical services covered by public and private sources, costs for transportation), indirect costs (productivity losses to the economy from working-age women not being able to work or dying prematurely), and informal care costs (value of the time spent providing unpaid care). Previous studies on breast cancer have found that direct costs and indirect costs are about equally large; see Figure 8. The high contribution of indirect costs is partly explained by the comparatively young age at breast cancer diagnosis, affecting many working-age women.

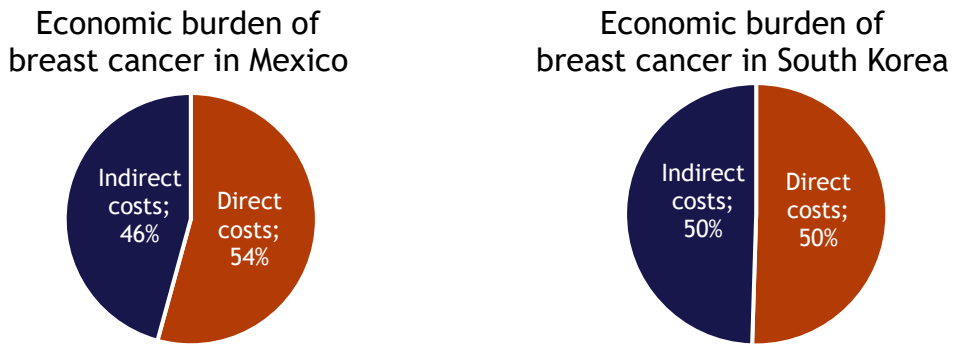


Figure 8: Composition of the economic burden of breast cancer in Mexico (2014) and South Korea (2010).

Notes: In Mexico, direct costs include medical costs as well as funeral costs, while indirect costs include productivity loss from being sick and from premature death. In South Korea, direct costs include medical costs (medical services paid for by insurance, copayments, non-covered services, medicines) and non-

[2] The increase in TNBC cases might be slightly lower because the median age at diagnosis of TNBC is lower than the median age of all breast cancer cases (see section 1.5).

medical costs (transportation, time spent by caregivers), while indirect costs include productivity loss from being sick and from premature death. Source: (85, 86).

There is limited evidence on the size of the economic burden of TNBC compared with other subtypes of breast cancer (2). Previous results indicated that (i) per-patient medical costs in TNBC cases are around three to four times lower than in HER2+ cases before the recent introduction of novel medical treatments for TNBC, and (ii) the lower survival and the younger age of TNBC patients might result in a higher productivity loss per patient compared with other breast cancer subtypes.

The economic burden of TNBC varies by disease stage. Figure 9 shows that per-patient medical costs for treating a metastatic patient (stage IV) are around three to five times higher than of early-stage patients (stage I–III) in high-income countries (87). This difference is caused by more frequent and longer hospitalizations of metastatic patients. Indirect costs of TNBC caused by work absenteeism and disability differ in working-age patients by recurrence status. Patients who had received initial treatment and who experience metastatic recurrence incur three times higher monthly costs from absenteeism and disability than patients with no recurrence in the United States (88). Patients with recurrence also had a 63% higher rate of leaving the workforce (88). Consequently, increasing the proportion of women diagnosed in early stages of TNBC, would not only save lives but also reduce health care costs and indirect costs.

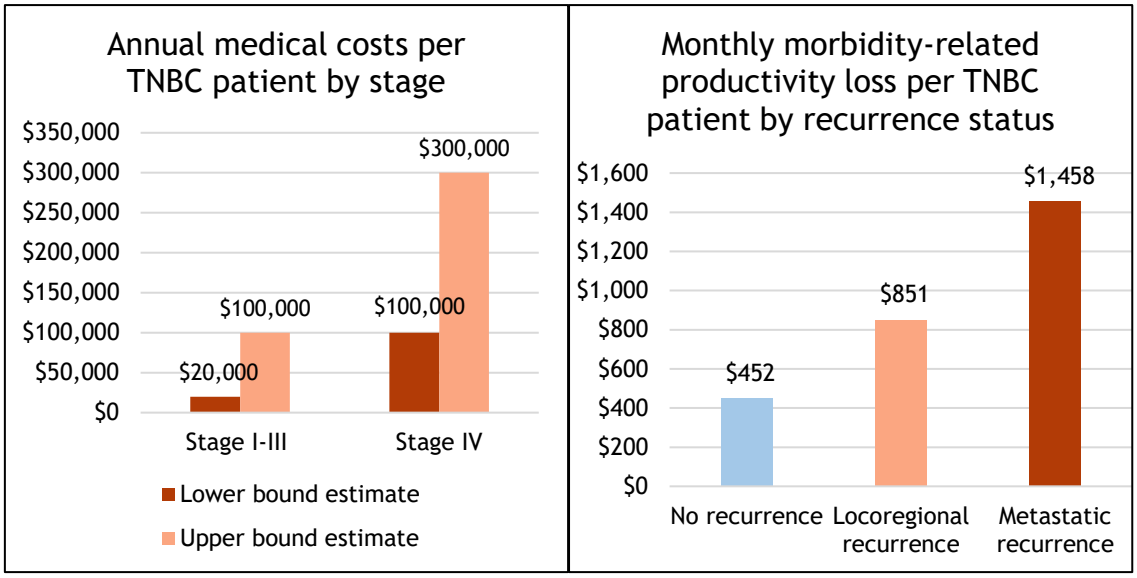


Figure 9: Average annual medical costs per TNBC patient by disease stage in high-income countries in 2021 USD (left figure) and monthly costs of productivity loss from morbidity per TNBC patient by recurrence status in the United States in 2019 USD (right figure).

Notes: Medical costs are an average from studies covering Belgium, Canada, France, Portugal, Spain, Sweden, and the United States. Morbidity-related productivity loss consists of medically-related absenteeism and disability in patients aged 18–65 years of all stages who were initially treated with surgery. Source: (87, 88).

3. Global challenges in TNBC care

The care pathway in TNBC starts with the detection of the tumor by the patient herself or through screening. This is followed by the diagnostic process. The diagnostic assessment informs the appropriate therapeutic approach. Different kinds of treatment options exist depending on the characteristics of the tumor.

Figure 10: Key stages of the TNBC care pathway.

