Improving the care of women with triple-negative breast cancer

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IMPROVING 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 present report describes characteristics of TNBC patients and the disease and economic burden to society in high-income countries around the world. It describes detection, diagnostics, and treatment of TNBC and discusses the societal impact of improved TNBC care. High-level recommendations for improvement of TNBC care are also provided.

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

Lund, March 2023

Peter Lindgren
Managing Director, IHE

Executive summary

Breast cancer accounted for 28% of new cancer cases and 14% of cancer deaths among women in high-income countries around the world in 2020. Triple-negative breast cancer (TNBC) is a subtype of breast cancer that occurs in about 10–20% of newly diagnosed breast cancer cases but is responsible for 30–40% of all breast cancer deaths.

Key characteristics of TNBC

- The survival rate of TNBC is the lowest of all subtypes of breast cancer; e.g., the five-year relative survival rate of TNBC is around 77% compared to 91% in all cases of breast cancer in the United States. The survival rate of TNBC is also lower at every stage of diagnosis than of all other subtypes.
- TNBC has high recurrence rates after initial treatment in non-metastatic patients; e.g., almost 40% of TNBC patients in Canada experience recurrence compared to less than 10% of patients with luminal A, the most common subtype of breast cancer.
- TNBC has a negative impact on all aspects of patients' quality of life, including psychological distress, decline in physical functioning, body image, infertility, job loss, and financial hardship.
- 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.

Future patient numbers of TNBC are expected to rise in high-income countries around the world. Population aging alone might increase the annual number of TNBC cases by around 5–10% between 2020 and 2040 in line with the overall rise in breast cancer cases. Unfavorable developments in TNBC-linked risk factors such as obesity and physical inactivity might augment future increases.

Innovations in medical treatment of TNBC

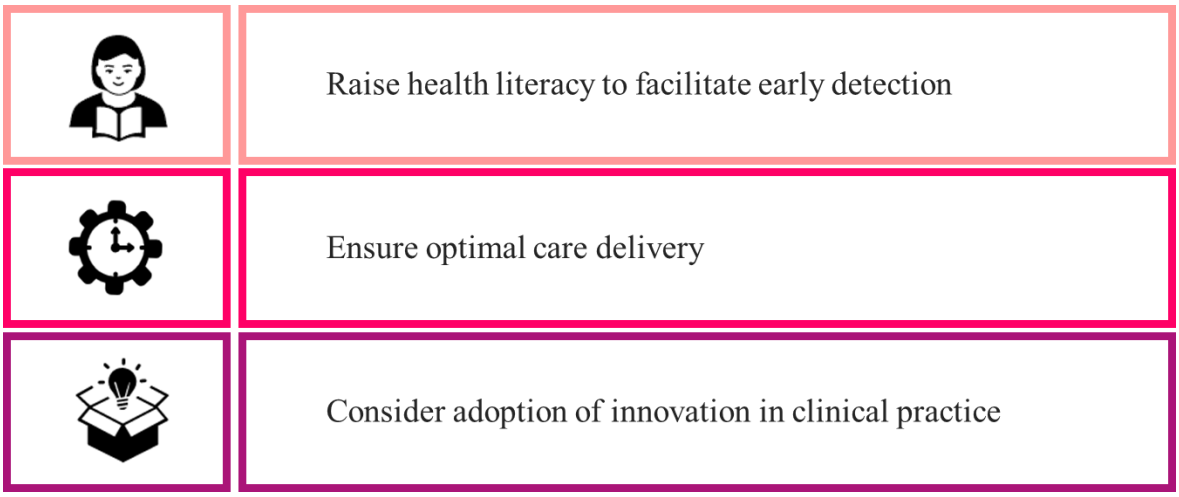
The low survival rate of TNBC compared to other subtypes of breast cancer indicates a lack of effective treatments. Medical treatment options have historically been limited to chemotherapy and remained unchanged since the 1990s. Recent advances in immunotherapy and targeted therapy are currently changing the standard of care by replacing or complementing chemotherapy.

- **Immunotherapy** helps the body to differentiate between cancer cells and normal cells so that the immune system can attack cancer cells. In 2019, the US FDA approved the first immunotherapy agent in TNBC for metastatic patients (stage IV) with an overexpression of the protein PD-L1. In 2021, the first immunotherapy agent for high-risk early-stage patients with TNBC (stage II and III) irrespective of PD-L1 expression was approved.
- **Targeted therapy** blocks mutations involved in the growth of cancer. In 2018, the US FDA approved the first two targeted therapies in TNBC for metastatic patients (stage IV) with BRCA1/2 mutations. In 2022, the first targeted therapy for high-risk early-stage patients (stage II and III) with BRCA1/2 mutations was approved.

Areas of improvement in TNBC care

Improving the care of TNBC patients through better early detection, diagnostics, and treatment can positively affect the survival of patients and their quality of life. This would help to reduce the future disease burden of TNBC. In addition, the cost differences by disease stage have economic implications for efforts to improve early detection of TNBC. Both medical treatment costs and productivity loss from premature mortality would decrease due to higher survival with early-stage disease compared to metastatic disease.

This report identified the following three broad areas of improvement in the care of TNBC patients.



List of abbreviations

ASCO	American Society of Clinical Oncology
BRCA1/2	Breast cancer gene 1/2
CDK	Cyclin-dependent kinase
DNA	Desoxyribonucleic acid
EMA	European Medicines Agency
ER	Estrogen receptor
ESMO	European Society for Medical Oncology
FDA	Food and Drug Administration in the United States
GP	General practitioner
HER2	Human epidermal growth factor receptor 2
HIC	High-income countries
HR	Hormone receptor
HRQoL	Health-related quality of life
IARC	International Agency for Research on Cancer
ICI	Immune checkpoint inhibitor
KPI	Key performance indicator
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PARP	Poly ADP ribose polymerase
PD-L1	Programmed death-ligand 1
PR	Progesterone receptor
SEER	Surveillance, Epidemiology, and End Results
TIL	Tumor-infiltrating lymphocyte
TNBC	Triple-negative breast cancer
USPSTF	United States Preventive Services Task Force
WHO	World Health Organization

Country abbreviations

AT	Austria	EU	European Union	MT	Malta
AU	Australia	FI	Finland	NL	Netherlands
BE	Belgium	FR	France	NO	Norway
BG	Bulgaria	HR	Croatia	NZ	New Zealand
CA	Canada	HU	Hungary	PL	Poland
CH	Switzerland	IE	Ireland	PT	Portugal
CY	Cyprus	IS	Iceland	RO	Romania
CZ	Czechia	IT	Italy	SE	Sweden
DE	Germany	JP	Japan	SG	Singapore
DK	Denmark	KR	South Korea	SI	Slovenia
EE	Estonia	LT	Lithuania	SK	Slovakia
EL	Greece	LV	Latvia	UK	United Kingdom
ES	Spain	LU	Luxembourg	US	United States

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1. Introduction

1.1 Breast cancer and subtypes of breast cancer

Breast cancer is the most commonly diagnosed cancer type and the leading cause of cancer death in women globally (1). Breast cancer occurs in every country of the world in women at any age after puberty, but with increasing likelihood later in life (2). In high-income countries (HIC), breast cancer accounted for 28% of new cancer cases and 14% of cancer deaths among women in 2020 (1); see Figure 1. The estimated lifetime risk for a woman to develop breast cancer in the European Union (EU) and the United States (US) was around 1 in 7 and in Japan 1 in 9 in 2020 (1, 3).

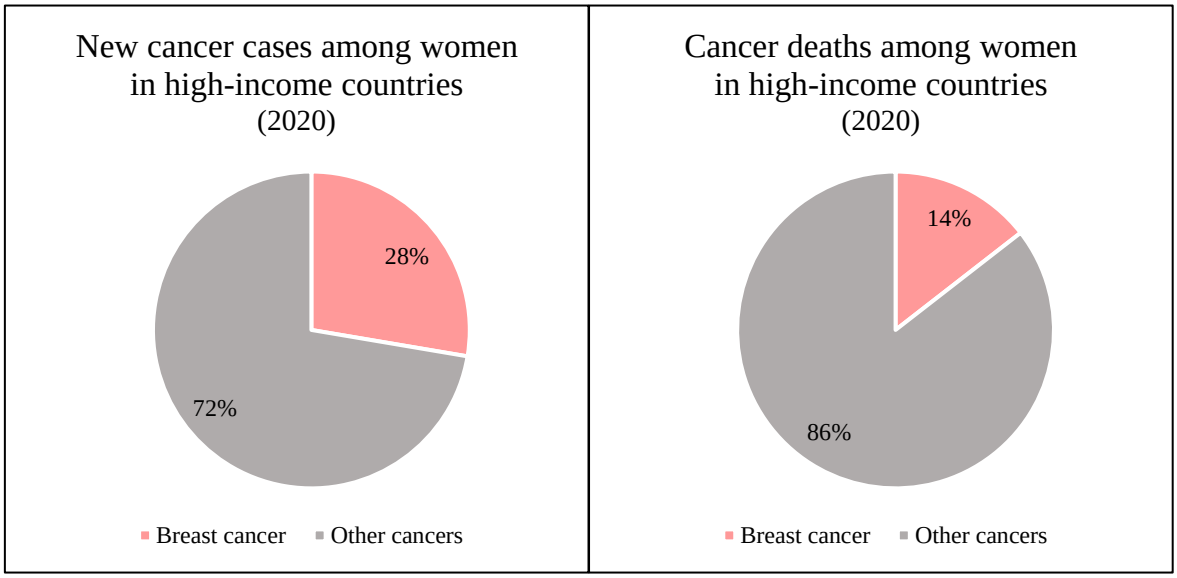

Figure 1: Estimated proportion of new breast cancer cases and deaths among women in high-income countries in 2020.

Notes: Cancer was defined as all types excluding non-melanoma skin cancer. High-income countries include AU, JP, KR, NZ, SG in Asia-Pacific, the 27 member states of the EU and CH, IS, NO, UK in Europe, and CA and US in North America. Source: IARC (1).

According to the WHO, survival rates in breast cancer changed little from the 1930s through to the 1970s (2). Starting from the 1980s, improvements in survival were achieved with the broad introduction of hormonal therapy and the establishment of screening programs for early detection in HIC (2). Between 1980 and 2020, age-standardized breast cancer mortality was reduced by 40% in HIC (2). Nowadays 80–90% of women with breast cancer are still alive five years after diagnosis in HIC, compared to 66% in India and 40% in South Africa (4, 5). In the Nordic countries, five-year survival rates improved from 59–72% at the beginning of the 1970s to just over 90% at the end of the 2010s; see Figure 2.

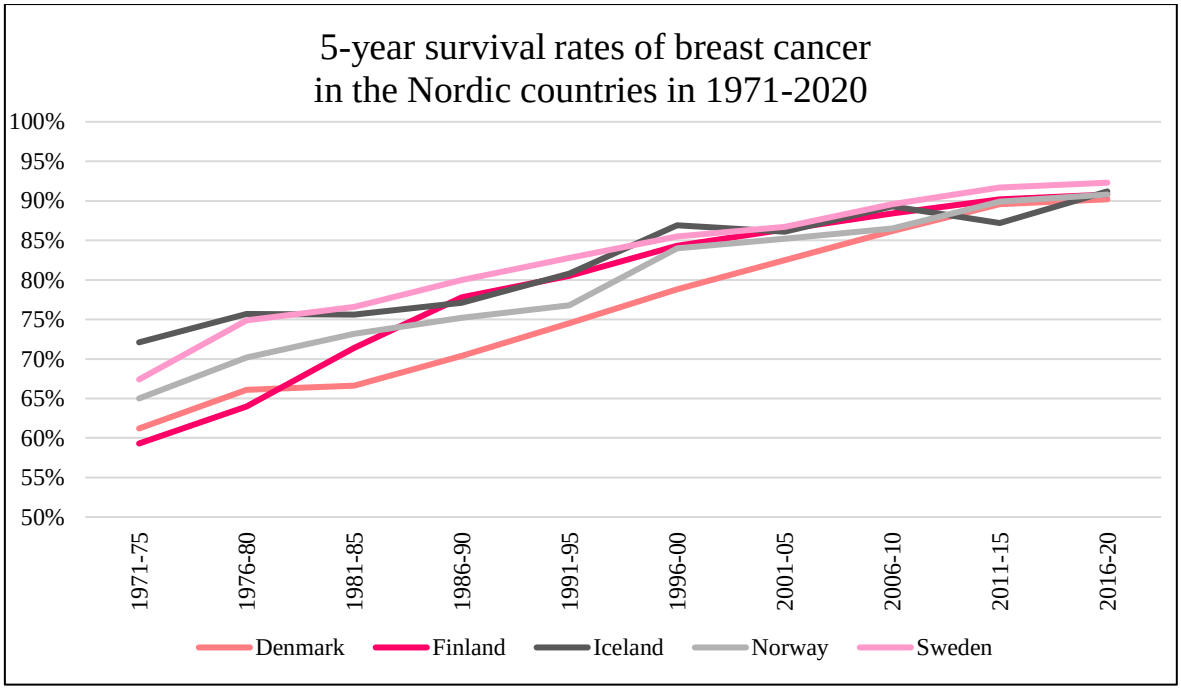

Figure 2: 5-year age-standardized relative survival rates of breast cancer in the Nordic countries in 1971–2020.

Source: Nordcan (6).

Early detection of breast cancer is crucial for the likelihood to survive (7). When the tumor is still small, the prognosis is considerably better than when the tumor has grown in size and started to spread to nearby lymph nodes or even beyond to other parts of the body (so-called metastasis). Screening programs and awareness among women of early symptoms of breast cancer (e.g., a lump in the breast) are vital to increase the proportion of women diagnosed early. Currently, more than 90% of breast cancer patients are diagnosed with early-stage breast cancer (stage I–III) in HIC (8-10). Patients with early-stage disease can generally be treated with surgery to remove the tumor and a possible addition of cancer medicines and/or radiation therapy. However, 20–30% of these patients will experience disease recurrence (i.e., the cancer grows back) months or several years after initial treatment (11, 12). Cancer recurrence is often metastatic. Patients with recurrent or newly diagnosed metastatic disease are generally considered incurable. This underlines the need for better treatment in both early-stage and metastatic breast cancer.

The overall progress in the treatment of breast cancer over the last decades was not shared by all subtypes of breast cancer. Breast cancer is composed of several distinct subtypes that differ in their biological behavior; see Figure 3. The standard classification of the subtypes is based on the presence of three receptors and gene expressions in the tumor cells; two hormone receptors (HR) called estrogen receptor (ER) and progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (13). Cancer medicines directed at these receptors have become available in the past decades. Tumors that are expressing ER and PR (called HR-positive breast cancer) respond to hormonal therapy (also known as endocrine therapy). Hormonal therapy has been standard of care

since the introduction of the medicine tamoxifen in 1977 (14). Since 2015, a new drug class of cyclin-dependent kinase (CDK) 4/6 inhibitors has been introduced in this patient group (15). Tumors that are expressing HER2 respond to HER2-directed targeted therapies, which have become standard of care since the introduction of trastuzumab in 1998 (14).

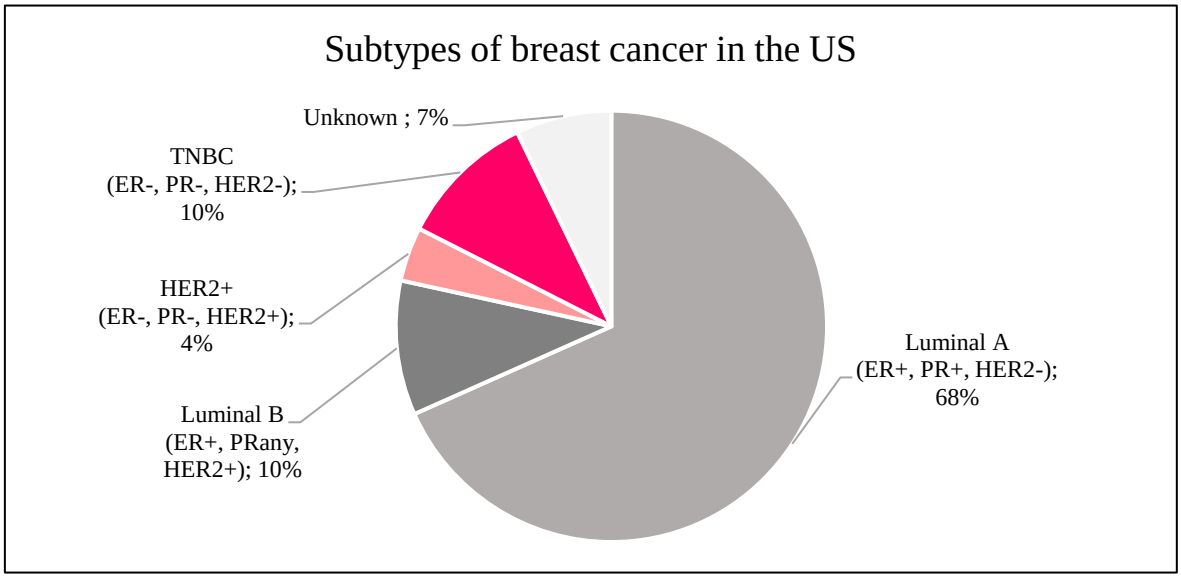

Figure 3: Proportion of breast cancer subtypes in newly diagnosed cases in 2015–2019 in the US.

