



# Breast Cancer: A Comprehensive Review from Diagnosis to Survivorship

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Received: 18 October, 2025; Revised: 10 December, 2025; Accepted: 17 December, 2025

## Abstract

**Context:** Breast cancer (BC) is the most prevalent malignancy among women worldwide and represents a major public health concern. In 2020, approximately 2.3 million new cases were reported globally. Despite advances in diagnostic and therapeutic approaches, BC remains a complex disease with significant clinical and survivorship challenges.

**Objectives:** This study aims to provide an overview of BC by summarizing its biological hallmarks, major risk factors, diagnostic approaches, treatment modalities, and the long-term needs of BC survivors.

**Data Sources:** Relevant information was obtained from previously published scientific literature, epidemiological reports, and clinical studies addressing BC biology, diagnosis, treatment, and survivorship.

**Study Selection:** Studies focusing on the incidence, molecular characteristics, risk factors, diagnostic methods, treatment strategies, and survivorship issues related to BC were considered.

**Data Extraction:** Key data regarding BC hallmarks, associated risk factors, diagnostic tools, treatment options, and post-treatment needs were extracted and synthesized narratively.

**Results:** Breast cancer is characterized by six major hallmarks, including evasion of programmed cell death, unlimited proliferative capacity, enhanced angiogenesis, resistance to growth-inhibitory signals, self-sufficiency in growth signaling, and metastatic potential. Identified risk factors include female sex, increasing age, family history, estrogen exposure, tobacco use, alcohol consumption, high-fat diet, and lifestyle factors. Diagnosis relies on physical examination, imaging techniques – particularly mammography – and tissue sampling, with image-guided core needle biopsy playing a central role. Treatment typically involves a multimodal approach combining surgery, chemotherapy (CT), radiotherapy, targeted therapy, and hormonal therapy, with more advanced disease requiring more intensive treatment. Survivors often face ongoing physical, psychological, and long-term health challenges.

**Conclusions:** Although significant progress has been made in the diagnosis and treatment of BC, it remains a multifaceted disease requiring comprehensive management. In addition to effective therapeutic strategies, addressing the long-term physical and emotional needs of BC survivors is essential to improve overall outcomes and quality of life.

**Keywords:** Breast Cancer, Risk Factors, Diagnosis, Treatment

## 1. Context

Breast cancer (BC) is a prevalent form of cancer that begins in the breast tissue, specifically within the inner

lining of milk ducts or the lobules responsible for supplying milk to the ducts (1). Breast cancer ranks as the second most prevalent cancer globally and is the leading cancer among women (2). It ranks as the fifth

most common cause of cancer deaths worldwide. In 2020, an estimated 2.3 million new cases of BC were diagnosed worldwide (3). The source of BC is the terminal duct lobular units (TDLUs), which serve as the functional building blocks of the breast's collecting ducts (4). Terminal duct lobular units are made up of cells that produce milk. When these cells grow abnormally, they can form a tumor (4). Many genetic mutations have been identified in women with BC. These mutations may result in uncontrolled cell proliferation and tumor development (5). Some of the most common genetic mutations in BC include amplifications, loss-of-function mutations, gain-of-function mutations, and deletions (6). Clinically significant molecular features in BC include the human epidermal growth factor receptor 2 (HER2), hormone receptors [estrogen receptor (ER) and progesterone receptor (PR)], and BRCA mutations – TNBC (ER–, PR–, HER2–: Lacking ER, PR, and HER2 expression) (7). These features play a critical role in guiding treatment decisions and serve as essential factors in research studies. Breast cancer is characterized by six major hallmarks, which are the traits that allow cancer cells to grow and spread (8). These hallmarks include:

- Evasion of apoptosis: Cancer cells are able to evade programmed cell death, which allows them to grow and multiply unchecked.
- Limitless capacity to divide: Cancer cells are able to divide indefinitely, unlike normal cells, which have a limited number of divisions before they die.
- Enhanced angiogenesis: Cancer cells have the ability to promote the formation of new blood vessels, which provides them with the nutrients they need to grow and spread.
- Resistance to anti-growth signals: Cancer cells can disregard signals that normally instruct them to cease growth.
- Induction of own growth signals: Cancer cells are able to produce their own growth signals, which further drives their growth.
- Capacity to metastasize: Cancer cells are able to spread to other parts of the body, which can make the disease much more difficult to treat.