Patients may face different challenges along the care pathway. In 2021, the WHO established the Global Breast Cancer Initiative to provide strategic guidance and coordination aimed at improving breast cancer care, with a focus on low- and middle-income countries (89). The aim is to reduce global breast cancer mortality by 2.5% per year, thereby averting 2.5 million breast cancer deaths globally between 2020 and 2040. The three pillars toward achieving this aim are:

1. Health promotion for early detection (pre-diagnostic interval)
    - KPI: >60% of cancer cases are stage I or II at diagnosis
2. Timely breast diagnostics (diagnostic interval)
    - KPI: diagnostic evaluation, imaging, tissue sampling and pathology within 60 days
3. Comprehensive breast cancer management (treatment interval)
    - KPI: >80% undergo multimodality treatment without abandonment

3.1 Early detection and screening

There are generally two ways to detect breast cancer; either the tumor is detected by the patient herself based on symptoms (such as a lump in the breast) or through screening before the experience of any symptoms. In Europe, around half of all new breast cancer cases are self-detected and the other half through screening programs (90). In countries without screening programs or low participation in these programs, the importance of awareness of signs and symptoms is particularly important.

Early detection of breast cancer is crucial to increase the likelihood to survive (91). Tumors are easier to treat successfully when they are still small and have not metastasized and spread to other parts of the body (91). A notable finding from a global study conducted in 2023 was the marked decrease in the proportion of breast cancer patients diagnosed with metastasis (92). From the early 2000s to 2015 and onwards, the rate of metastatic cases dropped from 3.8-35.8% to 3.2-11.6% in the countries surveyed (92). The highest rates of metastatic cases at diagnosis were observed in sub-Saharan African countries. Older women and women with lower socioeconomic status also had a higher rate of being diagnosed with metastatic disease around the world.

Figure 11 shows the stage distribution of newly diagnosed breast cancer cases in selected countries. High-income countries in the Asia-Pacific region, Europe, and Northern America as well as Chile detect a much higher proportion of cases in stage I than middle-income countries in the Asia-Pacific region, Latin America, and the Middle East and North Africa. The latter countries also fail to meet the aim of the WHO's Global Breast Cancer Initiative to detect >60% of cases in stage I or II.

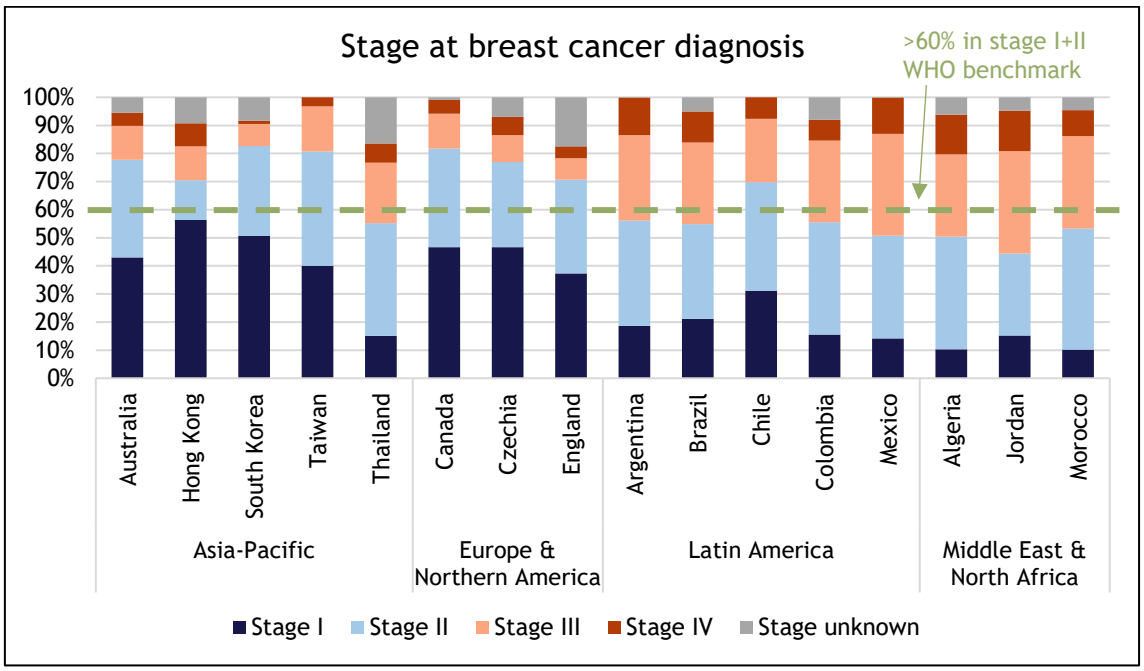


Figure 11: Stage distribution of breast cancer at diagnosis in selected countries per region.

Notes: Data for Australia include all diagnosed cases in 2011 (n=14,215). Data for Hong Kong and South Korea include newly diagnosed cases in 2018 (n=5,287) and (n=28,157), respectively, and data were extrapolated excluding stage 0. Data for Taiwan include patients diagnosed in 2011–2017 (n=49,426). Data for Thailand include patients diagnosed in the Maharaj Nakorn Chiang Mai Hospital in 2006–2015 (n=3,868). Data for Canada, excluding Quebec, include all diagnosed women aged 18-79 in 2011-2015. Data for Czechia include all women diagnosed in 2021 (n=7,437). Data for England include all women diagnosed in 2019 (n= 47,906). Data for Argentina were obtained from the Institutional Registry of Tumors (RITA) and cover cases diagnosed in 2012–2018 (n=9,900), and data were extrapolated excluding the "desc" category. Data for Brazil include cases from the hospital-based cancer registries in 2019. Data for Chile include cases from a public community hospital and an academic private hospital in 2010-2021 (n=5,806). Data for Colombia include all newly diagnosed cases treated in the public sector in 2021 (n=6,593). Data for Mexico include all patients diagnosed at the National Cancer Institute (INCan) with Seguro Popular in 2007–2013 (n=4,300). Data for Algeria cover patients in community and university hospitals from the public sector in 2016 (n=1436). Data for Jordan cover women diagnosed in UJH and Bashir Hospital in 2011-2014 (n=867). Data for Morocco cover women diagnosed in 2008-2017 in INO Rabat (n=1,020) and CM-VI Casablanca (n=635). Source: (18, 23, 93-108).

The WHO recommends countries to implement breast cancer screening programs (109). Most countries around the world have such programs, even though they often are opportunistic programs (i.e., women are merely recommended to get screened) and not organized population-based programs (i.e., all women in the target age population are actively and regularly invited) (110); Figure 12. In several high-income countries, these programs have been operating since the 1980s (111, 112).