Notes: Percentages do not sum up to 100% due to rounding. Source: SEER (16).

Tumors that are not expressing any of the three receptors (ER, PR, HER2) are called triple-negative breast cancer (TNBC). As these tumors would neither respond to hormonal therapy nor HER2-directed targeted therapy, their medical treatment has primarily relied on chemotherapy in the past (17). Recent advances in immunotherapy (first approval in 2019) and targeted therapy for BRCA1/2 mutations (first approval in 2018) are currently changing the standard of care in TNBC (17-19).

1.2 Purpose and outline of the report

The purpose of this report is to bring together evidence about the key characteristics of TNBC compared to other subtypes of breast cancer (chapter 2), the disease and economic burden of TNBC (chapter 3), the detection, diagnosis, and treatment of TNBC and associated challenges (chapter 4), and the societal impact of improved TNBC care (chapter 5). The report concludes with a set of high-level recommendations for improvement of the care of TNBC patients (chapter 6).

The geographic focus of the report is global, with a focus on “high-income countries” in Asia-Pacific, Europe, and North America (see page 6 for the full list of countries).

2. Characteristics of TNBC

This chapter summarizes essential characteristics of TNBC and provides comparisons with other subtypes of breast cancer. Key findings are the following:

- Non-modifiable and modifiable risk factors for TNBC (e.g., age, obesity) are mostly similar to other subtypes, even though the strength of the association between the risk factor and the development of TNBC might differ (e.g., higher risk of family history).
- Signs and symptoms of TNBC (e.g., lumps in the breast or armpit) are similar to other subtypes.
- TNBC affects slightly younger women than the most common subtype (luminal A).
- TNBC is typically diagnosed at slightly more advanced stages than the most common subtype (luminal A).
- The survival rate of TNBC is the lowest of all subtypes. This is also true for every stage at diagnosis.
- TNBC has the highest recurrence rates after initial treatment of all subtypes.
- The quality of life of TNBC patients is more impaired than of patients with other subtypes. This includes a higher risk of infertility due to chemotherapy treatment, more psychological distress, and a stronger decline in physical functioning.

2.1 What is TNBC?

Breast cancer is composed of several distinct subtypes that differ in their biological characteristics. They are typically classified into four subtypes based on the tumor's expression of ER, PR, and HER2 (20, 21); 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 defined as 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 US
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 (16).

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 (22). Systemic therapy options for TNBC used to be restrained to chemotherapy (23), 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 (24). Figure 4 shows that the proportion of TNBC is around 9–16% in selected populous HIC.

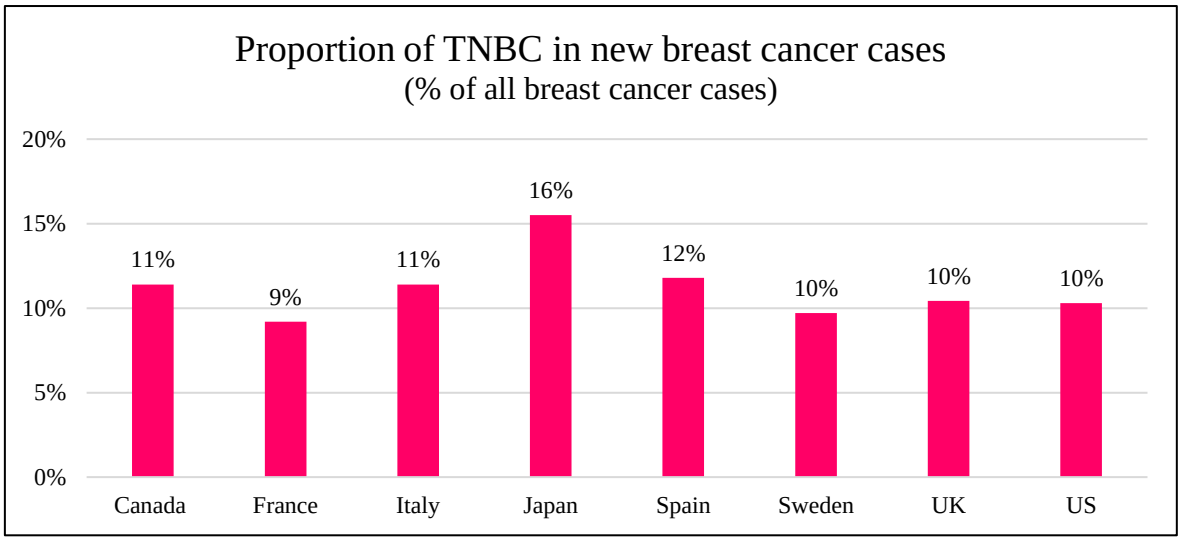

Figure 4: Proportion of TNBC in newly diagnosed cases of breast cancer in selected high-income countries.
Source: (16, 25-31).

2.2 Risk factors

Many potential risk factors for developing breast cancer have been identified with varying levels of supporting evidence. However, not all risk factors have been linked to TNBC. In general, risk factors can be divided into non-modifiable risk factors (see Table 2) and modifiable risk factors (see Table 3) (2). According to the WHO, at most 30% of all breast cancer cases are theoretically preventable as they are caused by modifiable risk factors (2).

Table 2: Non-modifiable risk factors in breast cancer and TNBC

Risk factor	Breast cancer	TNBC
Age	As women get older, their chances of developing breast cancer rises (32). Women under 50 years have a 1/53 risk of developing breast cancer, while women over 70 years have the highest risk at 1/15.	TNBC is more common in younger women than breast cancer overall (see section 2.4). The risk for women under 40 years to get TNBC is estimated to be twice that of the risk for the next most frequent subtype (HER2+) (32).
Family history	Approximately 5–10% of all breast	The likelihood of developing TNBC

(Heredity)	cancers have a hereditary background (33). The most common cause of hereditary breast cancer is an inherited mutation in the BRCA1 or BRCA2 gene (33). About 50 out of 100 women with BRCA1/2 mutations will develop breast cancer by the time they turn 70 years, compared to only 7 out of 100 women in the US (34).	is particularly high in women carrying BRCA1/2 mutations. Around one third of TNBC patients in the US have a BRCA1 mutation (35), and BRCA1/2 mutations are present in 21% of TNBC patients in Austria and Germany (36). BRCA1/2 carriers also tend to develop breast cancer at a younger age than non-mutation carriers and are at high risk of disease recurrence after initial treatment (37, 38).
Ethnicity	Caucasian women have the highest risk to develop breast cancer in the US, closely followed by Black women, while Asian and Hispanic women have a lower risk (39).	Black and Hispanic women are at an increased risk of developing TNBC compared to Caucasian women but reasons for this are unclear (40, 41). In the US, black women are nearly three times more likely than Caucasian women to be diagnosed with TNBC (42).
Breast density	Women with a greater breast density (i.e., a greater amount of fibrous and glandular tissues in their breasts) are at a higher risk of developing breast cancer (43).	The link between breast density and developing TNBC is stronger in premenopausal women than in postmenopausal women (42).

Table 3: Modifiable risk factors in TNBC

Risk factor	Breast cancer	TNBC
Obesity and overweight	It increase the risk for breast cancer and the link seems to be stronger in postmenopausal women than in premenopausal women (44).	A link with TNBC has been established (45).
Physical inactivity	A sedentary lifestyle is a risk factor for all breast cancer subtypes (46).	The link between physical inactivity and TNBC is stronger than in other subtypes (46).
No breastfeeding	Women who never breastfed their babies have a higher risk to get breast cancer (47).	A link with TNBC has been established (47).
No child births	Having given birth to children is associated with a lower risk of hormone receptor-positive breast cancer (48).	Some studies suggest that having given birth to children is associated with a higher risk of TNBC (49), while others failed to establish a link (48).
Alcohol consumption	It increases the risk for breast cancer (50).	The link with TNBC is less clear (51).
Cigarette smoking	It might increase the risk for breast cancer (52).	The link with TNBC is not clearly established (51).
Use of postmenopausal hormone replacement therapy to treat menopausal symptoms	It increases the risk for breast cancer overall (53).	The link with TNBC seems to be inconclusive (54).
Use of oral contraceptives	It does not seem to increase the risk to get breast cancer although some studies found a positive association (55).	For TNBC, an early study in the US found an increased risk from using oral contraceptives in younger women (56), but this could not be confirmed in a more recent, international review (51).

2.3 Signs and symptoms

Signs and symptoms of TNBC resemble those of other breast cancer subtypes. The most common symptoms are summarized in Figure 5.

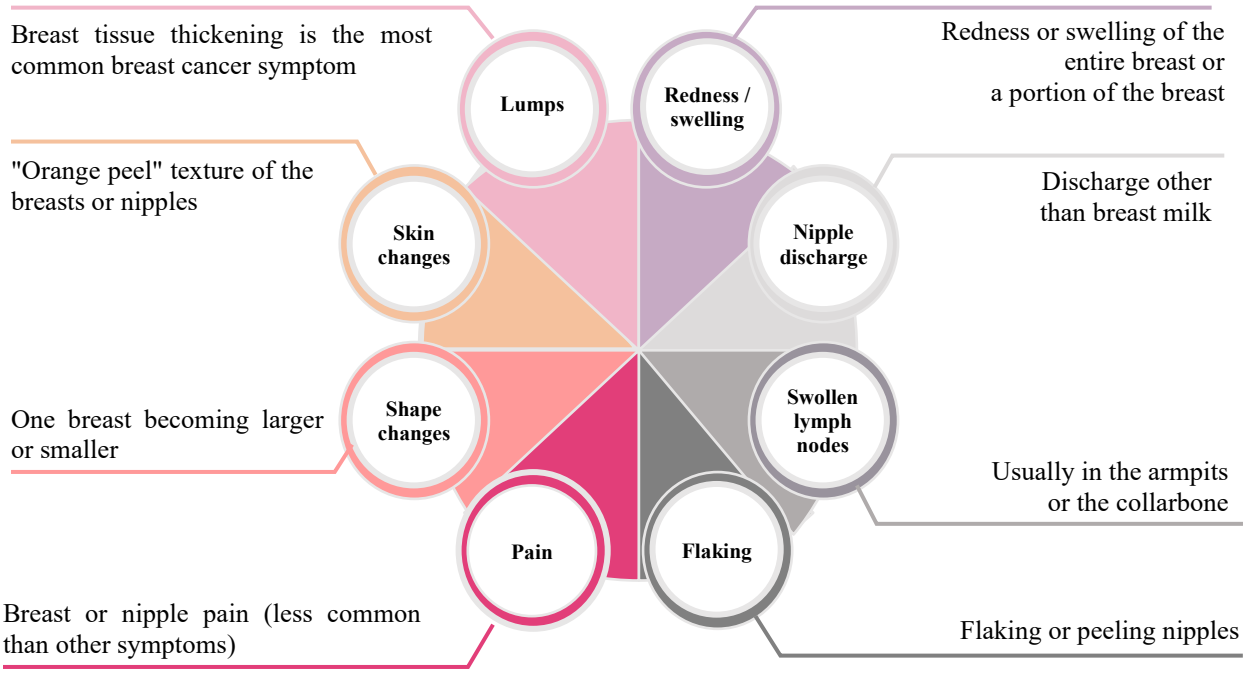

Figure 5: Common signs and symptoms of TNBC.
Source: (57).

2.4 Age at diagnosis

As noted above, the incidence of breast cancer increases with age. However, TNBC tends to affect slightly younger women than the average breast cancer patient; see Figure 6. Around 25% of all TNBC cases are diagnosed in women under 50 years, compared to 19% among all breast cancer cases in the US (58). The younger age of TNBC patients has negative consequences for various aspects of their quality of life (including risk of infertility, premature menopause, and worse bone health (59, 60), see also section 2.7) and their work life, which in turn affects the size of the economic burden of TNBC (see section 3.2).

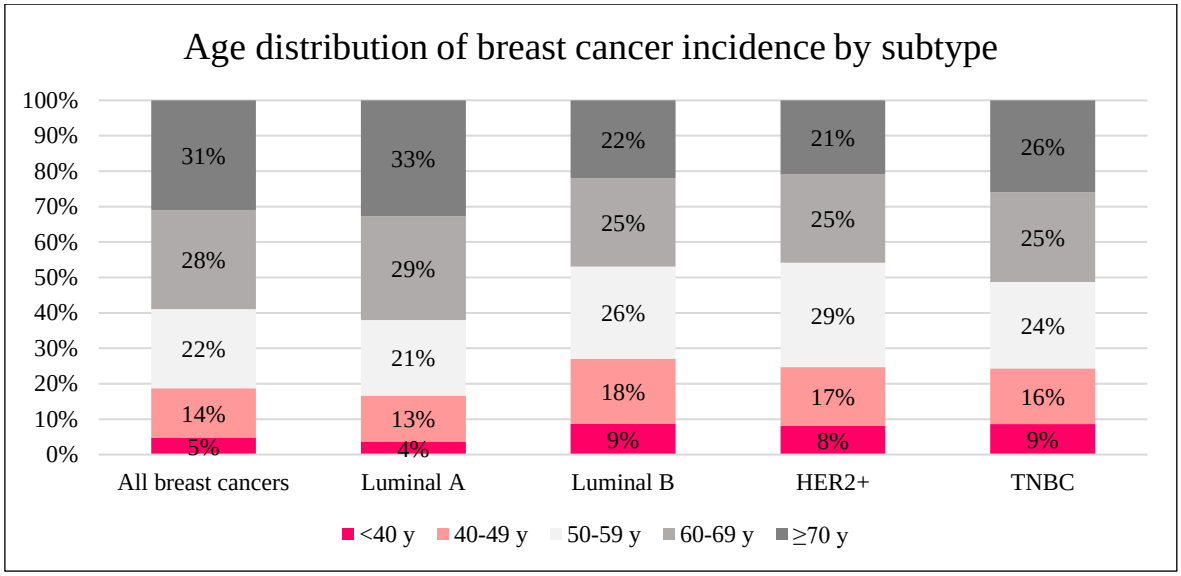

Figure 6: Breast cancer incidence by age group and subtype in the US (diagnosed 2015–2019, ages≥20 years).

Source: SEER (16).

2.5 Stage at diagnosis

TNBC tumors tend to grow faster than tumors of the most common subtype luminal A (61). Consequently, they are more likely to be diagnosed at a late stage when the tumor has spread regionally or metastasized (62). One contributing factor to late-stage diagnosis is that TNBC tumors may appear benign on mammograms (63). At the time of diagnosis, 38% of TNBC cases have a regional or distant spread (i.e., will soon or are already metastasized) in the US (16); see Figure 7. By comparison, there are fewer such cases (33%) among all breast cancer cases.

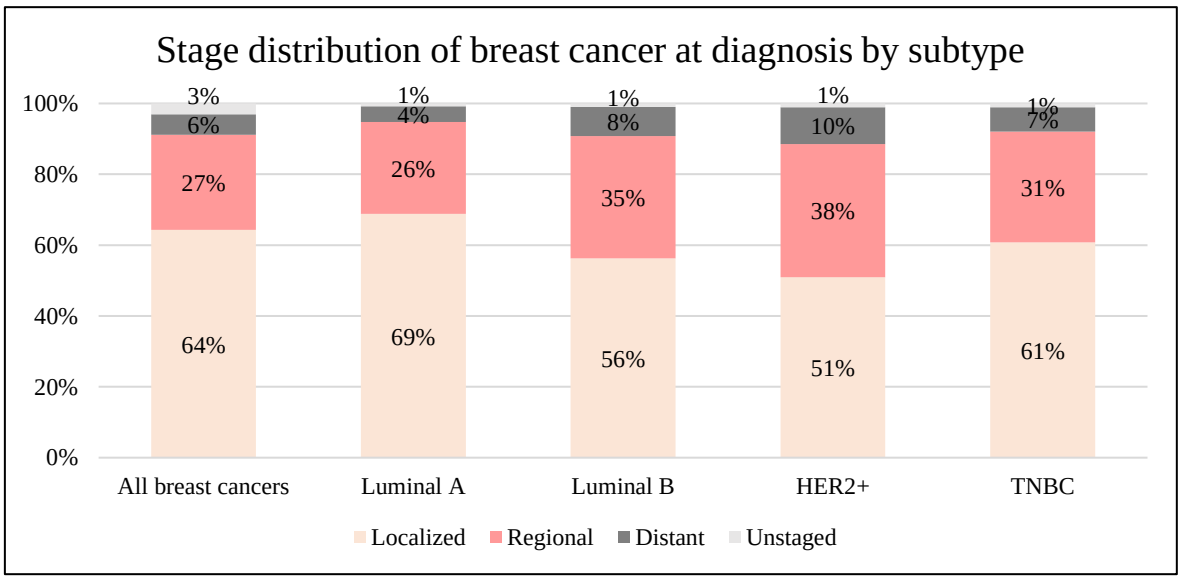

Figure 7: Stage distribution of breast cancer at diagnosis by subtype in the US (diagnosed 2010–2019, all ages).