## 2. Risk Factors

Understanding the underlying causes of BC, such as genetic abnormalities inside functional components of

the breast, lays the foundation for understanding the many risk factors that contribute to its development (4). These risk factors, which include genetic predisposition and hormonal impacts, as well as lifestyle choices and environmental exposures, highlight the significance of the approaches to prevention and management (9-14).

**Female sex:** Women are more likely to develop BC than men because their breast cells are more sensitive to hormones (9).

**Older age:** The risk of BC increases with age. This is likely due to the accumulation of genetic changes and exposure to carcinogens over time (10).

**Family history:** A family history of BC is a major risk factor for the disease. This is because inherited genetic mutations can increase the risk of developing BC (11).

**Genetic mutations:** Certain genetic mutations, such as BRCA1 and BRCA2, are strongly correlated with an enhanced BC risk. They are mainly associated with a higher risk of developing BC (12).

Estrogen is a hormone produced by the ovaries in premenopausal women and is also available as a medication in forms like oral contraceptives or hormone replacement therapy (HRT). However, its use has been associated with an increased risk of BC. This risk is higher in women using HRT or oral contraceptives and remains elevated for several years even after stopping HRT. Women with a history of BC who take HRT are at a greater risk of developing a new breast tumor (13). Estrogen is also found accountable for hormonal and reproductive events that contribute to BC risks, such as early age of the first menstruation and late age of the last menstruation (14).

**Lifestyle (13):** (1) Alcohol intake can increase the risk of BC by raising the levels of estrogen-related hormones in the blood. A meta-analysis of 53 epidemiological studies found that consuming 35-44 grammes of alcohol per day can increase the risk of BC by 32%. (2) Consumption of a high-fat diet, especially one rich in saturated fat, has also been associated with an increased risk of BC. This is because fat can enhance the production of estrogen, a hormone that promotes the growth of BC cells. (3) Tobacco use is also a risk factor for BC, however the evidence is not as strong as it is for alcohol and dietary fat. Some studies have discovered that smoking increases the risk of BC, while others have discovered no link. There is some evidence, however, that smoking, particularly at a young age, may raise the risk of BC (12).

### 3. Screening

Breast cancer screening is a way to find BC early, when it is most treatable. These risk factors emphasize the need for frequent BC screening, which is crucial in detecting suspected abnormalities in their early stages (15-22). Understanding risk factors and engaging in proactive screening practices allows individuals and healthcare professionals to take a comprehensive approach to BC management, thereby increasing the likelihood of survival.

- Mammography: The most successful way to screen for BC is with mammography, which utilizes low-dose X-rays to create images of the breasts. Mammography can help find BC early, even before there are any symptoms. This can lead to earlier treatment, which can improve the chances of survival (15). Early detection of BC can increase survival chances by detecting smaller tumors, which are less likely to have spread to the lymph nodes or to have a high grade. Smaller tumors are also easier to treat, which can lead to better outcomes (16).

- Diagnostic imaging after a mammography screening recall involves additional procedures to investigate questionable results. Diagnostic mammography includes additional views, such as spot compression and magnification views, while diagnostic ultrasonography is often used to detect lumps or asymmetries. In some circumstances, breast ultrasonography and diagnostic breast MRI may be employed (17).

- Ultrasonography: Although ultrasound is not used as an initial screening technique for BC, it has been used in addition to mammography in some high-risk groups (18), especially in women with dense breasts. Women with dense breast tissue may experience reduced sensitivity of mammography, and they also have a higher risk of developing BC. Mammography is less effective in these cases due to lower sensitivity (19). Ultrasound is a valuable tool for detecting invasive, small, node-negative cancers in dense breast tissue, a situation where mammography's sensitivity may be greatly diminished. In women with dense breasts, the mammography's sensitivity for detecting cancer can fall from 85% to as low as 47.8% or 64.4%. However, ultrasound can be more effective at detecting these cancers in dense breast tissue, with a sensitivity of up to 90% (20).