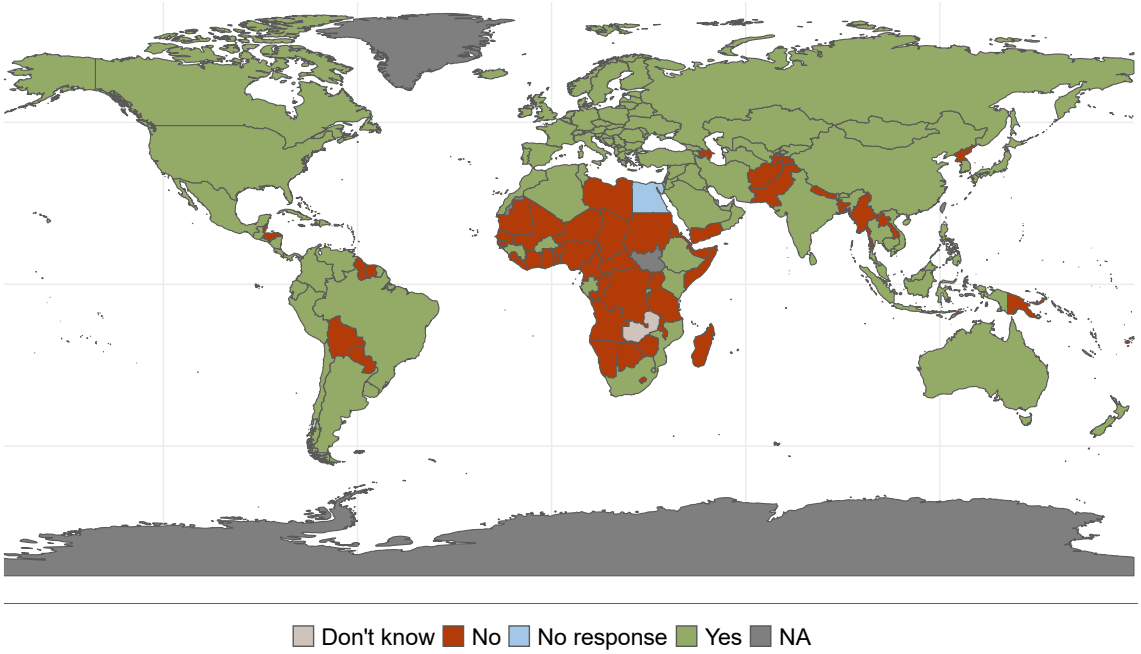


Figure 12: Existence of screening programs for breast cancer in 2021.

Notes: The coloring of the geographic areas does not imply an expression or opinion by IHE on the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Source: WHO (113).

Table 4: Recommendations for early detection of breast cancer by country or region

Geography	Age groups								
	<40	40-45	45-49	50-55	55-60	60-65	65-69	70-74	≥75
United States									
European Union 2022									
European Union 2003									
Pan American Health Organization									
South Korea									
Taiwan									
Thailand									
Morocco									
Saudi Arabia									
Türkiye									

Color code	Meaning
	Strong recommendation for mammography
	Moderate recommendation for mammography
	Weak or no recommendation for mammography
	Recommendation for clinical breast examination

Notes: Many countries have established specific recommendations for women at high risk, such as those with a family history of breast cancer or BRCA 1/2 mutations, but these recommendations are not included in this simplified table. Source: United States age group 40-49 grade C and age group 50-74 grade B recommendation (114), European Union age groups 45-49 and 70-74 conditional recommendation and age group 50-69 strong recommendation (115-117), Pan American Health Organization (118), South Korea (119), Taiwan (120), Thailand (121, 122), Morocco (123, 124), Saudi Arabia (125), Türkiye (126).

Different countries and regions develop their health care guidelines based on distinct population health data, resource availability, and infrastructure. This leads to diverse recommendations for average-risk women regarding (i) the optimal age for initiating and ending

routine breast cancer screenings, (ii) the screening method with either mammography or clinical breast examination (CBE), and (iii) the screening interval. Weighing the harms against the benefits of screening has led the WHO in 2010 not to recommend mammography screening in women younger than 50 years of age (109). Over time, recommendations have evolved in different parts of the world, reflecting a deeper understanding of various screening methods' effectiveness and the different risk profiles across age groups; see Table 4. For instance, in the European Union the target age group for breast cancer screenings with mammography initially women aged 50 to 69 since 2003, but an updated recommendation from 2022 expands the age group to women aged 45 to 74 (127). In Latin America, the first edition of the Latin America and the Caribbean Code against Cancer, issued in 2023, recommends women aged 40 years and older to visit a health care provider every two years for a CBE and from age 50 to 74 to get a mammogram every two years (118).

The success of a screening program can be measured by the participation of eligible women. High-income countries tend to have higher participation rates in breast cancer screening programs than middle-income countries; see Figure 13. However, even in most high-income countries, the participation rates are suboptimal. For instance, the Healthy People 2030 Target in the United States is a participation rate of 80.5% (128). In Europe, only Denmark and Finland exceed this target value in 2021 (129).

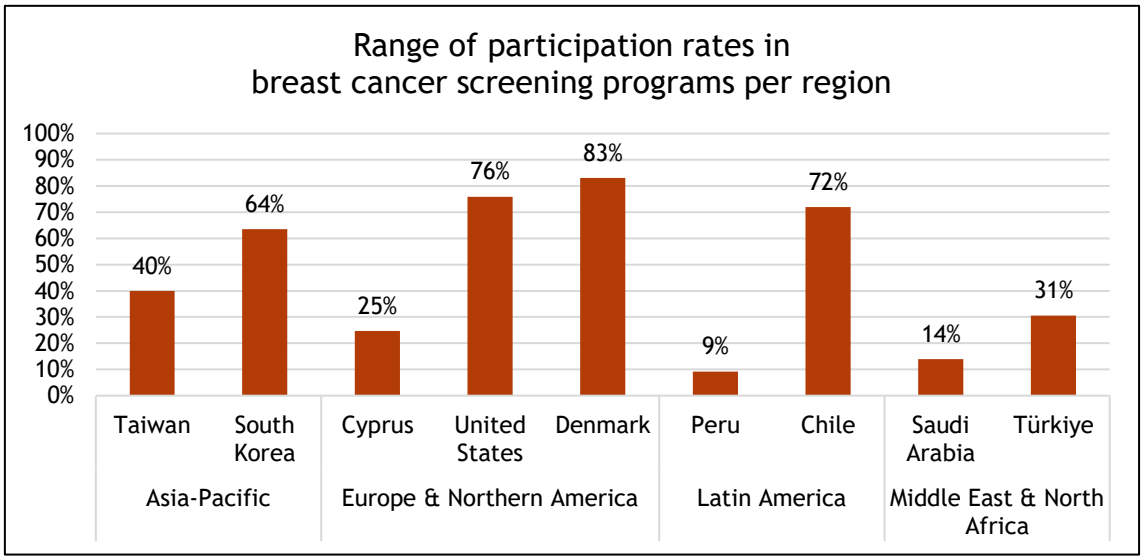


Figure 13: Mammography screening rates in women of the target age group.