Source: SEER (16).

Another feature of TNBC is the comparatively high proportion of younger women diagnosed at an advanced stage. In the US, 44% of TNBC cases in women under 50 years are diagnosed with a regional or metastatic spread, compared to 35% in women aged 65 years or older (16); see Figure 8. One explanation for this might be that breast cancer screening is only recommended in the age group 50–74 years in the US (see section 4.1), thus making it difficult for women below 50 to detect an asymptomatic tumor in their breast.

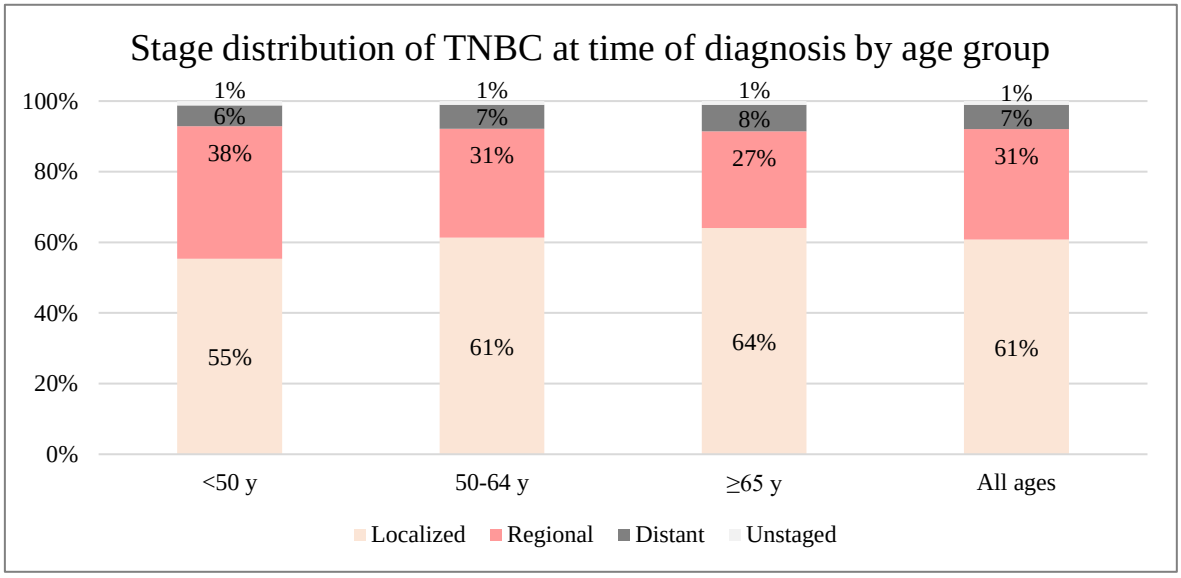

Figure 8: Stage distribution of TNBC at diagnosis by age group in the US (diagnosed 2010–2019).

Source: SEER (16).

2.6 Survival

TNBC is a subtype of breast cancer that is more aggressive than the hormone-receptor positive subtypes (luminal A and B) (64). TNBC tumors are associated with high metastatic potential, a high tendency of recurrence, and poor prognosis (64). The limited number of medical treatment options in the past (only chemotherapy) contributed to TNBC having the poorest prognosis of all breast cancer subtypes (23).

The 5-year relative survival rate of all breast cancers stood at 91% for cases diagnosed in 2012–2018 in the US, see Figure 9. TNBC had the lowest survival rate of all subtypes corresponding to 77%, while luminal A had the highest survival rate of 94%. In all three age groups shown in Figure 9, TNBC had the lowest survival rate of all subtypes, with rates close to 77% in all age groups. The lower survival rate of TNBC despite a higher proportion of TNBC cases being diagnosed earlier than luminal B and HER2+ cases (see Figure 7) hints at less effective treatments for TNBC than for luminal B and HER2+.

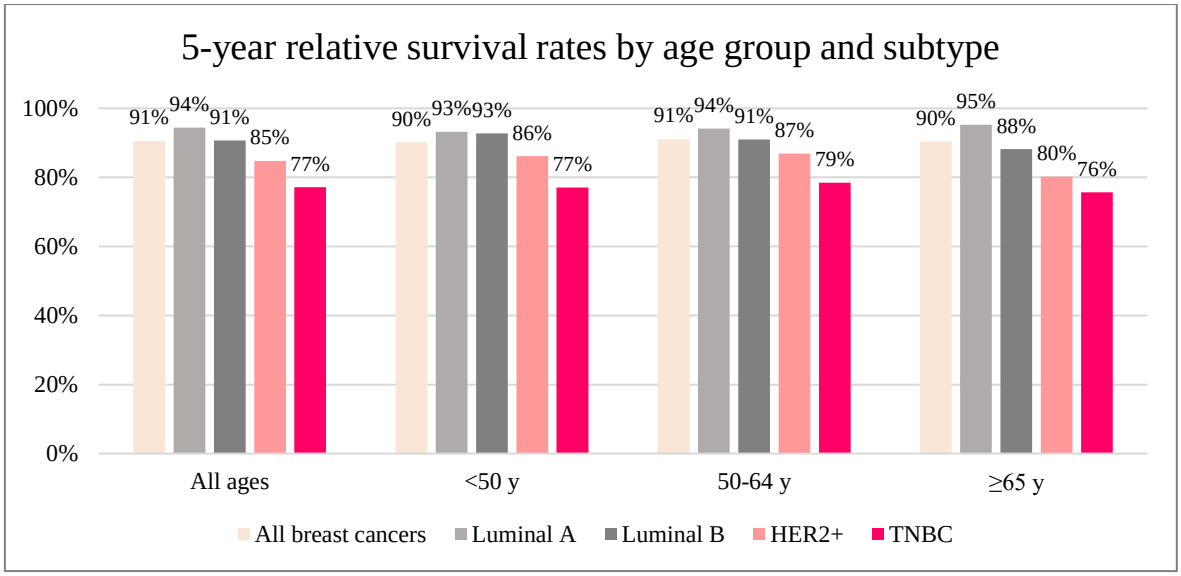

Figure 9: 5-year relative survival rates by age group and breast cancer subtype in the US (diagnosis period 2012–2018).
Source: SEER (65).

Cancer stage at diagnosis is heavily associated with survival chances. The earlier the diagnosis is made, the higher the chances to survive; see Figure 10. When the tumor is still localized at diagnosis (stage I), the 5-year relative survival rates of all breast cancer subtypes was close to 100% except for TNBC for which the rate was 91% for cases diagnosed in 2012–2018 in the US. TNBC also had significantly lower survival rates than the other subtypes in newly diagnosed tumors with a regional spread (66% for TNBC vs. 90% for luminal A) and metastatic spread (12% for TNBC vs. 46% for luminal B) in 2012–2018 in the US. The comparatively low survival rate of TNBC at all disease stages indicates that treatment modalities used in 2012–2018 were less effective than for other subtypes.

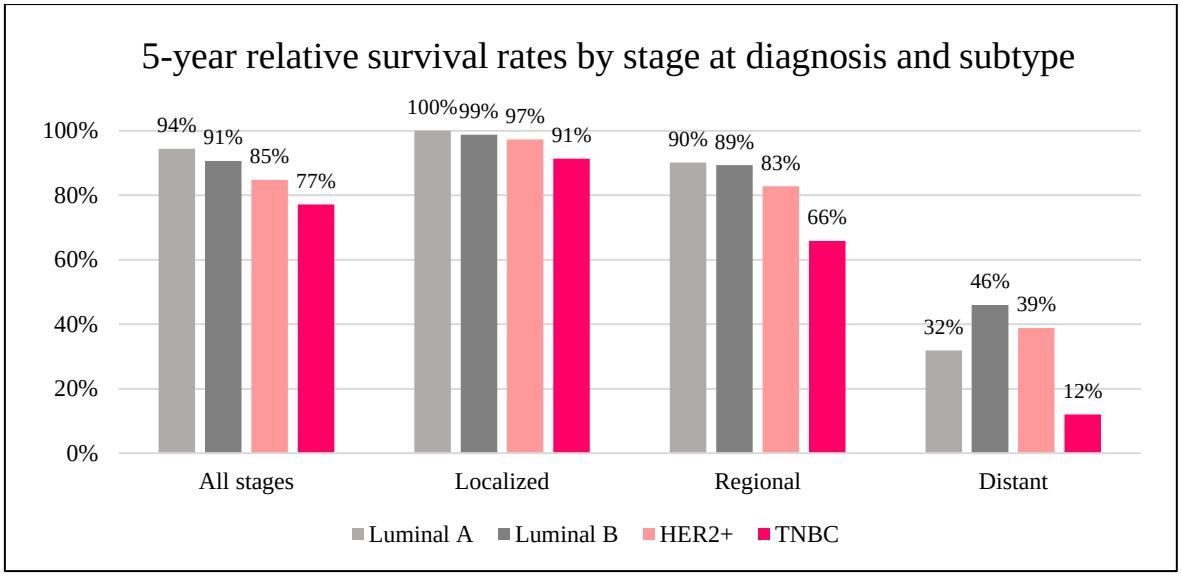

Figure 10: 5-year relative survival rates by stage at diagnosis and breast cancer subtype in the US (diagnosis period 2012–2018).
Source: SEER (65).

A contributing factor to the comparatively low survival rates of TNBC are higher recurrence rates among non-metastatic patients after initial treatment (66). Figure 11 shows that the rates of both locoregional recurrence and distant/metastatic recurrence in non-metastatic TNBC are significantly elevated. While almost 40% of non-metastatic TNBC patients diagnosed in 2004–2012 in Canada experienced recurrence, fewer than 10% of luminal A patients did.

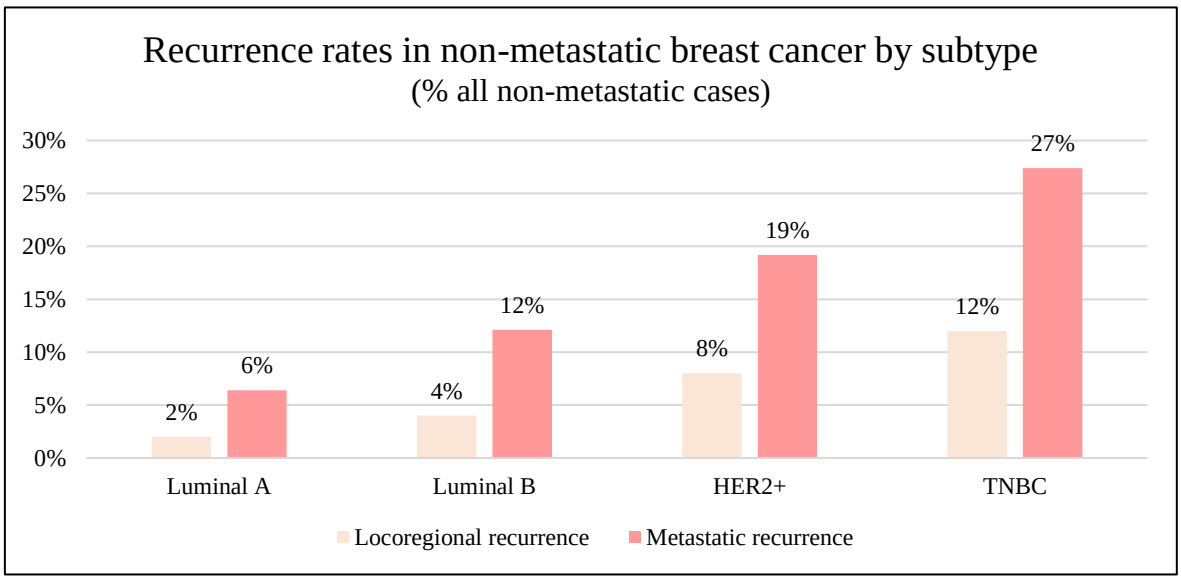

Figure 11: Recurrence rates in non-metastatic breast cancer by subtype in Canada (diagnosis period 2004–2012).
Source: (67).

TNBC patients with metastatic disease have a poor prognosis. Data from Canada show that the median survival time of metastatic TNBC patients was 9 months in 2012–2016, whereas patients with other subtypes of breast cancer had around 3 years left to live; see Figure 12.

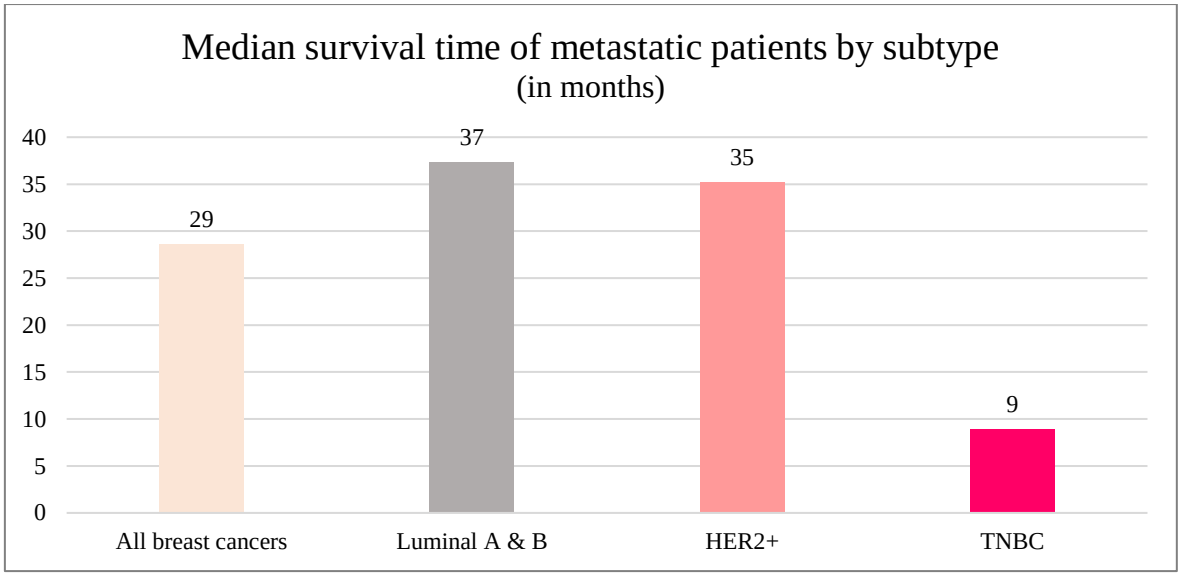

Figure 12: Median survival time (in months) in metastatic breast cancer patients by subtype in Canada (diagnosis period 2012–2016).

Source: (68).

2.7 Quality of life

TNBC has a negative impact on all aspects of patients' quality of life. Previous studies have pointed to a multitude of factors that may affect quality of life negatively; see Table 4.

Table 4: Aspects of quality of life affected in TNBC

Psychological distress	TNBC patients report significantly more depression, anxiety, intrusive thoughts, fear of cancer, stress, and feelings of inadequacy than patients with other breast cancer subtypes (69, 70).
Decline in physical functioning	TNBC patients report lower functional well-being, including limitations in the patient's professional and personal activities as well as a lack of sleep quality, than patients with other breast cancer subtypes (70).
Body image	Patients who undergo mastectomies (removal of the entire breast) can experience long-lasting negative effects on women's self-esteem and be a threat to their gender identity (71).
Infertility	Medical treatments such as chemotherapy, which used to be the cornerstone treatment in TNBC, can temporarily or permanently cause infertility (72).
Job loss / financial hardship	Concerns about losing a job during and after treatment, facing discrimination at work, the possibility of financial instability, and long-term unemployment are among the most prevalent worries among breast cancer patients of working age (73, 74).

3. Disease and economic burden of TNBC

This chapter provides an overview of the disease burden and the economic burden of TNBC. Key findings are the following:

- Future numbers of TNBC cases (per 100,000 women) in HIC might increase by 5–10% between 2020 and 2040 in line with the overall rise in breast cancer cases. This increase is solely driven by population aging. Unfavorable developments in breast cancer-linked risk factors such as obesity/overweight and physical inactivity might augment future increases.
- The comparatively low survival rates of TNBC lead to an overrepresentation among breast cancer deaths. Although TNBC accounts for 10–20% of all new cases of breast cancer, TNBC accounts for 30–40% of all breast cancer deaths.
- Per-patient medical costs for TNBC were around three to four times lower than in HER2-positive breast cancer in New Zealand and Portugal before the introduction of novel medical treatments for TNBC since 2018.
- Per-patient medical costs of metastatic patients are around three to five times higher than of early-stage patients (stage I–III) in high-income countries, driven by more frequent and longer hospitalizations.
- The lower survival and the younger age of TNBC patients compared to other breast cancer subtypes might result in a higher per-patient productivity loss from premature mortality and sick leave.

3.1 Incidence and mortality

The annual numbers of newly diagnosed cases (i.e., incidence) and deaths (i.e., mortality) are key parameters to measure the disease burden of a specific cancer type to society. Information on the estimated proportion of TNBC cases among all newly diagnosed breast cancer cases in different countries are available for many HIC (see section 2.1). However, these proportions are not always based on country-wide analyses of cancer registry data. Information on time trends in the incidence of different breast cancer subtypes is generally limited. This is because cancer registries only began routinely measuring the current standard set of molecular markers (i.e., ER, HR, HER2) during the last decade (75). Information on time trends in the mortality of different breast cancer subtypes is even more limited than of incidence.

The comparatively low survival rates of TNBC lead to an overrepresentation among breast cancer deaths. Although TNBC accounts for 10–20% of all new cases of breast cancer, TNBC accounts for 30–40% of all breast cancer deaths (76, 77).

In Sweden, the estimated incidence of TNBC increased only slightly from 15 to 16 cases per 100,000 women between 2008 and 2021 according to the National Quality Registry for Breast Cancer (31). This corresponded to a 5% increase over the whole period. Figure 13 shows that the growth rate in the number of TNBC cases was negative and behind the growth rates of other subtypes during most of the 2010s, but towards the end of the period the total growth rate picked up and was fairly similar to other subtypes and the overall development (+5% in TNBC vs. +11% total breast cancer). The proportion of TNBC cases in all breast cancer cases fluctuated mostly around 8–10% in 2008 to 2021.

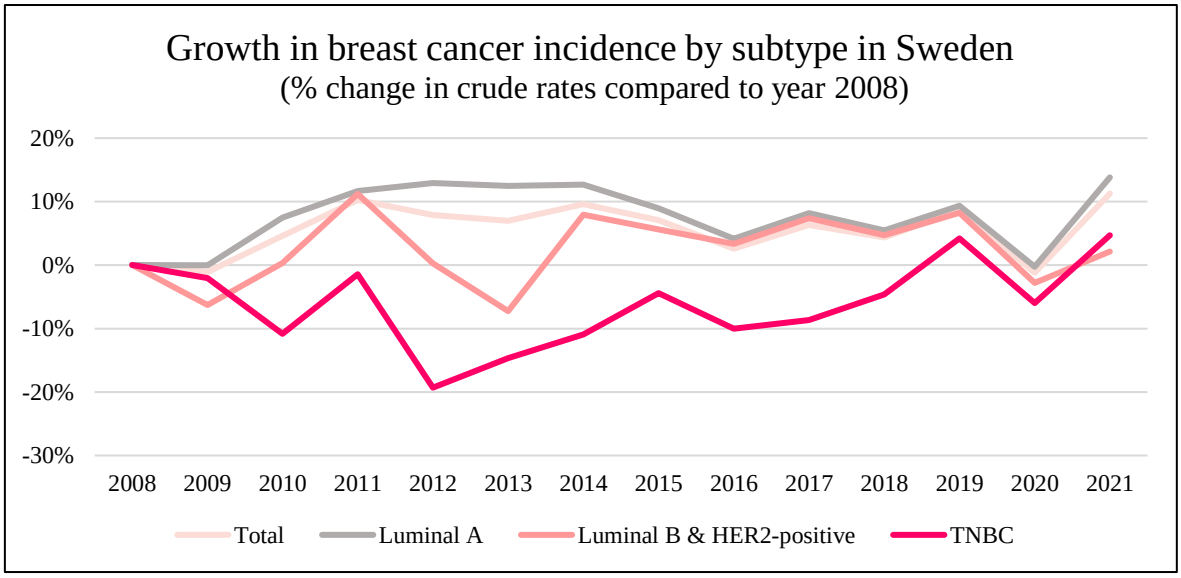

Figure 13: Growth in breast cancer incidence (crude rates per 100,000 women) by subtype in Sweden between 2008–2021.

Notes: Cases with unknown molecular status were proportionally allocated to the cases with known molecular status in all years. Source: Swedish National Quality Registry for Breast Cancer (31).

An analysis of mortality data from 2010 to 2017 in the US has shown that mortality rates in TNBC seem to have declined less than the rates in luminal A and luminal B (78).

The overall incidence of breast cancer has been increasing for many decades in HIC (79, 80). This is partly the result of demographic changes, in particular overall population growth and population aging. Unfavorable developments in lifestyle factors such as obesity (see section 2.2) may also have contributed to the overall increase. In addition, the implementation of breast cancer screening programs since the 1980s (see section 4.1) might have led to an overdiagnosis of slow-growing tumors with low-risk profile (81). For overall breast cancer mortality, many studies have documented that the rates are increasing at a slower pace than incidence rates. If the effect of population aging is taken into account, cancer mortality has been decreasing across most HICs in the past decades (79, 80). The decoupling of trends in mortality from trends in incidence are driven by the increasing survival rates of breast cancer patients over time (see section 1.1).

Figure 14 shows past and future trends of breast cancer incidence and mortality. Incidence rates in the past were highest in HIC countries in Europe and North America and lowest in Asia-Pacific. All regions recorded increasing trends in incidence; from 107 to 158 cases per 100,000 women between 1995 and 2020 in Europe (+48%), from 116 to 151 cases per 100,000 women in North America (+30%), and from 70 to 134 cases per 100,000 women in Asia-Pacific (+90%). By contrast, breast cancer mortality rates decreased in Europe (-2%) and North America (-22%) and increased only around half as much as incidence in Asia-Pacific (+52%) between 1995 and 2020.

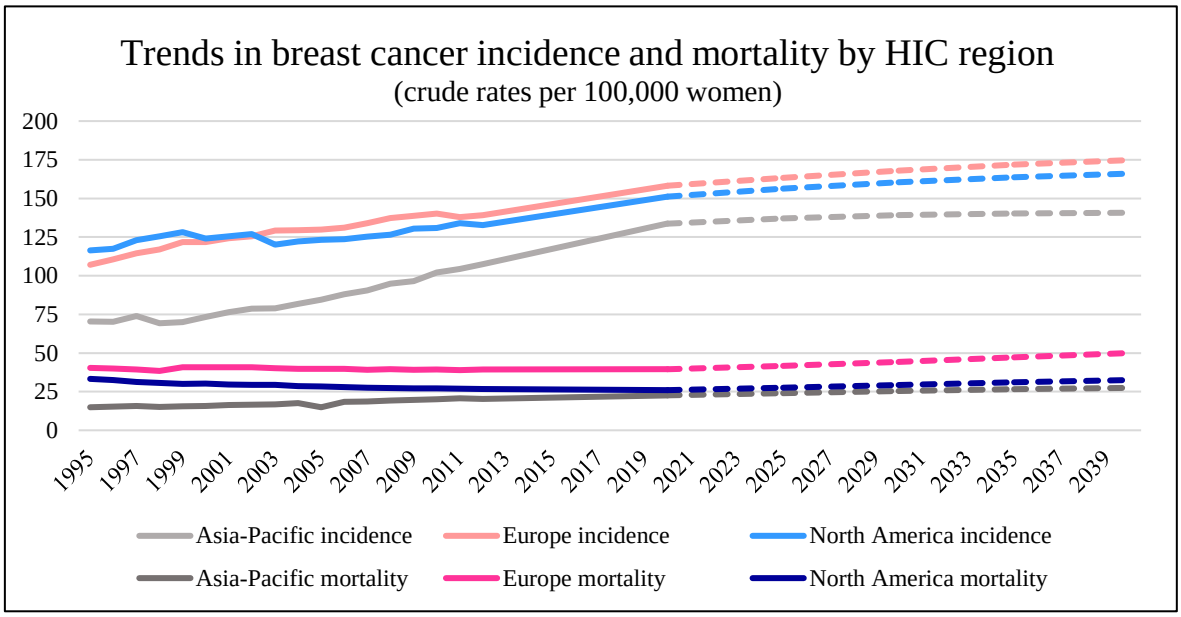

Figure 14: Estimated trends in breast cancer incidence and mortality crude rates per 100,000 women in selected regions with HIC, 1995–2040.

Notes: Asia-Pacific includes AU, JP, KR, NZ. Europe includes AT, CH, CY, CZ, DE, DK, EE, ES, FR, HR, IE, IS, IT, LT, MT, NL, NO, PL, SI, SK, UK. North America includes CA, US. Numbers between 2020 and 2040 are predictions based on unchanged age-specific risks to get breast cancer. Source: IARC (82, 83).

Between 2020 and 2040, the number of new breast cancer cases is expected to increase in all HIC regions. Population aging will raise the number of new cases per 100,000 women by around 5% in Asia-Pacific and 10% in both Europe and North America, assuming no changes in the age-specific risks to get breast cancer; see Figure 14.[1] The age-specific risks are partly linked to the future development in modifiable risk factors. One of the major modifiable risk factors in breast cancer and also in TNBC is obesity. In the past, obesity levels have increased considerably in all HICs; see Figure 15. Projections by the OECD point to continued increases in obesity levels in the future (84), which will contribute to rising numbers of breast cancer and TNBC.

[1] The actual increase in TNBC 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 2.4). The effect of population aging might thus lead to a somewhat less pronounced increase in TNBC compared to other subtypes.

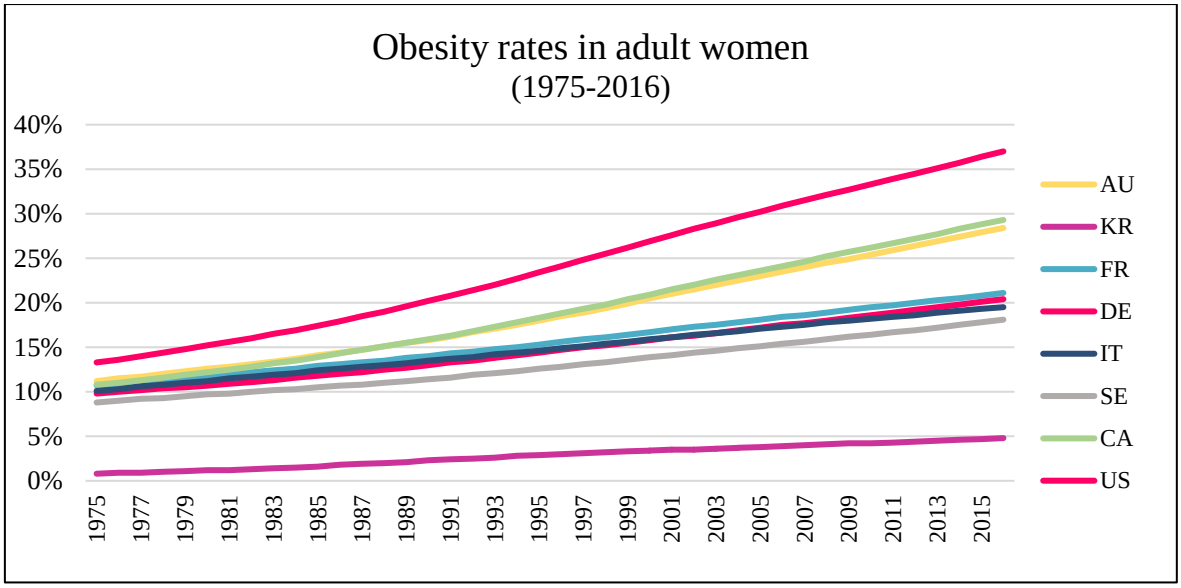

Figure 15: Prevalence of obesity in adult women (aged ≥18 years) in selected HIC, 1975–2016.

Notes: Obesity is defined as BMI ≥ 30. Source: WHO (85).

3.2 Economic burden

The burden of TNBC on society can also be measured in monetary terms. The cost of TNBC is here defined more broadly than in an everyday meaning. Generally, three types of costs can be distinguished (86); see Table 5.

Table 5: Components of the economic burden of cancer

Direct costs	These are costs of disease-related resource consumption. They include both public and private expenditure for services within the health care system, such as diagnostic procedures, surgeries, radiation therapy, and medicines. Expenditure for social support services outside of the health care system are also direct costs. Expenditure by patients for travelling to receive treatment are also direct costs.
Indirect costs (productivity loss)	These are costs of patients' productivity loss arising from the inability to work due to the disease. They consist of the temporary or permanent inability to work in the formal labor market (called morbidity) and from premature death (called mortality) of working-age patients.
Informal care costs	These costs represent the value of the time spent by family members and friends to provide unpaid care, such as transportation to a health care facility and assistance with household chores.

Recent studies that include all three components of the economic burden of breast cancer or TNBC are scarce. A comprehensive study of all EU countries showed that breast cancer accounted for 12% of the economic burden of all cancers in 2009 (87). This placed breast cancer in second place after lung cancer. Figure 16 shows a comparison of the relative contribution of the different cost components to the economic burden of breast cancer compared to all cancers. Direct costs and informal care costs of breast cancer account for a larger share of the economic burden compared to all cancers. This might relate to the longer survival of breast cancer patients which entails longer treatment duration and longer spells of supportive care. The contribution of mortality-related

indirect costs is comparatively small in breast cancer which might be explained by the high survival rates in breast cancer compared to other cancer types. By contrast, the contribution of morbidity-related indirect costs is larger in breast cancer, which might be related to the younger age at diagnosis of breast cancer patients (and hence a larger proportion of working-age patients) compared to other cancer patients.

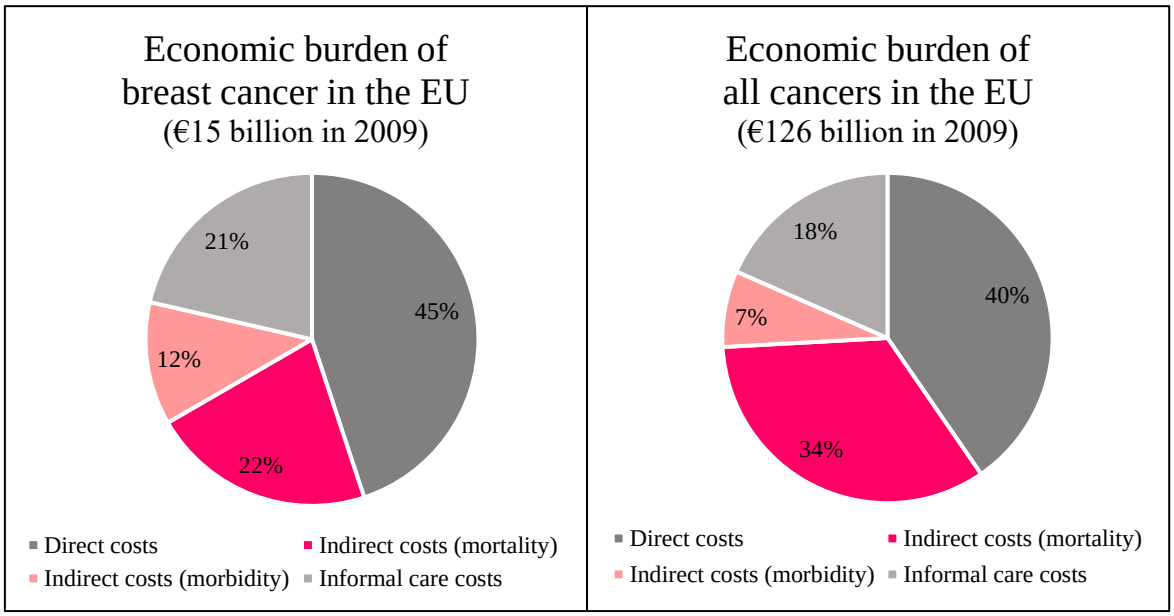

Figure 16: Economic burden of breast cancer vs. all cancers by cost component in the EU in 2009.