Notes: The participation rates shown come from different sources, data periods, age groups, and samples, thus restricting their comparability. Data for Taiwan refer to 2018, South Korea 2020, Cyprus 2021, United States 2021, Denmark 2021, Peru 2022, Chile 2017, Saudi Arabia 2019, Türkiye 2022. Source: Asia-Pacific (130, 131), Europe & Northern America (128, 129), Latin America (132, 133), Middle East & North Africa (129, 134).

Table 5: Challenges in early detection

Challenge	Description
Low breast health awareness	Knowledge of breast health awareness – common signs and symptoms as well as the importance of screening - is often inadequate in countries around the world. Women with lower socioeconomic status tend to have lower levels of health literacy about breast cancer.
Social stigma and cultural beliefs	Misconceptions about cancer lead to a reluctance to seek primary care when symptoms arise in some regions in Asia and in the Middle East. A breast cancer diagnosis is associated with a negative stigma ("punishment from God") and is a taboo.
Shortage of primary care staff and inadequate training	The increasing demand for health care services overburdens primary care providers and limits access of patients with breast cancer symptoms in certain locations. In some countries in Asia-Pacific and Latin America primary health care workers do not have any training of breast cancer detection.
Lack of genetic risk assessment (genetic counseling)	Genetic testing for BRCA1/2 mutations in healthy women is only recommended in high-risk groups, including women with a family history of breast/ovarian/pancreatic cancer, in clinical guidelines in Europe and in Chile. Yet this approach misses a potentially large group of BRCA1/2 carriers.
Lack of organized screening programs and/or free access	Many countries in Asia-Pacific, Latin America, and the Middle East lack organized population-based screening programs. In other countries with screening programs, women may need to pay a copayment for accessing screening services.
Low participation in screening programs	Despite the availability of screening programs in most countries, many women choose not to get screened due to a lack of sense of urgency, fear of diagnosis, or fear of the potential harms of getting screened. Other barriers, especially in Latin America and the Middle East, include lack of clarity about which screening facility to attend, long waiting lists to get a screening appointment, low perceived quality of screening services in the public sector, and uneven geographical distribution of mammography machines.
Inequalities in access to breast cancer screening	Participation in breast cancer screening programs is often unequal across socioeconomic groups. Women living in rural areas, with lower education levels, with lower income, and women from indigenous groups typically have lower participation rates.
Narrow target age group in screening programs	The target age group in breast cancer screening programs in many Western countries is often limited to women aged 50–69 years. The latest recommendation in the European Union is to expand screening programs to women aged 45–74 years. In the United States, the recommended age interval is 50–74 years and selective screening in women aged 40–49 years based on patient preferences and women who place a higher value on the potential benefit than the potential harms of screening.

Source: IHE reports on TNBC (Asia-Pacific, Europe/Northern America, Latin America) and on breast cancer (Middle East and Africa) (1-4).

3.2 Diagnostic process

Breast cancer is diagnosed with a triple assessment that involves a physical examination (a CBE by a physician), a mammography/ultrasound imaging, and a biopsy (90). Mammography, which is a low-dose X-ray imaging method, is the most common method to diagnose breast cancer. An ultrasound of the breast might also be used as an imaging method. A magnetic resonance imaging (MRI) scan of the breast might be recommended in some clinical situations, for instance when there is a suspicion of BRCA mutations or when the conventional test results are unclear (135).

A breast biopsy is performed if the imaging test results indicate the possibility of breast cancer (136). The procedure entails removing a sample of breast tissue, e.g., with a core needle biopsy. The sample is then examined by a pathologist to determine tumor characteristics. This process also involves biomarker testing of ER, PR, and HER2 status to determine the breast cancer subtype. The staging of the breast cancer (i.e., the size and spread of the tumor) might require additional scans with mammography, MRI, or other scanners as well as blood tests. Based on all information collected, the most suitable therapeutic approach can be decided.

For TNBC in particular, novel treatment options require additional biomarker testing of the tumor sample for the presence of BRCA1/2 mutations (present in around 10–30% of TNBC patients (33)) in both early-stage and metastatic patients and testing of PD-L1 status (positive expression in around 20–40% of TNBC patients (137, 138)) in metastatic patients prior to treatment initiation. As of 2022, international clinical guidelines by ASCO, ESMO, and NCCN recommend these novel biomarker tests as part of the diagnostic process (139-141).

Keeping the time between the diagnosis of breast cancer and the start of treatment as short as possible increases the chances of survival (142). Breast cancer patients with a long delay of ≥61 days between diagnosis and start of neoadjuvant systemic therapy have a 28% increased risk of subsequent mortality compared with patients with a short delay of 0–30 days (143).

Table 6: Challenges in the diagnostic process

Challenge	Description
Poor coordination of service providers and delays in the diagnostic process	Timely management of patients is impeded by poor coordination between primary care, diagnostic service providers, and treatment providers due to unclear referral routes, especially in Latin America and the Middle East.
Shortages of pathologists and radiologists	Countries in all regions face shortages of pathologists and diagnostic radiologists, which creates delays in the diagnostic process.
Shortages of diagnostic infrastructure	Many middle-income countries in Asia-Pacific, Latin American, and the Middle East lack a sufficient number of mammography machines. Across Latin America, shortages of pathology laboratories lead to tissue samples being transported long ways, potentially delaying diagnosis and increasing chances of quality failures.
Low quality of breast cancer imaging and pathology	In addition, available mammography machines might not be maintained properly, leading to inaccurate diagnoses and necessitating repeated tests. Moreover, most pathology departments are general and may lack pathologists experienced in the increasingly complex area of breast pathology and/or lack sufficient volume of cases to develop and maintain expertise.
Lack of comprehensive biomarker testing	The adoption of novel biomarker tests, such as BRCA1/2 mutations and PD-L1, is often delayed in clinical practice. Reasons for this may include lack of diagnostic laboratory infrastructure, inefficient organization, knowledge gaps of health care providers of why to test, when to test, and/or how to action the test results, test results not being available within a clinically meaningful time, and insufficient public reimbursement.
Start of treatment before full assessment of ER/PR/HER2 status	Biomarker tests for ER, PR, and HER2 status are routinely carried out in all high-income countries and most middle-income countries. However, these tests are not always performed during the diagnostic process based on the biopsy but rather only after surgery based on the surgical sample. This limits the choice of the optimal treatment approach, such as neoadjuvant systemic therapy.