Notes: Direct costs include only medical costs and do not include costs for screening services. Source: (87).

There is limited evidence on the size of the economic burden of TNBC compared to other subtypes of breast cancer. The following studies have compared the direct medical costs of TNBC to other breast cancer subtypes in HIC. They also identified main drivers of the costs.

- New Zealand (88): The median public per-patient health care costs of TNBC were the second lowest (NZD 31,722), behind luminal A (NZD 28,481), and three times lower than of HER2+ (NZD 106,428). These cost differences were observable across all disease stages. Over half of the costs for HER2+ were costs for targeted therapy, whereas surgery and radiation therapy incurred the biggest costs in both TNBC and luminal A.
- Portugal (89): In early-stage (stage I–III) breast cancer, patients with TNBC had the second lowest median per-patient health care costs (EUR 11,224). The costs for luminal A were slightly lower (EUR 10,540), whereas the costs for HER2+ were almost four times higher (EUR 41,513). Costs for HER2-targeted therapies were the main cost driver in HER2+. Surgery, radiation therapy, and hospitalizations were the main cost drivers in both TNBC and luminal A.
- United States (90): The annual per-patient health care costs of early-stage (stage I–III) TNBC were higher than of non-TNBC. TNBC patients had higher inpatient costs and costs

for emergency department visits, driven by higher numbers of hospitalizations, hospitalization days, and emergency department visits. Part of the higher health care utilization was driven by the higher likelihood of disease recurrence compared with non-TNBC.

There are significant differences between the direct medical costs of TNBC by disease stage. A recent review of studies from HIC found that annualized direct medical cost ranged from around $20,000 to $100,000 in early-stage TNBC (stage I–III) and from around $100,000 to $300,000 in metastatic TNBC (stage IV) (91); see Figure 17. Direct medical costs for a metastatic patient might thus be around three to five times higher than the costs for an early-stage patient, driven mainly by more and longer hospitalizations.

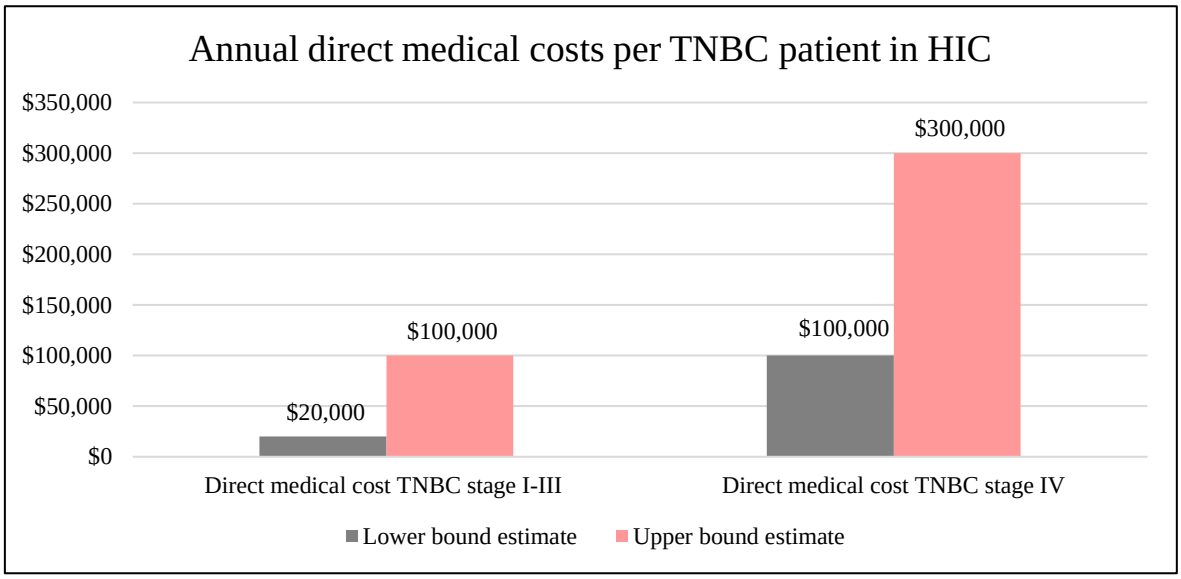

Figure 17: Range of average annual direct medical costs per TNBC patient by disease stage in HIC (in 2021 USD)

Notes: Evidence from BE, CA, ES, FR, PT, SE, US. Source: (91).

Comprehensive estimates of the indirect costs of breast cancer subtypes do not seem to be available (91). A Swedish study of productivity losses in breast cancer patients calculated the loss of working years from sick leave and premature mortality in women aged 50 years at the time of diagnosis. Compared to women without breast cancer and assuming a retirement age at 65 years, the estimated loss in working years ranged from 0.5 years in stage I to 8.1 years in stage IV (92), see Figure 18.

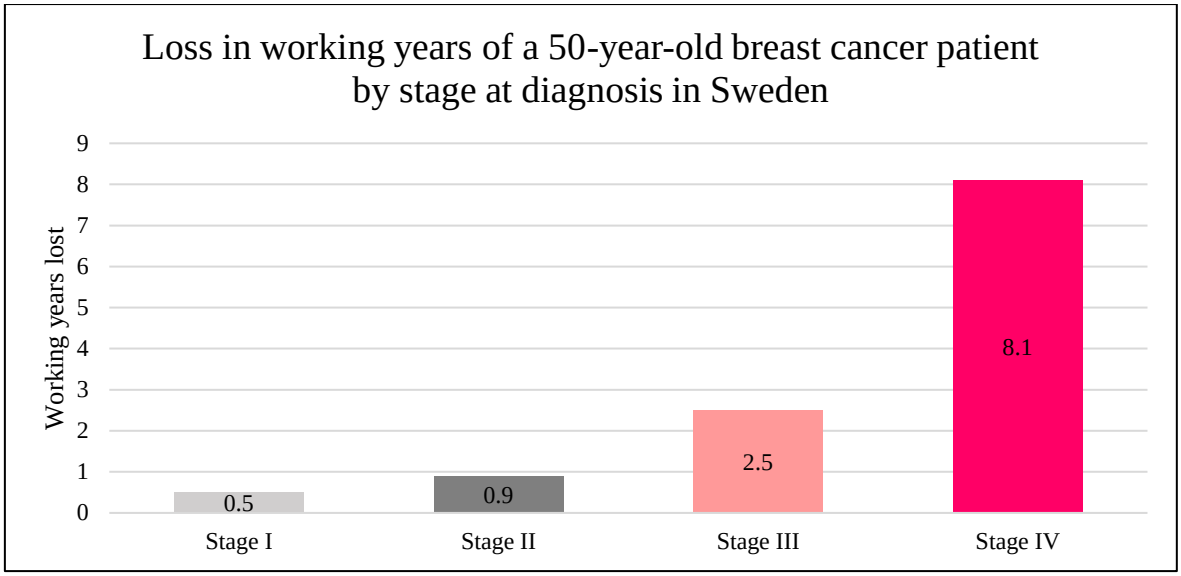

Figure 18: Loss in working years of a 50-year-old breast cancer patient by stage at diagnosis in Sweden.

Notes: The loss in working years until the retirement age at 65 includes both time lost due to sick leave and premature mortality compared to a matching sample of women without breast cancer. Source: (92).

For morbidity-related indirect costs of TNBC, a recent study for the US showed that these costs differ in working-age patients by recurrence status (93); see Figure 19. Patients (virtually all of them diagnosed with stage I–III) who had received initial treatment and who experienced no recurrence incurred monthly costs of $452 from absenteeism and disability, whereas patients with locoregional and metastatic recurrence incurred costs of $851 and $1,458, respectively. Patients with recurrence had a 63% higher rate of leaving the workforce.

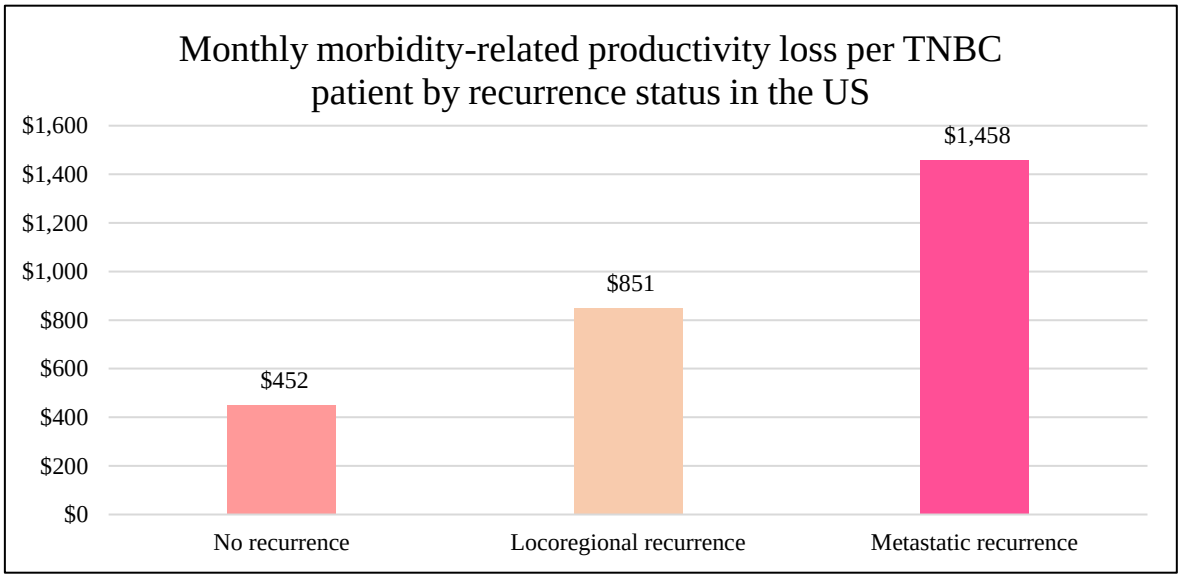

Figure 19: Monthly costs of productivity loss from morbidity per TNBC patient aged 18–65 years by recurrence status in the US.

Notes: Morbidity-related productivity loss consisted of medically related absenteeism and disability. Patients of all stages who were initially treated with surgery were included. Source: (93).

No estimates for mortality-related indirect costs of TNBC could be sourced. Nonetheless, a hypothesis is that indirect costs from premature mortality of working-age patients are higher in TNBC compared to other subtypes, because TNBC patients have a lower survival rate and tend to be younger.

4. Detection, diagnostics, and treatment of TNBC

This chapter describes the typical patient pathway in TNBC; see Figure 20 for an overview. It starts with the detection of the tumor, followed by the diagnostic process. Depending on the characteristics of the tumor, different kinds of treatment options exist. The chapter also describes recent advances and the global standard of care along the key stages of the patient pathway based on international guidelines. General challenges in high-income countries for every key stage of the patient pathway are also included.

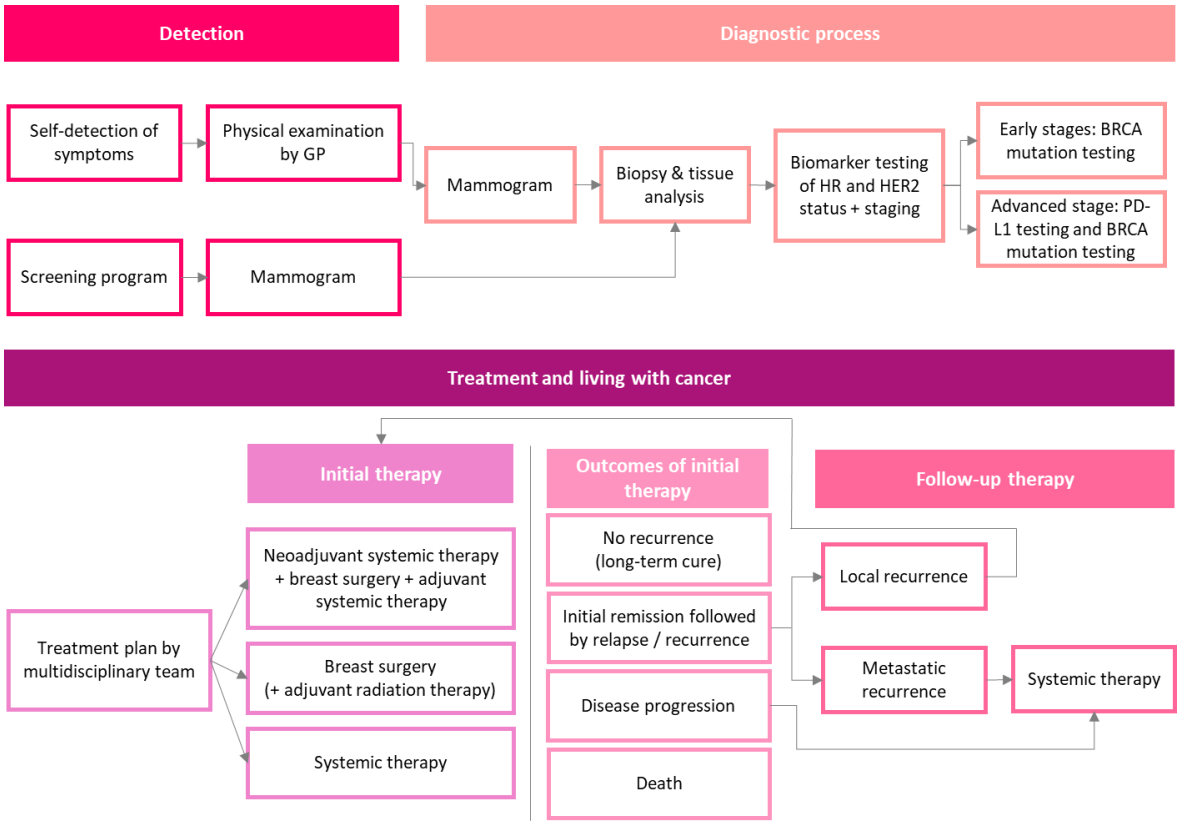

Figure 20: Stylized patient journey in TNBC.
Source: Based on American Cancer Society and ASCO, ESMO, and NCCN guidelines (94-98).

The detection, diagnostics, and treatment of breast cancer are also the three pillars in the WHO's Global Breast Cancer Initiative launched in 2021 (99). This initiative provides strategic guidance and coordination aimed at improving breast cancer care, with a focus on low- and middle-income countries. 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

4.1 Detection

Detection of breast cancer at the earliest possible stage increases the chances for survival; see section 2.6. In general, breast cancer is either detected by the patient herself based on symptoms or through screening before the experience of any symptoms. Around half of all new breast cancer cases in Europe are nowadays self-detected and the other half through population-based screening programs (100).

4.1.1 Self-detection by the patient

TNBC symptoms, such as lumps in the breast or armpit, are similar to those of other breast cancer subtypes (see section 2.3). Regular self-examination by women for breast cancer symptoms is considered crucial. Upon detection of symptoms, the first step for the patient would be to present to her general practitioner (GP) in primary care. The GP might conduct a physical examination before referring the patient to a specialist to perform a mammography.

Early diagnosis upon first symptoms is essential. According to the WHO, there are two main areas to ensure early diagnosis (101).

1. Awareness of first signs of cancer
    a. Knowledge about common symptoms of breast cancer is key and health literacy is a critical skill for early detection (102). Awareness campaigns on symptoms (and on the opportunity of screening programs) can increase the health literacy in the population. The “Breast Cancer Awareness Month” in October every year is an example of an awareness campaign. The “TNBC Awareness Day on March 3” is another example. These campaigns may be run jointly by governments and patient organizations to maximize outreach.
    b. Primary care providers (GPs, nurses) need to be trained to recognize symptoms of breast cancer.
2. Accessibility and affordability of health services and quick referral from primary care to specialized care

a. Geographical and financial barriers might prevent patients from accessing health services rapidly.

b. Psychosocial barriers (e.g., fear and stigma of getting cancer) might delay the time until patients access health services for a diagnostic confirmation.

c. Clear referral guidelines are needed to facilitate the quick referral from primary care to diagnostic services in specialized care.

Genetic risk assessment (also called genetic counseling) has become common in the recent decade (103). As described in section 2.2, women with inherited BRCA1/2 mutations have higher chances of getting breast cancer. They might also get breast cancer at younger ages, and they are at an increased risk of developing TNBC. Uncovering genetic risks can therefore be vital for women carrying BRCA1/2 mutations. Women with a family history of breast, ovarian or pancreatic cancer are primary targets for genetic testing according to guidelines by the NCCN (104). Women who have these mutations may be advised to begin breast cancer screening earlier and more frequently.

4.1.2 Detection through screening programs

The WHO recommends breast cancer screening (101). Screening programs for breast cancer have been implemented in most countries around the world (105), and in several HICs these programs have been running since the 1980s (106, 107). The screening programs entail the invitation of healthy women of a certain age group to undergo a mammography at regular intervals in order to detect tumors before they cause any symptoms.

The main features of screening programs concerning the target group may differ slightly from country to country; see Table 6. For example, the initial recommendation by the Council of the EU from 2003 was to screen women aged 50–69 years with mammography (108), and guidelines from 2013 further specified that mammography should take place every 2 years (109). In 2022, these recommendations were updated by the European Commission and subsequently approved by the Council of the EU to extend the target age group to women aged 45–74 years (110, 111).

Table 6: Breast cancer screening recommendations in the EU and the US

	Target group	Interval	Recommendation
European Union	Women aged 45–49	2–3 years	Conditional recommendation
	Women aged 50–69	2 years	Strong recommendation
	Women aged 70–74	3 years	Conditional recommendation
United States	Women aged 40–49	2 years	Recommended selectively (grade C)
	Women aged 50–74	2 years	Recommended (grade B)

Notes: In the US, for women aged 40–49 years, the United States Preventive Services Task Force (USPSTF) only recommends selective screening every two years based on patient preferences and women who place a higher value on the potential benefit than the potential harms. Source: European Commission and USPSTF (112, 113).

Despite the existence of screening programs in HICs, the participation rates are not optimal. One aim of the Europe's Beating Cancer Plan is to make sure all EU countries offer breast cancer screening to 90% of the target population by 2025 (114). The most recent evidence from 2019 shows that the coverage of the target population ranged from 9% in Romania to 95% in Sweden; see Figure 21. The EU-average screening rate was 66% in women aged 50–69 years. The screening rate in the US was 76% in women aged 50–74 years in 2019 (115). In Japan, only 45% of the target women (40 years and older) had undergone mammography screening within the past 2 years in 2016 (116).

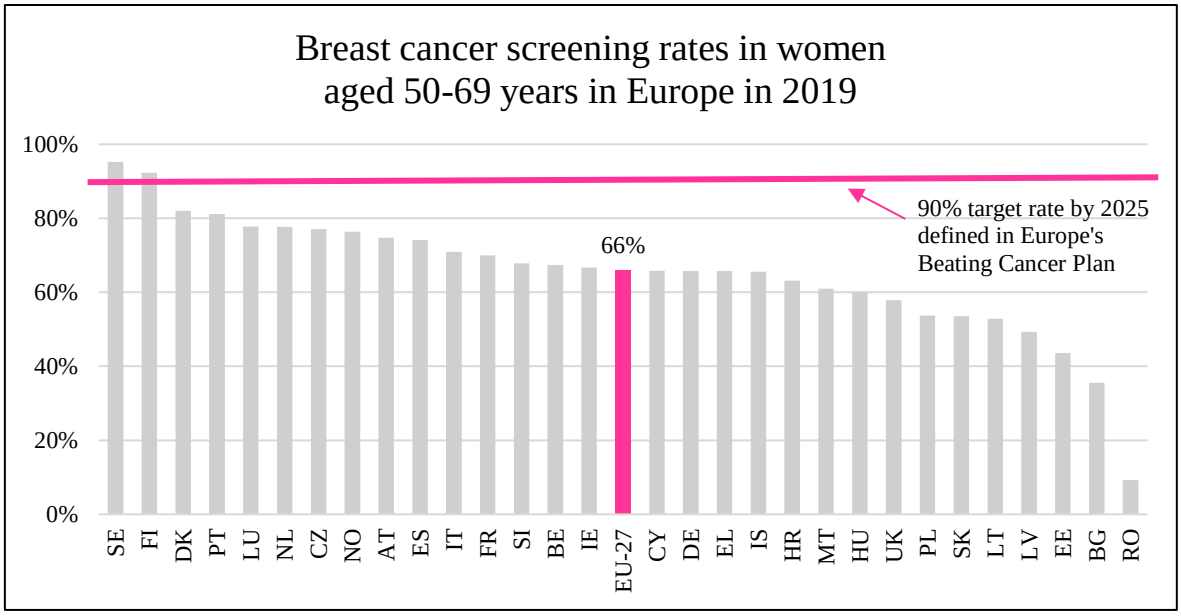

Figure 21: Mammography screening rates (self-reported) in women aged 50–69 years within the past 2 years in 2019 in Europe.

Source: Eurostat – European Health Interview Survey (EHIS) survey (117).

4.1.3 Challenges in early detection

Low breast health awareness / health literacy

Education on breast health awareness is often lacking in European countries and should target girls at school as well as adult women (100). Regular public and private information campaigns, also using social media, to raise awareness and to inform people about (i) common symptoms of breast cancer (e.g., the "Know Your Lemons" initiative (118)), and (ii) the availability and benefits of screening are needed. Previous reviews have shown that these measures are effective (119, 120).

Low involvement of primary care

In view of the common occurrence of breast cancer in women, primary care can play an active role in the early diagnosis of symptoms (100). Primary care workers (GPs and nurses) should be aware of common signs of breast cancer. Upon suspicion of cancer, a close collaboration and fast referral from primary care to specialists is needed (100). Primary care workers can also encourage women in the target age group to attend screenings when called upon.

Lack of genetic risk assessment

Uncovering genetic risks can be crucial for early diagnosis but systematically assessing the BRCA1/2 mutation status among adult women is challenging. For example, guidelines in Europe only recommend genetic testing for BRCA1/2 mutations for high-risk people, which includes women with a family history of breast/ovarian/pancreatic cancer (37). However, there is evidence that with this approach, approximately half of women diagnosed with mutations remain unidentified (37). This is because women might have inherited the BRCA1/2 mutation through paternal lineage transmission or because of being part of a small family, which in both cases means that women lack a female family history of breast and/or ovarian cancer (121).

Low participation in screening programs

Population-based mammography screening programs may suffer negative publicity around the controversy about the benefits and harms (e.g., false-positive and false-negative mammography results leading to anxiety and other psychological stress, increase of the risk of breast cancer from exposure to radiation during the mammography) of breast cancer screening. This might discourage women to attend screening. While it is true that there are benefits and harms, women must be given information that allows them to make informed choices about program participation (100). Systematic reviews have identified a large number of determinants of participation in breast cancer screening. Effective measures to increase participation were simple low-cost interventions such as invitation letters, basic information on screening, multiple reminders, fixed appointments, prompts from health care professionals, and health care organizational factors (e.g., close proximity to screening facility) (122).

Narrow target age group in screening programs

The age bracket of the target group for a screening program affects the costs of running the program. Extending the age bracket from 50–69 years to 45–74 years, as recently recommended in the EU, would increase the program costs but also give more women a chance to get screened. In 2020, an estimated 46% of all breast cancer diagnoses were made in the age group 50–69 years and 65% in the age group 45–74 years in the EU (123). Generally, breast cancer screening programs are tailored to the most common subtypes, using a one-size-fits-all approach (124). The extension of the age bracket to younger women in the EU and the US would be especially relevant for TNBC, as TNBC tends to affect younger women (see section 2.4). In addition, the screening interval of 2 years might not be ideal for TNBC. As TNBC tends to grow faster than other subtypes, TNBC is considered an interval cancer, which is defined as cancer that is likely to be diagnosed between a mammogram with normal results and the next one (42).

4.2 Diagnostic process

Breast cancer is diagnosed with a triple assessment that involves a physical examination of the breast, imaging of the breast, and a biopsy (100). To determine the breast cancer subtype, biomarker testing of HR and HER2 status is required. Together with information on the stage (i.e., the spread of the cancer), the therapeutic approach can be decided. For TNBC in particular, some novel treatment options require additional biomarker testing prior to treatment initiation.

4.2.1 Imaging

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 (96). Key features of the three imaging methods in relation to TNBC are summarized in Table 7.

Table 7: Imaging methods for breast cancer diagnosis

Mammography	Mammography entails a low dose of radiation to produce an image (called mammogram) used to detect tumors. Some complications with mammograms are the following: • Mammograms involve a risk of false-positive and false-negative test results, and some studies have found that younger women and TNBC patients are more likely to receive false-negative results (125). • TNBC tumors are more difficult to detect. They do not exhibit the standard mammographic features of breast cancer, such as the irregular shape of breast lumps, typical patterns of calcifications (white spots on the mammogram), or lack of lines radiating from the margin (known as spiculated lesions) (126). TNBC are more likely to appear benign, necessitating complementary MRI, a method that is not common in population-based screenings (63).
Ultrasound	An ultrasound captures computer images of the inside of the breasts using sound waves. Evidence suggests that ultrasound has a higher sensitivity for TNBC than mammograms (126). However, in population-based screenings, ultrasound is not routinely used as a screening method. Instead, ultrasound is used to supplement mammography results in certain clinical situations, such as lumps that can be felt but are not visible on mammograms, or in women with dense breast tissue (127).
MRI	Breast MRI creates detailed cross-sectional images of the inside of the breast using radio waves and magnets. It is considered highly accurate for the detection of TNBC (126), but it is not recommended as a routine screening method for women with an average risk of breast cancer. It is mostly recommended for women with high-risk profiles, which includes carriers of BRCA1/2 mutations, women with no known mutation but a family history of breast cancer, women with dense breasts, and women with breast implant ruptures (96).

4.2.2 Biopsy

A breast biopsy is performed if the imaging test results indicate the possibility of breast cancer. 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. The pathological assessment includes examinations of the following features:

- Histological type of the tumor (e.g., ductal carcinoma, lobular carcinoma)
- Receptor status of the three central biomarkers, ER, PR, and HER2
- Size of the tumor
- Grade of cancer cells that determine how fast the tumor is spreading

A new biopsy should be carried out in patients with recurrent breast cancer to confirm tumor characteristics and to allow for additional biomarker testing (see section 4.2.4).

4.2.3 Staging

The staging of breast cancer describes the extent and spread of the tumor. More recently, additional elements such as information about hormone-receptor and HER2 status, tumor grade, and recurrence scores have been added (128). The traditional anatomic staging has four main stages for invasive breast cancer (i.e., excluding non-invasive / in situ cases), shown in Table 8.

Table 8: Stages of breast cancer

Stage I	Tumor is small and limited to the breast tissue or to a lymph node near the breast.
Stage II	Tumor is still in an early stage and is located in the breast, nearby lymph nodes, or both. However, the tumor has not yet spread to other tissues.
Stage III	Tumor has spread to lymph nodes, skin, or the chest wall, and there is a risk that it will spread to other distant organs beyond the breast region.
Stage IV (metastatic)	Tumor has spread beyond the breast to surrounding areas or distant organs. The most common sites for metastasis are the brain, liver, and lungs.

Source: (129).

4.2.4 Biomarker testing

For the past decades, biomarker testing consisted mainly of determining the receptor status of ER, PR, and HER2. These tests are required to determine whether a breast cancer is triple-negative. The test results are used to inform the therapeutic approach.

In the past decade, other biomarkers that are relevant to inform the therapeutic approach in TNBC have been discovered:

- Tumor-infiltrating lymphocytes (TIL) levels have prognostic value in TNBC (130). A high TIL level is associated with a better response to chemotherapy and a better prognosis (96).
- BRCA1/2 mutations have become relevant since the approval of the first poly ADP ribose polymerase (PARP)-directed medicines in breast cancer in 2018 (see section 4.3). As described in section 2.2., around one fifth to one third of TNBC patients in Europe and the US have these mutations.

  - In early-stage breast cancer, ESMO guidelines from 2019 recommend testing for inherited BRCA1/2 mutations only in high-risk groups such as premenopausal women, TNBC patients under 60 years, women with a history of ovarian cancer or a strong family history of cancer (96). Following the approval of the first PARP-directed medicine in early-stage breast cancer in 2022, routine BRCA testing in early-stage breast cancer has been recommend in NCCN guidelines (98).
  - In metastatic breast cancer that tested negative for HER2, ESMO guidelines from 2021 and current ASCO and NCCN guidelines recommend BRCA testing as a key component for determining treatment strategies (97, 98, 131).

- Programmed death-ligand 1 (PD-L1) status has become relevant since the approval of the first immunotherapy medicine in TNBC in 2019 (see section 4.3). High levels of PD-L1 in cancer cells, in general, predict favorable outcomes of immunotherapy (132). Around one fifth to two fifths of metastatic TNBC patients have a positive PD-L1 expression (133, 134).
  - In metastatic TNBC, ESMO guidelines from 2021 and current ASCO and NCCN guidelines recommend PD-L1 testing for metastatic TNBC patients (97, 98, 131).

4.2.5 Challenges in the diagnostic process

Low patient involvement in decision-making

The European Society of Breast Cancer Specialists (EUSOMA) recommends that patients must be fully informed about each step in the diagnostic and therapeutic pathway and must be given adequate time to consider the options and make an informed decision (100). They also recommend that patients should be informed about diagnostic and treatment options not offered by their breast center if these options are covered in current guidelines (100). A well-informed patient could, for instance, insist on receiving certain kinds of diagnostic exams and tests before the start of treatment. In addition, patient involvement in Europe is hampered by a lack of dedicated breast care nurses and patient navigators who can help guide patients through the complex care pathway and explain the different options along the pathway (100).

Delays in the diagnostic process

Keeping the time between the diagnosis of cancer and the start of treatment as short as possible increases the chances of survival. 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 to patients with a short delay of 0–30 days (135). A recent review also showed that (ii) a four-week delay in the start of breast cancer surgery (in cases without neoadjuvant systemic therapy) is associated with an 8% increase in subsequent mortality, and (ii) a four-week

delay between the end of neoadjuvant systemic therapy and start of breast cancer surgery is associated with a 28% increase in subsequent mortality (136).

Misinterpretation of imaging results

The appearance of TNBC tumors on imaging results may differ from other breast cancer subtypes. Tumors can often appear benign on a mammogram, and this may also occur with ultrasounds, albeit less frequently (63). As a result, there is an increased risk of misdiagnosis and diagnostic delays. These delays are especially concerning as TNBC tends to grow faster than other subtypes.

Shortcomings in the quality of breast cancer pathology

A high accuracy of assessing relevant parameters during the diagnostic process is important for treatment decision-making. In Europe, the quality of breast cancer pathology can vary considerably from country to country (100). Most pathology departments are general and may lack pathologists experienced in the increasingly complex area of breast pathology and may also lack sufficient volume of cases to develop and maintain expertise. In many countries in Europe but also partly in Canada and the US there is a shortage of pathologists (137), which can create delays in the diagnostic process of cancer patients (138, 139).

Start of treatment before full assessment of ER/PR/HER2 status

Clinical guidelines from ESMO and NCCN recommend full assessment of ER/PR/HER2 status before the start of treatment (97, 98). Unpublished market research from 2021 showed that around 20–25% of non-metastatic TNBC patients in countries such as France and the US were taken directly to surgery without full assessment of their ER/PR/HER2 status.

Restricted adoption of comprehensive biomarker testing

An increasing need for biomarker testing has characterized oncology in the last decade. Since 2018/2019, testing for predictive biomarkers for BRCA and PD-L1 have become a necessity for the administration of the latest cancer medicines in TNBC to the appropriate patients. The expansion of testing requires additional resources devoted to breast cancer care, similar to when HER2-testing was added to the routine diagnostic workup over 20 years ago. Several barriers have been identified that prevent cancer patients from accessing biomarker testing. In Europe, these include a 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 result not being available within a clinically meaningful time, and insufficient public reimbursement of the tests (140-142).

4.3 Treatment

The optimal treatment of TNBC patients differs by disease stage and tumor characteristics. 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) (100). In general, TNBC patients may be treated with surgery, radiation therapy, systemic therapy (i.e., cancer medicines), or a combination of these treatment modalities; see Table 9.