Source: IHE reports on TNBC (Asia-Pacific, Europe/Northern America, Latin America) and on breast cancer (Middle East and Africa) (1-4).

3.3 Treatment

TNBC patients may be treated with surgery, radiation therapy, systemic therapy (i.e., cancer medicines), or a combination of these treatment modalities. The optimal treatment differs by disease stage and tumor characteristics: see Figure 14. A treatment plan should be drawn up by a multidisciplinary team (including at least a radiologist, radiographer, pathologist, surgeon, medical oncologist, radiation oncologist, breast care nurse, and breast data manager) (90).

The treatment of early-stage TNBC typically always involves surgery (with the possible addition of radiation therapy) and systemic therapy. In stage I, systemic therapy is only given after surgery. In stage II-III, surgery should be both preceded ('neoadjuvant') and succeeded ('adjuvant') by the administration of systemic therapy for a limited amount of time. Metastatic TNBC encompasses women with newly diagnosed metastatic TNBC and women who were previously diagnosed with stage I-III disease and later developed distant recurrence (144). Systemic therapy is the primary treatment option for metastatic TNBC (140).

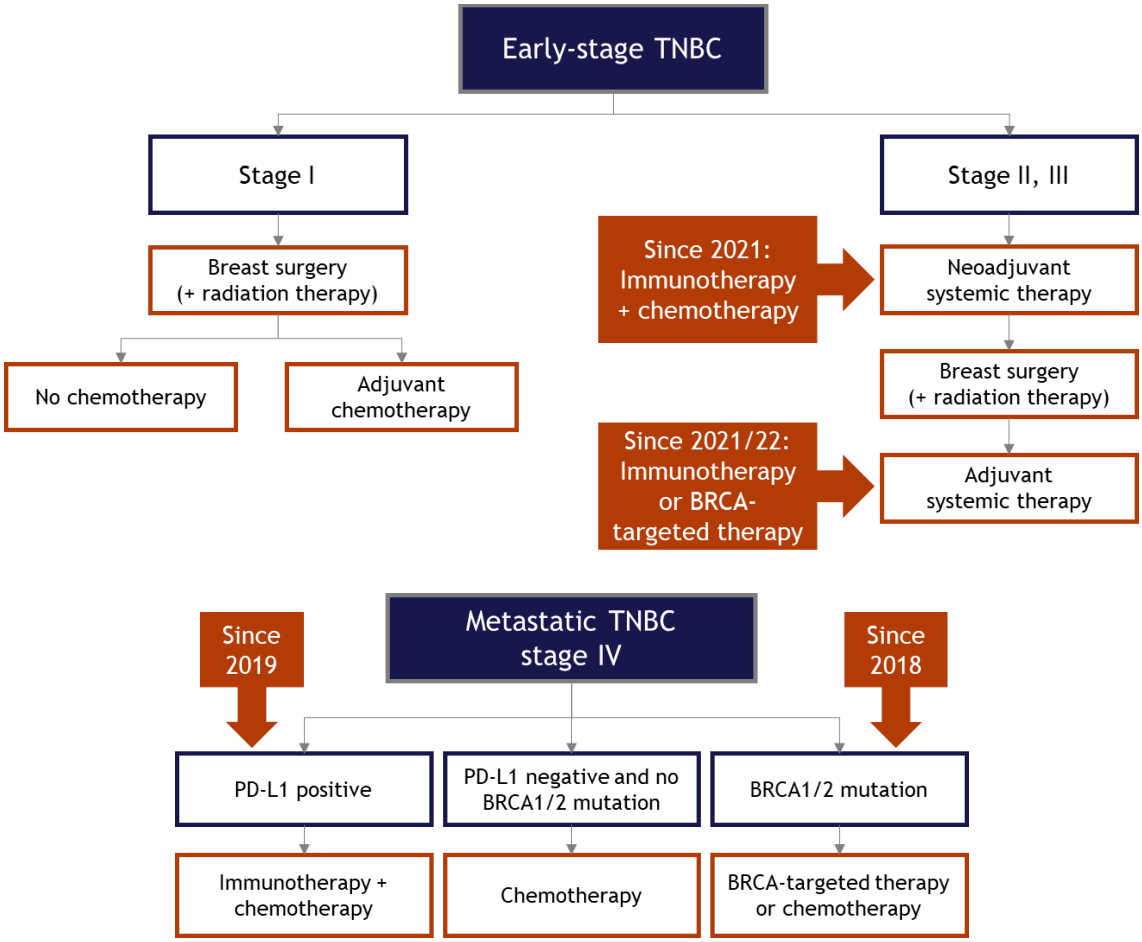


Figure 14: Stylized treatment algorithm in TNBC in 2022.

Notes: BRCA-targeted therapies in the metastatic setting are only recommended as first-line treatments if the patient has received (neo)adjuvant chemotherapy unless the patient was not suitable for chemotherapy. Source: Adapted from ESMO and NCCN guidelines (135, 140, 141).

Systemic therapy options in TNBC have been historically limited to chemotherapy because hormonal therapy and HER2-directed targeted therapies that are used in other breast cancer subtypes were not helpful due to the absence of hormone receptors and HER2 expression (145). Since 2018, novel systemic therapy options have become available with the introduction of

immunotherapy and BRCA-targeted therapy in both early-stage and metastatic TNBC; see Figure 14. ASCO, ESMO, and NCCN guidelines recommend this new therapeutic option for appropriate patients (135, 140, 141, 146-149).