Table 9: Treatment modalities in TNBC

Surgery	There are two main types of surgery to remove a tumor in the breast. • Breast-conserving surgery (also known as lumpectomy) is a surgery to remove the tumor as well as some surrounding normal tissue. Only the part of the breast containing the tumor is removed. • Mastectomy is a surgery in which the entire breast that contains the tumor is removed, including all of the breast tissue and sometimes other nearby tissues. Some women may also have both breasts removed in a double mastectomy.
Radiation therapy	Radiation therapy is treatment with high-energy rays (or particles) that destroy cancer cells. In TNBC, radiation therapy is typically given after surgery (especially after breast-conserving surgery) to help destroy remaining cancer cells so as to lower the chances of the cancer growing back in the same breast or nearby lymph nodes.
Systemic therapy (cancer medicines)	There are three types of systemic therapy for TNBC: • Chemotherapy uses chemicals to kill fast-growing cells in the body. Fast-growing cells are a major feature of tumors and especially of TNBC. However, chemotherapy may also damage fast-growing healthy cells alongside malignant cells in the body. • Immunotherapy in TNBC refers to the use of immune checkpoint inhibitors (ICIs). To initiate an immune response against malignant cells, the immune system must be able to distinguish between cancer and healthy cells. ICIs are proteins that cover cells and assist the body in differentiating between normal and malignant cells. Cancer cells are capable of "fooling" checkpoint proteins and use them as shields to avoid an immune response against them. ICIs block these proteins, resulting in a better immune response to attack cancer cells. In the case of TNBC-approved treatments, the checkpoint protein that gets "blocked" is the protein PD-1. • Targeted therapy in TNBC refers to the use of PARP inhibitors that target BRCA1/2 mutations of cancer cells. Cancer cells have a way of getting repaired with the help of PARP proteins that also play a significant role in fixing DNA. PARP inhibitors prevent PARP DNA repair and thus enhance local DNA damage in cancer cells, thereby preventing cancer cells from spreading further.

Source: American Cancer Society (133).

Systemic therapy options in TNBC have historically been limited to chemotherapy, because hormonal therapy and HER2-directed targeted therapies that are used in other breast cancer subtypes were not effective due to the absence of HR and HER2 expression (143). 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.

4.3.1 Early-stage TNBC

The treatment of early-stage TNBC typically always involves surgery. Breast-conserving surgery is preferred over mastectomy, as it is associated with increased quality of life and better survival (96). Surgery is usually combined with either systemic therapy or radiation therapy or both; see Figure 22.

- For stage I TNBC, when the tumor is still small, it will be removed by surgery. After surgery, some women will receive chemotherapy to reduce the chances of the cancer coming back. They might also receive or radiation therapy for the same purpose.
- For stage II–III TNBC, when the tumor is larger and has started to spread to nearby lymph nodes, patients are recommended to start with neoadjuvant (i.e., pre-operative) systemic therapy to shrink the tumor. Neoadjuvant systemic therapy increases the chances of being eligible for breast-conserving surgery (144). After surgery, patients continue with adjuvant (i.e., post-operative) systemic therapy and may also receive radiation therapy to reduce the chances of the cancer coming back. In the past, it was more common in stage II–III TNBC to start directly with surgery followed by adjuvant chemotherapy and/or radiation therapy.

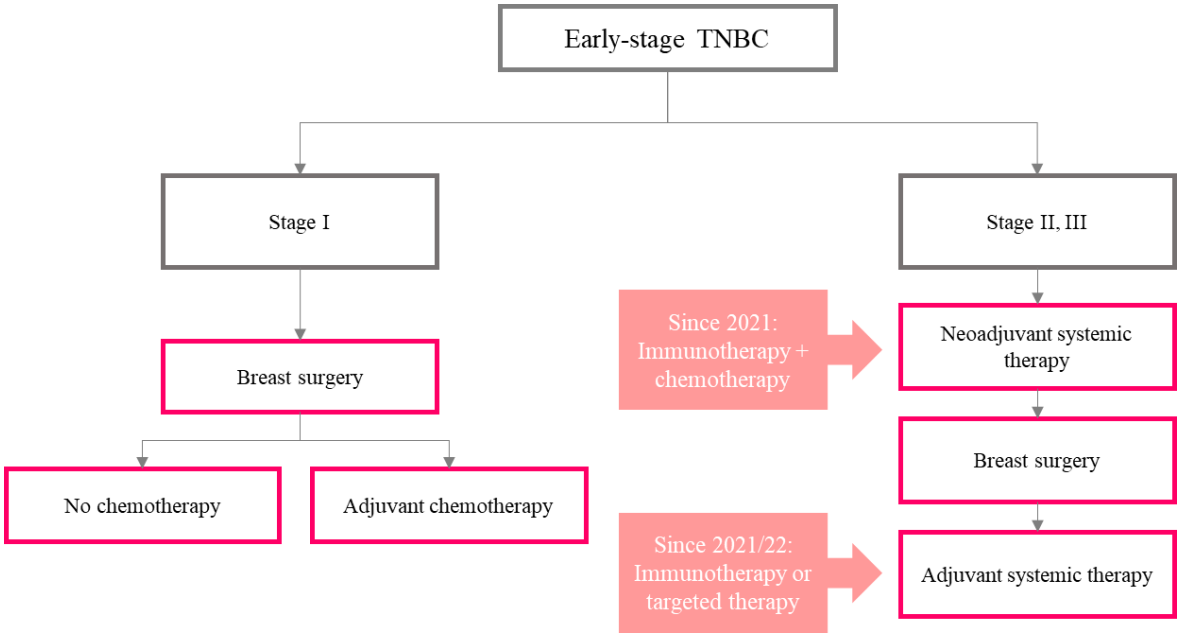

Figure 22: Stylized treatment algorithm in early-stage TNBC in 2022.
Source: Adapted from ESMO and NCCN guidelines (96, 98).

Traditional treatment with chemotherapy

Chemotherapy has been the cornerstone treatment for all systemic therapy in early-stage TNBC (144-146). In most cases, neoadjuvant and adjuvant chemotherapy contained anthracyclines and taxanes (96). However, the efficacy of adjuvant chemotherapy is low, leaving patients at risk of tumor recurrence (147). In addition, chemotherapy toxicities can have long-term side effects that are linked to decreased quality of life in breast cancer patients (148). Chemotherapy in young

women also involves a risk of impairing fertility, and thus prior to the administration of chemotherapy, international clinical guidelines recommend providing information about fertility preservation (96). Clinical guidelines from both ASCO and EMSO used to recommend the use neoadjuvant and adjuvant chemotherapy in TNBC (149, 150).

Advances in immunotherapy

A recent option for early-stage TNBC treatment resulted from the approval of immunotherapy with pembrolizumab in high-risk early stages (stages II–III) by the US FDA in 2021 and by the European Medicines Agency (EMA) in 2022 (151, 152). ASCO and NCCN guidelines recommend this new therapeutic option for appropriate patients (98, 153).

Advances in targeted therapy

Another recent advancement in early-stage TNBC treatment was the approval of targeted therapy with olaparib for BRCA1/2 mutation in high-risk early stages (stages II–III) by the US FDA and the EMA in 2022 (154, 155).[2] ASCO and NCCN guidelines nowadays recommended this as an adjuvant treatment for patients who have been previously treated with neoadjuvant or adjuvant chemotherapy in (98, 156).

4.3.2 Metastatic TNBC

Women with metastatic TNBC encompass both women with newly diagnosed metastatic TNBC and women who were previously diagnosed with stage I–III disease and later developed distant recurrence (157). Systemic therapy is typically the primary treatment option for metastatic TNBC, as surgery is no longer possible (but might be done to some extent to alleviate symptoms) (97). ESMO guidelines recommend to begin treatment no later than four weeks after receiving imaging results to avoid further spread of the cancer (97).

Before 2018, systemic therapy consisted solely of chemotherapy medicines such anthracyclines, taxanes, capecitabine, gemcitabine, and eribulin (133). These medicines were either given alone (in frail patients) or in combination with each other. Since 2018, several immunotherapy medicines and targeted therapies have been introduced. Their administration necessitates prior testing of PD-L1 status and BRCA1/2 mutations, respectively (see section 4.2.4). PD-L1 status and presence of BRCA1/2 mutations are nowadays major deciding factors for choosing the appropriate first-line treatment options; see Figure 23.

[2] The approval was not just limited to TNBC but included all high-risk early-stage breast cancers with BRCA1/2 mutations that are HER2-negative.

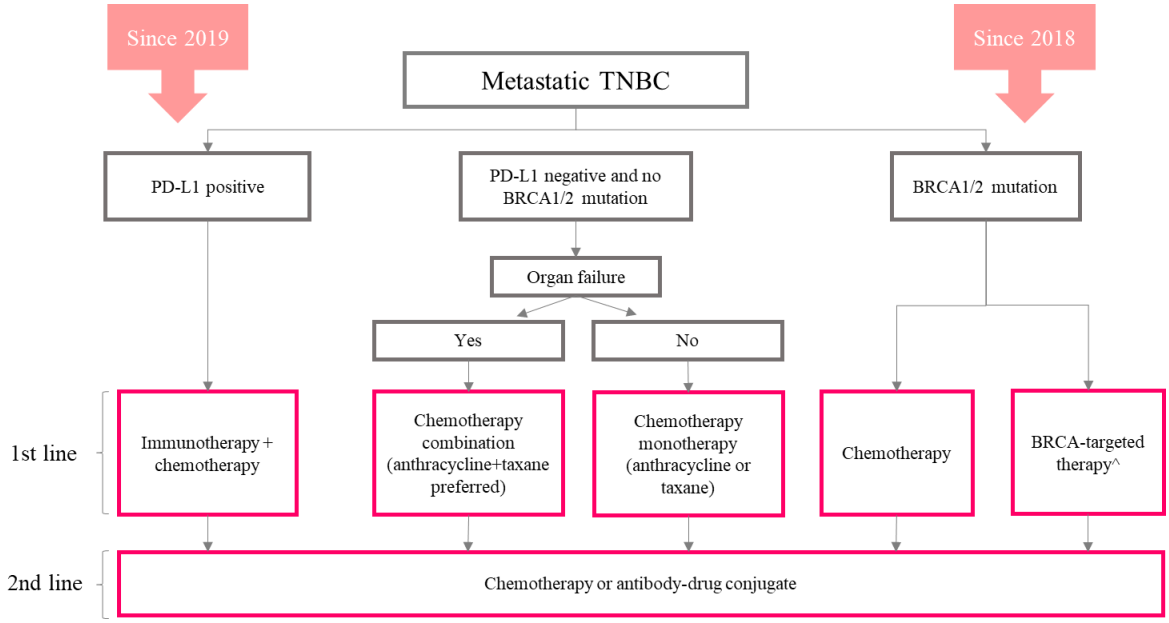

Figure 23: Stylized treatment algorithm in metastatic TNBC in 2022.

Notes: ^ BRCA-targeted therapies 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 (97, 98).

Advances in first-line treatment

Adding immunotherapy to chemotherapy has emerged as a novel treatment alternative for metastatic patients, albeit only for patients with a positive PD-L1 status. In 2019, atezolizumab in combination with chemotherapy was approved by the US FDA (158), yet after inconclusive evidence of added clinical benefits in a post-marketing trial, the producer decided to withdraw the indication in the US in 2021 (159). In Europe, atezolizumab plus nab-paclitaxel was approved by the EMA in 2019 and is still approved and also recommended in ESMO guidelines (97, 160). A second immunotherapy, pembrolizumab in combination with chemotherapy, was approved by the US FDA in 2020 and by the EMA in 2021 (151, 161). This has been the recommended treatment option for PD-L1 positive patients since then in ASCO, ESMO, and NCCN guidelines (97, 98, 131).

For metastatic TNBC patients with BRCA1/2 mutations, two targeted therapies, olaparib and talazoparib, were approved by the US FDA in 2018 and by the EMA in 2019 (154, 162-164). Both therapies are currently recommended in ASCO, ESMO, and NCCN guidelines (97, 98, 165), but require patients to have previously been treated with chemotherapy in the (neo)adjuvant or metastatic setting unless patients were not suitable for chemotherapy in these settings.

Advances in later-line treatments

Patients who progressed on first-line chemotherapy, immunotherapy or BRCA-targeted therapy still have further treatment options. Traditionally, another chemotherapy agent, such as eribulin,

capecitabine, or vinorelbine was recommended (97). In 2020, the first antibody-drug conjugate,[3] sacituzumab govitecan, was approved by the US FDA for metastatic TNBC patients who have received at least two prior systemic therapies for metastatic disease (166). In 2021, this approval was amended to include metastatic TNBC patients who have received two or more prior systemic therapies, at least one of them for metastatic disease (167). In 2022, the US FDA approved another antibody-drug conjugate, trastuzumab deruxtecan, for metastatic breast cancer patients with low HER2 scores (traditionally treated as HER2-negative patients, which includes some cases of TNBC) who have received a prior chemotherapy in the metastatic setting or developed disease recurrence during or within six months of completing adjuvant chemotherapy (168).

4.3.3 Challenges in treatment

Limited patient involvement in treatment choice

Active involvement in decision-making for treatment has been shown to improve breast cancer patients' perception of quality of life (169). Women experiencing problems with involvement in treatment and care decisions may experience significantly higher psychological distress (170). However, not all patients want to be involved in decision-making. A recent systematic review indicated that the median percentage of cancer patients preferring an active, shared, or passive role in decision-making was 25%, 46%, and 27%, respectively, while the median percentage of patients perceiving an active, shared, or passive role was 27%, 39%, and 34%, respectively (171). Patients experiencing discordance between the preferred and the perceived role in decision-making report lower levels of quality of life (172).

Outdated local clinical guidelines

Despite the availability of international clinical guidelines (such as those by ASCO, ESMO, or NCCN), local guidelines need to be updated when novel treatments become available in the local setting. If clinical guidelines do not include novel treatments, their prescription might be limited even though they are reimbursed by the public payer. Regularly updating clinical guidelines is important, because choosing the appropriate treatment in TNBC becomes increasingly complex as treatment options expand (100). Up-to-date local clinical guidelines also help to ensure that all breast specialists can give coherent advice to patients within a country (100).

Hesitant adoption of new treatment approaches

Treating physicians may be reluctant to adopt novel treatment regimens, such as neoadjuvant or adjuvant systemic therapy in TNBC patients who previously would not have received such therapy.

[3] Antibody-drug conjugates are a new class of cancer medicines that are a combination of a monoclonal antibody (targeted agent) and a small-molecule cytotoxic agent (chemotherapy). Each molecule of the antibody has several molecules of the cytotoxic agent attached. Since the antibody binds to tumor characteristics, it allows the cytotoxic agent to specifically target cancer cells and not healthy cells.

In Europe and the US, underuse of neoadjuvant[4] systemic therapy in breast cancer has been reported (100, 173). A reluctancy to prescribe neoadjuvant treatments to women with high-risk early-stage breast cancer has also been reported among Australian surgeons (174). Unpublished market research from 2021 showed that around 20–25% of non-metastatic TNBC patients in countries such as France and the US were taken directly to surgery without full assessment of their HR/HER2 status.

Limited and delayed reimbursement of novel cancer medicines

The regulatory approval of new cancer medicines (e.g., by the FDA in the US, and the EMA in Europe) is only the first step for patient access. In public-funded health care systems, reimbursement of new medicines by the public payer is the critical second step for patient access. In Europe, the time from regulatory approval to reimbursement of new cancer medicines varies considerably, from fewer than 150 days in Germany and Denmark to almost 1000 days in Estonia and Romania (175). In addition, in many Western European countries only around 50% of new cancer medicines have full reimbursement several years after EMA approval and in Eastern Europe only around 20% (175). Similar patterns of limited and delayed reimbursement of new cancer medicines have also been documented in high-income countries in Asia-Pacific (176).

Slow adoption of newly reimbursed cancer medicines

The reimbursement of new cancer medicines in public health care systems is no guarantee for access for all clinically eligible patients. Various factors may cause slow uptake of new medicines in clinical practice (86). This includes different budget control mechanisms at the national or hospital level, lack of necessary biomarker testing, outdated local clinical guidelines, and lack of training of medical staff on how to use new medicines.

[4] The source for Europe uses the term “primary” instead of “neoadjuvant” (100).

5. Societal impact of improved TNBC care

The previous chapter highlighted ample opportunities to improve the care of TNBC patients along the entire patient pathway. This chapter describes the societal impact of improved TNBC care by considering various elements shown in Figure 24.