Table 7: Challenges in treatment

Challenge	Description
Limited patient involvement in decision-making	Patient involvement around the world is generally limited. This is partly explained by a scarcity of specialist breast nurses and patient navigators who can guide patients through the complex care pathway and explain the various alternatives available.
Fragmented treatment provision	In some countries in Latin America and the Middle East and Africa, cancer care is highly fragmented across multiple institutions, with patients receiving surgery, radiation therapy, and systemic therapy at different centers. Receiving cancer care from multiple centers is associated with longer treatment times, higher health care costs, lower survival, and lower quality of life for patients.
Shortages of oncologists	Although the number of medical oncologists is rising in countries around the world, the supply might not be enough to meet the demand from the increasing number of cancer patients. Shortages of oncologists in Latin America and the Middle East may lead to long waiting times for treatment or treatment being provided by physicians not specialized in cancer treatment. The latter might be more common in rural areas due to the concentration of oncologists in urban areas.
High copayments for medical services	Patient copayments for medical services are common in many countries around the world. The absence of caps or high caps on copayments limits access to treatment, especially for economically disadvantaged patients who cannot afford high out-of-pocket payments. The financial burden and psychological distress associated with high copayments may lead to nonadherence to treatment (e.g., delaying, modifying, forgoing, or not completing recommended treatment).
Use of alternative non-prescribed treatments or counterfeit medicines	The use of alternative non-prescribed medicines (e.g., herbal treatments) by patients is common in some countries in Asia-Pacific and the Middle East. The use of counterfeit medicines in Latin America also occurs. This may put women at serious health risks.
Outdated local clinical guidelines	Despite the availability of international clinical guidelines (such as those by ASCO, ESMO, or NCCN), local guidelines are not always up to date. If clinical guidelines do not include novel treatments, their prescription might be limited even though they are reimbursed by the public payer.
Hesitant adoption of new treatment approaches	Treating physicians may be reluctant to adopt new treatment regimens, such as neoadjuvant or adjuvant systemic therapy in TNBC patients who previously would not have received such treatments.
Limited and delayed reimbursement of new cancer medicines	The regulatory approval of new cancer medicines (e.g., by the FDA in the United States) is only the first step for patient access. The reimbursement of new cancer medicines by public payers after regulatory approval is generally limited and delayed by several years in many middle-income countries in Asia-Pacific, Eastern Europe, Latin America, and the Middle East.
Slow adoption of newly reimbursed cancer medicines	The reimbursement of new cancer medicines by public payers is no guarantee for access for all clinically eligible patients in the public sector. Different budget control mechanisms, at the national or hospital level, can impair patient access. This results in slow adoption of new medicines in clinical practice.

Source: IHE reports on TNBC (Asia-Pacific, Europe/Northern America, Latin America) and on breast cancer (Middle East and Africa) (1-4).

4. Recommendations for improved TNBC care

Women with TNBC face worse prognosis than women with other subtypes of breast cancer. However, there are many opportunities to improve the care of TNBC patients. This compendium report concludes with a list of recommendations to improve TNBC care that builds on the findings from previous reports covering selected countries in Asia-Pacific, Europe, Northern America, Latin America, and the Middle East and Africa. The recommendations fall into three broad areas, as shown in Figure 15. Further details are listed in Figure 16 and in the Appendix.

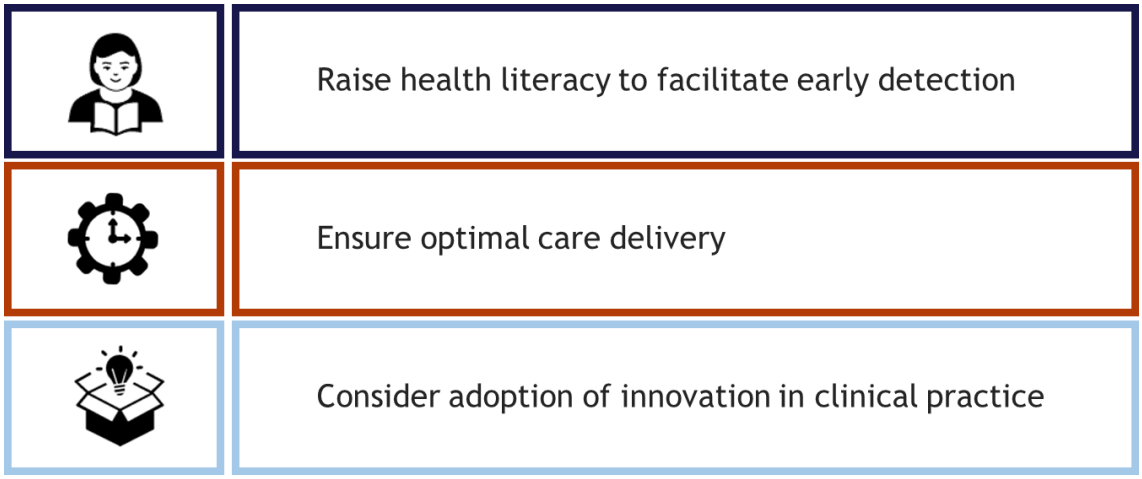


Figure 15: Main areas of improvement for TNBC care.

The implementation of these recommendations will require the cooperation of various stakeholders in each area. This includes patient advocacy groups, health care professionals (both in primary care and breast cancer specialists), hospitals and diagnostic centers, medical associations, the media, and the Ministry of Health and the Ministry of Finance.

The recommendations vary in terms of the amount of time and money required to put them into action and the effect they are expected to have on women's health. Some recommendations can be immediately acted upon or within a short period of time, such as raising awareness about common signs and symptoms of breast cancer, the significance of early detection, and increasing participation in organized screening programs. Recommendations such as recruitment and training of pathologists and radiologists or streamlining diagnostic services might take several years to implement. Some recommendations may take several years or even decades to realize their full potential, such as the promotion of a healthy weight and regular physical activity to prevent breast cancer.