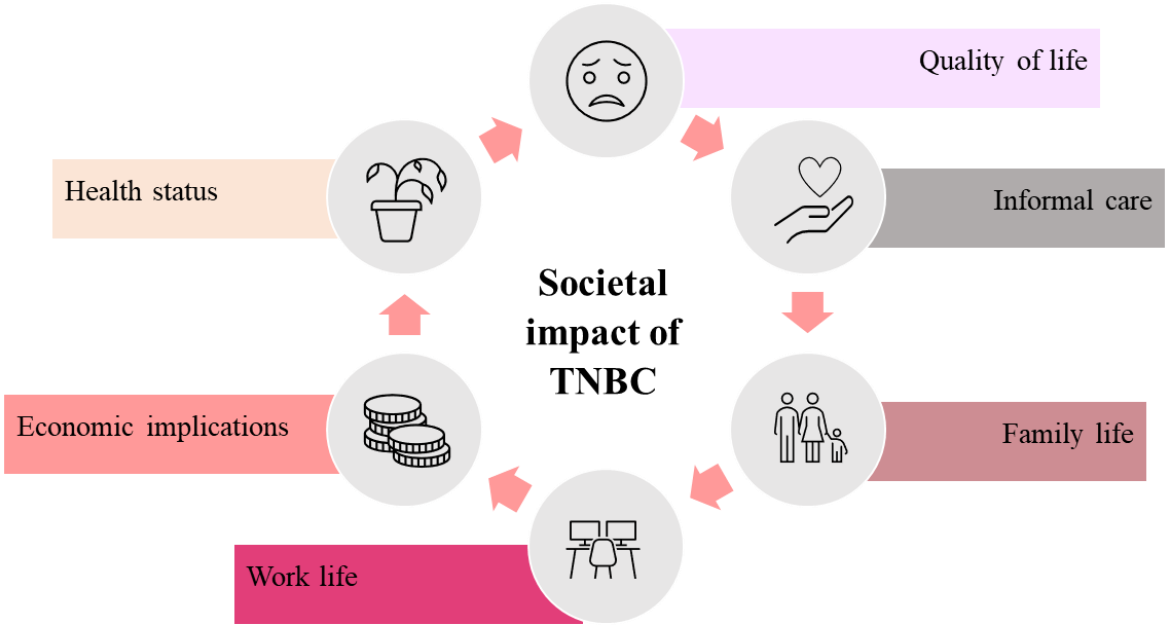

Figure 24: Elements of the societal impact of TNBC.

5.1 Health implications

Improving the care of TNBC patients through better early detection, diagnostics, and treatment can positively affect the health status of patients (such as survival; see section 2.6) and patients' quality of life (see section 2.7). This would help to reduce the future disease burden of TNBC.

Big gains in patient health can be made by improving early detection. In the US, the five-year survival rate in TNBC was 91% in stage I (localized disease) but only 12% in stage IV (distant spread of disease) in 2012–2018 (65); see section 2.6. More cancer cases can be detected at an early stage by increasing (i) the proportion of women who self-detect their tumor as early as possible, and (ii) the participation of women in the target age group in screening programs.

Avoiding delays in the diagnostic process until treatment start increases the chances to survive. Even though timely diagnostics is vital, it is also important to ensure that a complete diagnostic assessment has been made before treatment start. This will allow the choice of the optimal therapeutic approach in the increasingly complex treatment landscape for TNBC.

5.2 Family life and informal caregiving

A breast cancer diagnosis and the ensuing treatment may considerably affect family members (177). There is a toll that breast cancer patients' family members bear that may affect them psychologically, professionally, and financially.

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. Help with transportation to the hospital may also be required. This may affect the partner's ability to continue to work or productivity at work, resulting in additional income loss for the family (178). Previous studies of caregivers to cancer patients have indicated a productivity loss due to absenteeism/presenteeism in the range of 21–27% (179). Furthermore, family caregivers frequently report feeling physically exhausted because their tasks can be demanding, requiring them to assist patients with their daily routines for extended periods of time as well as help them manage treatment-related symptoms. Time for family caregiving for breast cancer patients averaged 6.4 hours per day in the US (180).

Family members often suffer from emotional devastation and fear of a loved one dying (177). The dynamics of the relationship in terms of emotional support, sexuality, and intimacy may be impaired. 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 (181).

Improving the care of TNBC through early detection, timely diagnostics, and adequate treatment may positively affect informal caregivers and family members. Indeed, previous studies have shown that improving the quality of life of a cancer patient can directly lead to an improvement in the quality of life of the informal caregiver (182).

5.3 Work life

TNBC is commonly diagnosed in women of working age. Almost half of all TNBC cases are diagnosed in women below the age of 60 in the US; see section 2.4. Some breast cancer patients who are employed may continue to work full-time or part-time while undergoing treatment. Other patients affected by a high symptom burden may be forced to be on sick leave or permanently quit their jobs.

Patients may desire or be required to work for a variety of reasons, including financial reasons, a sense of normality, and control over their lives. Even patients with metastatic disease may continue to work. A study mainly with patients from the US estimated that around 35% of working-age

people with various metastatic cancers (including breast cancer) continue to work full- or part-time (183). For breast cancer patients, a systematic review showed that the likelihood to return to work varies from 43% to 93% within one year of diagnosis across HIC (184).

The choice of treatment is a major factor related to the return to work among breast cancer patients (184). In TNBC, chemotherapy is often associated with debilitating symptoms making it one of the leading causes of sick leave and late return to work (185). Chemotherapy is associated with side effects during treatment, such as nausea and vomiting, but also with long-lasting side effects such as depression, exhaustion, and cognitive impairment (184).

Disease progression or severity, treatment-related side effects, treatment-associated cognitive impairments, and use of chemotherapy have been identified as factors impairing the ability of cancer patients to work in a recent systematic review (179). Improving the care of TNBC through early detection, timely diagnostics, and adequate treatment thus may positively affect the work life of patients.

5.4 Economic implications

TNBC carries a significant economic burden, with substantially greater costs associated with increasing disease severity. As described in section 3.2, the annual medical costs per TNBC patient in HIC range from around $20,000–100,000 in early-stage disease (stage I–III) to around $100,000–300,000 in metastatic disease (stage IV) (91). In addition, the morbidity-related productivity loss in the US was more than three times higher in patients experiencing metastatic recurrence compared to patients without recurrence ($1458 vs. $452 per month per patient), which was driven by women leaving the workforce at a 63% higher rate than women without recurrence (93).

The costs differences by disease stage have economic implications for efforts to improve early detection of TNBC. For instance, enhanced participation in screening programs would increase the proportion of women diagnosed with early-stage breast cancer and decrease the proportion of women with metastatic breast cancer. This would increase medical costs for the treatment of early-stage disease but avoid higher treatment costs for metastatic disease. In addition, productivity loss from premature mortality would decrease due to higher survival with early-stage disease compared to metastatic disease; see Info Box below.

Info Box – How much would regular participation in breast cancer screening reduce the productivity loss from premature mortality?

Hypothetical example: 50-year-old woman diagnosed either with cancer in situ, localized, regional, or distant stage of TNBC in South Korea.

Setting: Based on a study that explored the impact of screening habits on the stage of breast cancer diagnosis using data between 2002–2011 from the Korea National Cancer Screening Program (186), two scenarios were compared: (1) woman did not attend any screenings in the past 10 years vs. (2) woman attended biennial screenings in the past 10 years.

Method: The distribution of breast cancer by stage of diagnosis by screening participation behavior (according to scenario 1 and 2) was obtained from the aforementioned South Korean study (186). The observed stage distribution was assumed to also apply to TNBC. The risk of death from TNBC by stage of diagnosis was approximated by the complement of the 5-year survival rates from the SEER database in the United States (65); see section 2.6 and assuming a 100% survival rate for cancer in situ. Using a human-capital approach, the productivity loss from premature mortality was calculated. The productivity loss was defined as the present value of earnings lost after death during the remaining working age. The retirement age was assumed to be 60 years (187). Deaths was assumed to occur 5 years after diagnosis. Potential years of working life lost were calculated and multiplied by the average annual earnings and employment rate of women in South Korea (188, 189). Future lost earnings were discounted at a 3.5% rate. All costs were expressed in 2021 USD.

Result: Screening results in a higher proportion of women with cancer in situ (14% vs 11%) and localized disease (51% vs. 47%), and a lower proportion with regional disease (29% vs. 31%) and metastatic disease (3% vs. 8%). A woman diagnosed at age 50 dying five years later would lose 5 years of potential work (4.5 discounted years) until her retirement at age 60. In scenario (1), when she never participated in screening, the productivity loss from premature mortality is $14,812, whereas in scenario (2), with biennial screenings, the productivity loss is $11,370. The improved chances of diagnosing TNBC early rather than late reduce the losses to the economy by around $3,441, equivalent to a 23% reduction.

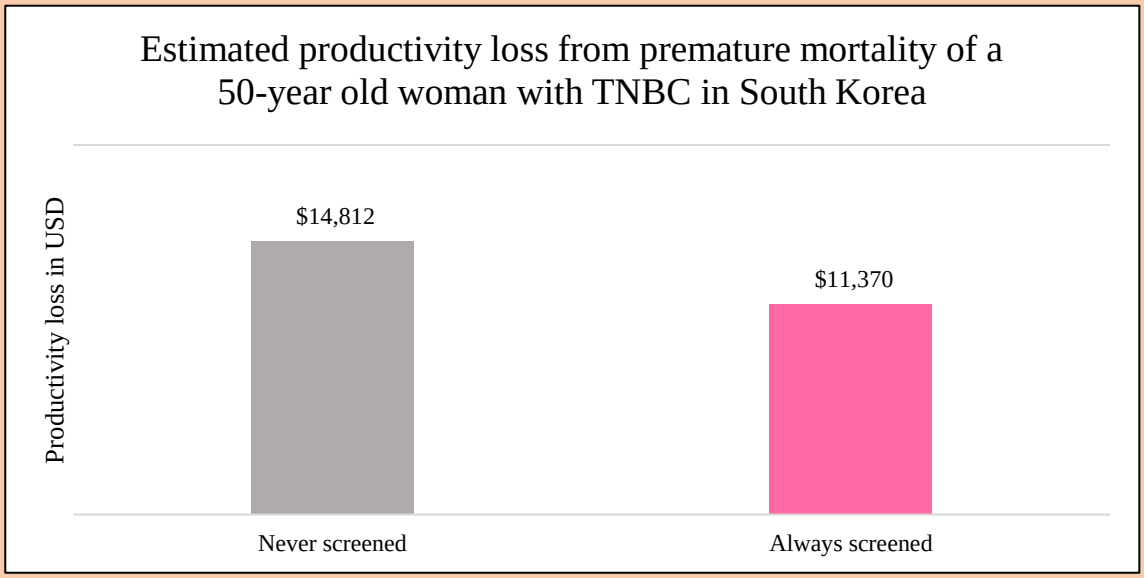

Figure 25: Estimated productivity loss from premature mortality of a 50-year-old woman in South Korea with different screening habits.

6. Areas for improvement

The evidence gathered in this report shows that women with TNBC face worse prognosis than women with other subtypes of breast cancer. Patients face many challenges along the care pathway. This report concludes with broad recommendations for the improvement of TNBC care. They can be grouped into three areas as shown in Figure 26.

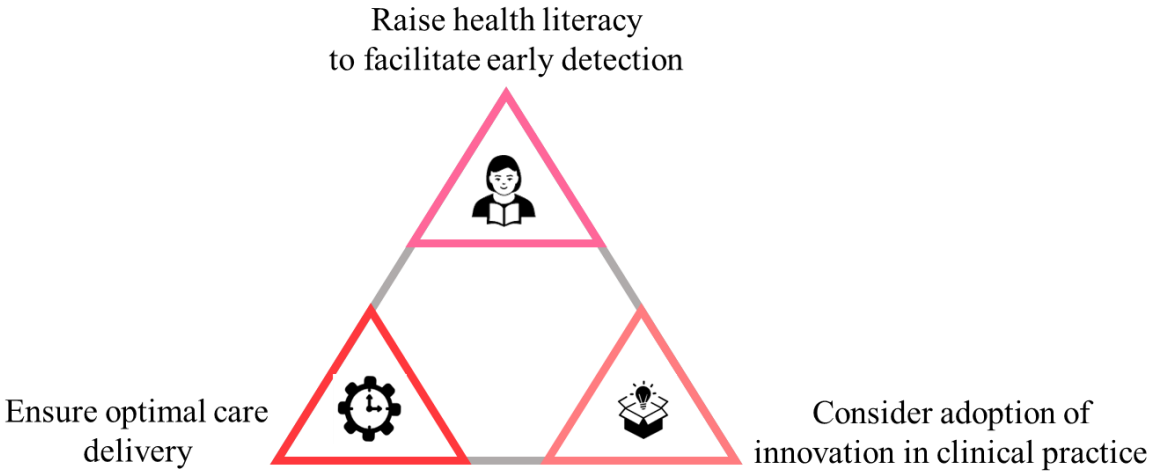

Figure 26: Main areas of improvement for TNBC care.

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

Area 1: Raise health literacy to facilitate early detection

Action	Why?
Improve breast cancer prevention 	Up to 30% of breast cancer cases are theoretically preventable, because they are caused by modifiable risk factors (such as obesity/overweight, physical inactivity). The promotion of a healthy diet and lifestyle is therefore important to avoid future cases of breast cancer. Every cancer case avoided saves not just lives, but also saves money for the health care system. However, cancer prevention is a long-term effort because there is a significant time lag between risk exposure and cancer development.
Raise awareness of breast cancer symptoms 	Awareness among women of signs and symptoms of breast cancer is crucial for early diagnosis. Regular self-examination needs to be encouraged. This is important for adult women of all ages, and especially for women outside the age range of screening programs (54% of all breast cancer diagnoses in the EU are made outside the age range 50–69 years) and for women who do not attend screening.
Enhance involvement of primary care in early detection 	Primary care has a key role to play in improving outcomes for breast cancer patients. Primary care workers need to receive adequate training to detect early indicators of the disease. They should also encourage regular participation in screening among the women they treat. Swift referral pathways from primary care to diagnostic services need to be put in place or strengthened.
Personalize risk assessment through BRCA genetic testing 	Uncovering genetic risks can help to pay particular attention to early symptoms of breast cancer. Around 5–10% of all breast cancers have a hereditary background, mostly related to BRCA1/2 mutations. Many women with BRCA1/2 mutations are unaware of having them. Offering genetic testing/counseling to women who are at an increased risk of developing TNBC (such as women with a family history of breast, ovarian, or pancreatic cancer) can potentially increase the chances of early diagnosis.
Promote participation in screening programs 	Raising awareness among women on the benefits of participating in organized screening programs is imperative for increasing early detection. Current screening rates are far from ideal in most countries, e.g., 76% in the US, 66% in the EU (ranging from 9% in Romania to 95% in Sweden), and 45% in Japan. Europe's Beating Cancer Plan aims for a screening rate of 90%.

Area 2: Ensure optimal care delivery

Action	Why?
Broaden the target age group in screening programs 	Countries that still have screening programs with a narrow target group, e.g., women aged 50–69 years, could consider broadening the target to 45–74 years in line with the latest recommendation from the Council of the European Union. The expansion to younger ages would especially help to detect more cases of TNBC early.
Provide patient-centered care and support 	Patients should be fully informed about each step in the diagnostic and therapeutic pathway and be given adequate time to consider the options to make an informed decision. They should also be informed about diagnostic and treatment options not offered by their breast center if these options are covered in current guidelines. Active involvement in decision-making for treatment has been shown to improve breast cancer patients' quality of life. To foster patient involvement and support, it is important that patients have access to dedicated breast care nurses and patient navigators.
Establish clear care pathways 	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 to patients with a short delay of 0–30 days. 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.
Assure high quality of breast cancer imaging 	Imaging results from mammograms may miss the particular features of TNBC. Easier access to alternative imaging methods for women at an increased risk of TNBC (e.g., high breast density, known BRCA1/2 mutations, or Black/Hispanic ethnicity) could be considered.

Ensure a swift and complete pathological assessment before treatment start 	An accurate pathological assessment is a prerequisite for optimal treatment decision-making. 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 delay the start of treatment.
Recruit and train pathologists 	Current shortages of pathologists delay the diagnostic process. In view of the anticipated increase in the number of (breast) cancer patients as well as more extensive biomarker testing in the coming decades, the demand for pathologists will rise. The recruitment and training of pathologists should therefore be prioritized.

Area 3: Consider adoption of innovation in clinical practice

Action	Why?
Expand access to comprehensive biomarker testing 	Testing for BRCA1/2 mutations in both early-stage and metastatic TNBC and testing for PD-L1 expression in metastatic TNBC are required to inform the treatment decision for targeted therapy and immunotherapy, respectively. These diagnostic tests need to be incorporated in local clinical guidelines to enhance patient access.
Update local clinical guidelines 	Novel treatment approaches in TNBC are already incorporated in international clinical guidelines. However, local guidelines need to be updated as well when novel treatments became available in the local setting. This helps to choose the appropriate treatment in the increasingly complex treatment landscape for TNBC.
Update care pathways and provide training to clinical staff 	Recent changes in the treatment landscape of TNBC require some adaptations of the care pathway, e.g., to include additional biomarker tests and to accommodate the fact that more patient groups are recommended to receive neoadjuvant and/or adjuvant therapy, as well as training of clinical staff to ensure appropriate care provision.

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