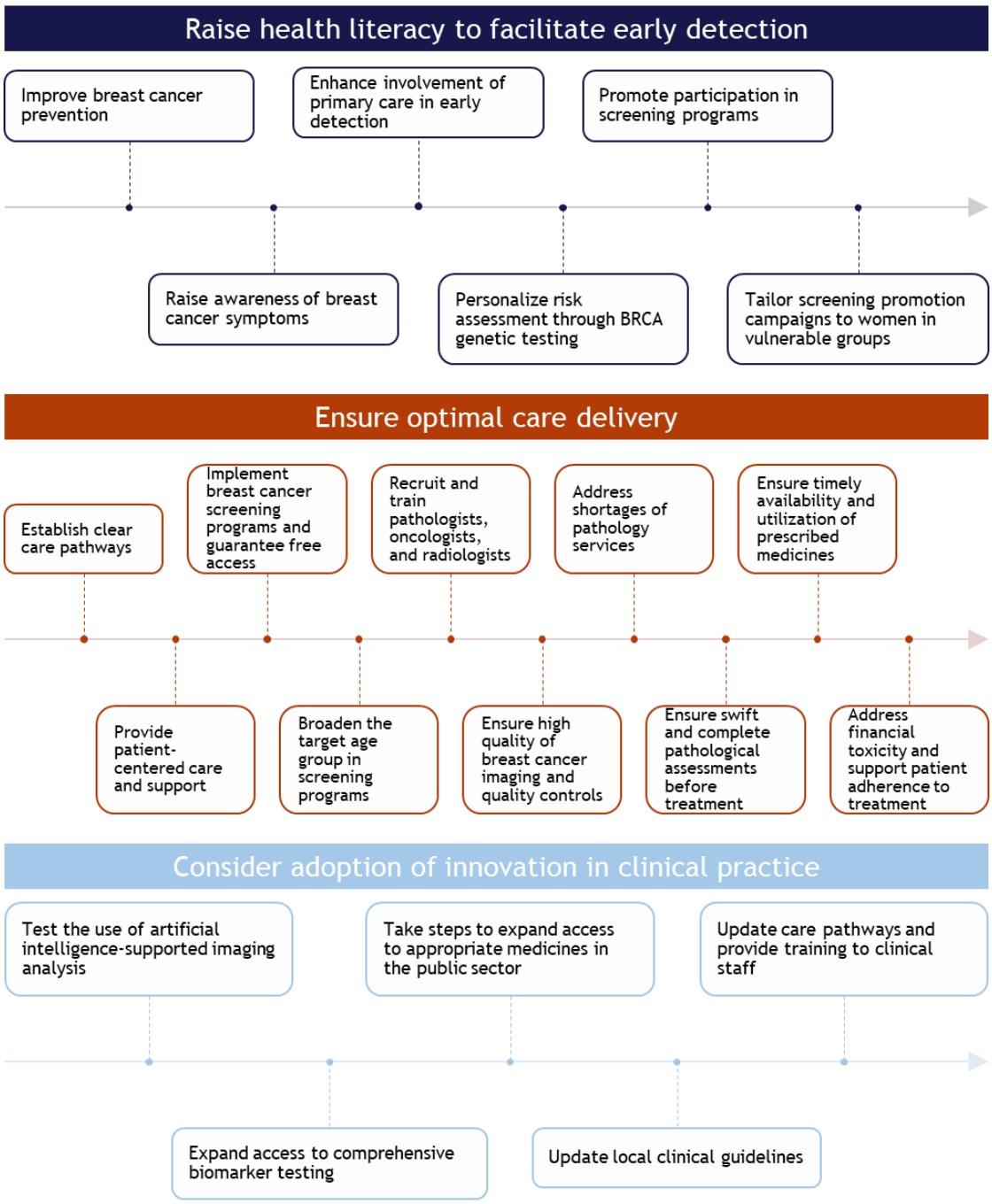


Figure 16: Main recommendations for improved TNBC care.

4.1 Societal impact of improved care

As explained above, there are ample opportunities to improve the care of TNBC patients along the entire patient pathway from early detection to diagnostics and treatment. Working towards better TNBC care would enhance patient outcomes and reduce the disease and economic burden to society; see Figure 17.

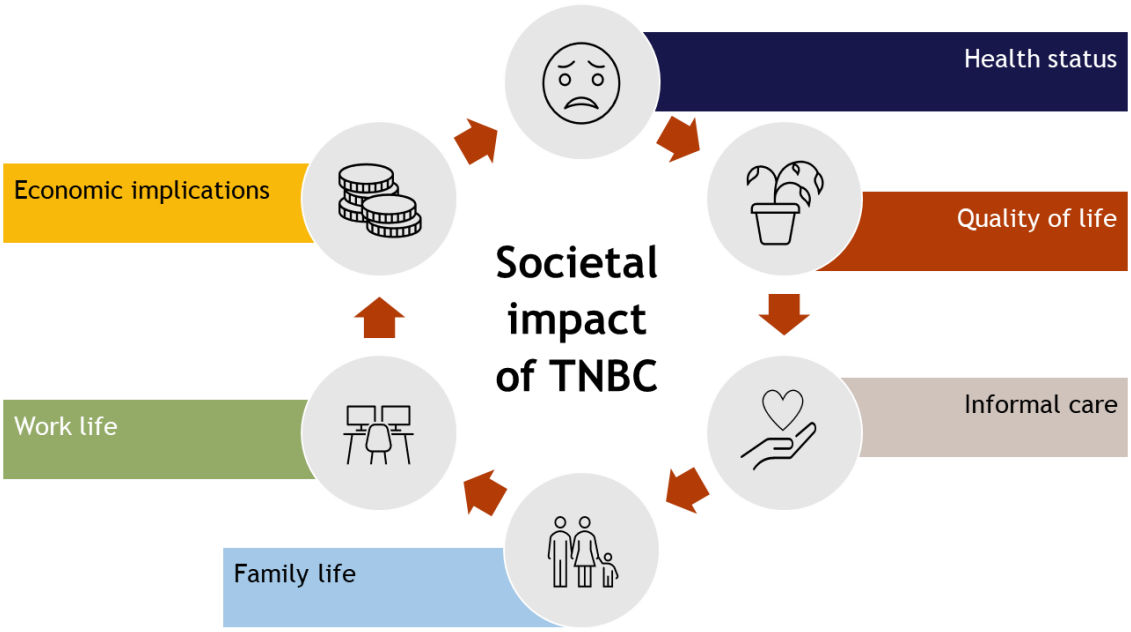


Figure 17: Elements of the societal impact of TNBC.

Case: Improving early detection

Many women, especially in middle-income countries in Asia-Pacific, Latin America, and the Middle East and North Africa, are diagnosed late at advanced stages of breast cancer; see section 3.1. The following effects of improved early detection through better awareness of symptoms in women and in primary care workers and through participation in screening programs may be anticipated:

- **Health implications**: The number of cancer survivors would increase. This is because more women are diagnosed at early stages and because the survival rates in TNBC are much higher in early stages than in late stages (e.g., 5-year survival rate of 91% in stage I and 12% in stage IV in the United States; see section 1.7).
- **Family life and informal care**: The lower symptom burden of breast cancer in early stages than in late stages may reduce the amount of informal care required by patients. This may also positively affect family life. A diagnosis at an earlier stage may also lower the psychological burden on family members due to a reduced likelihood of losing a mother/spouse/partner.
- **Work life**: More women could continue to work during their initial treatment or resume work after it, because of the lower symptom burden of breast cancer in early stages than in late stages.
- **Economic implications**: For the patient and her family, the out-of-pocket expenditure might be lower in early stages than in late stages, because of a lower consumption of

medical services. For the health care system, treatment costs would decrease because the costs of treating TNBC are lower at early stages than at late stages (around $20,000–100,000 in stage I–III and around $100,000–300,000 in stage IV in high-income countries; see section 2.2). For the economy, the increased number of women surviving TNBC and being able to resume work would reduce the indirect costs (productivity losses). Figure 18 shows a hypothetical example of a 50-year-old woman diagnosed with TNBC in South Korea for whom the mortality-related productivity loss would decrease by 23% from $14,812 to $11,370 if she had regularly participated in screening during the last ten years and therefore had a higher likelihood to be diagnosed early compared to if she did not participate in screening.

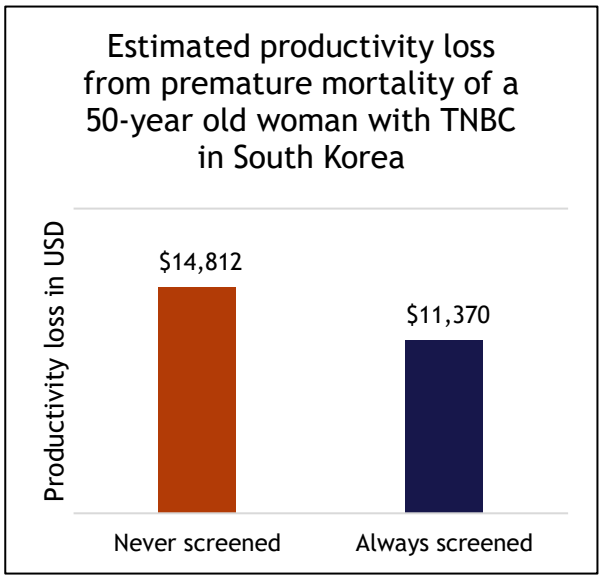


Figure 18: Estimated productivity loss from premature mortality of a 50-year-old woman in South Korea with different screening habits.

Source: (2).

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Appendix – Detailed recommendations

Area 1: Raise health literacy to facilitate early detection

Recommendations
Improve breast cancer prevention The promotion of a healthy diet and lifestyle is important to avert as many future incidences of breast cancer as possible.
Raise awareness of breast cancer symptoms Awareness of early signs of breast cancer needs to be improved. This is important for adult women of all ages, and especially for women outside the age range of screening programs and women who do not attend screening.
Enhance involvement of primary care in early detection The recruitment of primary health care workers should be prioritized, and they need to be trained in early breast cancer detection. They should also encourage regular participation in screening among the women they treat. Swift referral pathways from primary care to diagnostic services should be established.
Personalize risk assessment through BRCA genetic testing Genetic testing/counseling could be offered and reimbursed for women who are at an increased risk of developing breast cancer and TNBC (such as women with a family history of breast/ovarian/pancreatic cancer) in order to increase the chances of early diagnosis.
Promote participation in screening programs Public information campaigns to improve knowledge of the benefits of participating in organized screening programs are crucial. Effective measures to promote participation can include invitation letters, basic information on screening, multiple reminders, and fixed appointments.
Tailor screening promotion campaigns to women in vulnerable groups Screening programs must prioritize reaching out to vulnerable groups, such as women with lower socioeconomic status or indigenous groups, by enhancing geographical access to mammography and lowering cost barriers to ensure that the programs are accessible to everyone.

Area 2: Ensure optimal care delivery

Recommendations
Establish clear care pathways The timely diagnosis and treatment of breast cancer requires good coordination between different service providers along the care pathway. Clear pathways starting from suspicion of breast cancer in primary care (or from mammography screening) until treatment start should be established or strengthened.
Provide patient-centered care and support Patient participation in treatment decision-making should be prioritized as it improves the quality of life of breast cancer patients. Access to specialized breast nurses and patient navigators should be guaranteed to accompany the patient along the care pathway.
Implement breast cancer screening programs and guarantee free access The implementation of organized population-based breast screening programs (instead of opportunistic programs) should be prioritized in countries where they do not yet exist. Screenings at regular intervals should be made free of charge.
Broaden the target age group in screening programs The latest recommendation in the European Union is to expand screening programs to women aged 45–74 years. Countries that still have screening programs with a narrow target age group could consider broadening the group.
Recruit and train pathologists, oncologists, and radiologists Create incentives to recruit, train, and retain more pathologists, oncologists, and radiologists given the rising number of breast cancer patients.
Ensure high quality of breast cancer imaging and quality controls An adequate number of mammography machines needs to be put in place. The machines need to be maintained properly to ensure accurate diagnosis. Easier access to alternative imaging methods (MRI) for women at an increased risk of TNBC (e.g., high breast density, known BRCA1/2 carriers) could be considered.
Address shortages of pathology services Small and general pathology laboratories could be consolidated into larger conglomerates to achieve a sufficient volume of cases. This would facilitate the adoption of national and international best practices, and enable specialization of pathologists in specific disease areas, including breast pathology.
Ensure swift and complete pathological assessments before treatment A full assessment of staging and ER/PR/HER2 status should be completed before the start of treatment in order to enable the choice of the most suitable therapeutic approach. At the same time, the pathological assessment should not unnecessarily delay the start of treatment.
Ensure timely availability and utilization of prescribed medicines Despite regulatory approval and reimbursement of medicines by public payers, bottlenecks in the supply of medicines may occur. This may limit the prescription of appropriate treatments to eligible patients, or it may cause interruptions in their treatment. It is essential to prioritize adequate public funding and effective supply chain management to minimize the risk of stock-outs of prescribed medicines.
Address financial toxicity and support patient adherence to treatment Caps on patient copayments for reimbursed cancer care services should be introduced in countries where they do not yet exist. The caps should be of a size that prevents nonadherence to treatment because of financial reasons, especially among economically disadvantaged patients.

Area 3: Consider adoption of innovation in clinical practice

Recommendations
Test the use of artificial intelligence-supported imaging analysis A growing body of evidence supports the safe use of artificial intelligence-supported imaging analysis. AI-supported reading of mammograms instead of the standard double reading of mammograms by two radiologists could substantially lower screen-reading workload.
Expand access to comprehensive biomarker testing Testing for BRCA1/2 mutations and PD-L1 expression are required to inform the treatment decision in TNBC for targeted therapy and immunotherapy (only in the metastatic setting), respectively. Patient access to these tests needs to be guaranteed to enable the choice of the most appropriate therapeutic approach. Adequate testing infrastructure also needs to be put in place.
Take steps to expand access to appropriate medicines in the public sector Public payers could prioritize reimbursing cancer medicines with significant clinical benefits. The introduction of effective medicines has the potential to alleviate certain aspects of the economic burden (productivity loss and informal care) of TNBC.
Update local clinical guidelines Recent changes in the treatment landscape of TNBC require local clinical guidelines to incorporate novel biomarker tests and treatments when they become available in the local setting.
Update care pathways and provide training to clinical staff The introduction of novel treatment options requires some adaptations of the care pathway, e.g., because more patient groups are recommended to receive neoadjuvant and/or adjuvant systemic therapy. Clinical staff needs to be trained to ensure optimal use of novel treatment options.

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