- Magnetic resonance imaging (MRI) is a powerful imaging tool that can create high-resolution images of the breast without using harmful radiation. Magnetic resonance imaging creates images of tissue by utilizing a powerful magnetic field combined with radio waves. The images produced by MRI can be used to detect BC, assess the extent of cancer, and guide biopsy procedures (21). Because of its increased sensitivity in identifying BC, breast MRI is largely utilized for screening high-risk people (20). Breast MRI is not utilized for low-risk individuals since it has lesser specificity and is more expensive than mammography (22). If imaging results are concerning or highly suggestive of cancer, tissue diagnosis is needed through core needle biopsy or excisional biopsy. The method of biopsy used is determined for each specific scenario and diagnostic findings (23).

- Fine-needle aspiration biopsy (FNA) can be performed for smaller masses, but core needle biopsy is recommended for nonpalpable tumors. Fine-needle aspiration biopsy has the advantage of being less invasive and less expensive, but core needle biopsy has the following advantages:

1. Greater accuracy: Core needle biopsy is more accurate than FNA in diagnosing nonpalpable tumors.

2. Ability to obtain larger tissue samples: Core needle biopsy can obtain larger tissue samples than FNA, which can be helpful for confirming cancer and for determining the type and grade of cancer (15).

- Excisional biopsy is an option for obtaining larger tissue samples or for specific histologies (22). It is also the best option for determining the depth of a suspected melanoma, as the depth of the lesion offers crucial information for diagnosis and prognosis (24).

### 4. Symptoms

The identification of symptoms is a critical step in the early detection and therapy of BC. A breast lump is the most common BC symptom in women, and it has a roughly high chance of being cancerous (25). A classification system for presenting symptoms was created by grouping individual symptoms into three primary categories (26): (1) Breast lump, (2) non-lump breast symptoms (including breast skin or shape abnormalities, nipple abnormalities, and breast pain), (3) non-breast symptoms (including back pain, neck lump, axillary symptoms, breathlessness, and fatigue).

Another research — Bodai and Tusso — describes the following breast symptoms as being indicative of primary or recurrent/local-regional BC (27): (1) Lump in the breast/chest wall/axilla: This is an abnormal mass in the breast, chest wall, or armpit; (2) dimpling of the skin: This is a change in the appearance of the skin, such as a dent or puckering; (3) nipple retraction: This is the inward pulling of the nipple; (4) clear or bloody nipple discharge: This is a discharge from the nipple that is clear or bloody; (5) redness, scaling, thickening of nipple-areolar complex: This is a change in the appearance of the nipple and areola, such as redness, scaling, or thickening; (6) rash on breast, unresponsive to antibiotics: This is a breast rash that does not get better with antibiotic treatment.

In this investigation, Bodai and Tusso also describe the following breast symptoms as being indicative of distant recurrence of BC (27).

- Continual new-onset localized bone pain for more than 2 weeks (long bones, ribs, spine): This is pain in a bone that has lasted for more than 2 weeks.
- Persistent chest pain, with or without cough: This is pain in the chest that does not go away, and may or may not be accompanied by a cough.
- Persistent abdominal pain: This is pain in the abdomen that does not go away.
- Unintended weight loss: This is weight loss that is not intentional.
- Persistent headache: This is a headache that does not go away.
- Personality changes: This is a change in the way a person thinks, feels, or acts.
- New-onset seizures: This is a sudden attack of uncontrolled electrical activity in the brain.
- Loss of consciousness: This is the loss of awareness of one's surroundings.

## 5. Staging and Prognosis

Classification based on stages: The stage of a BC patient's disease is a major indicator of their likelihood of survival. The TNM staging system is used to classify BCs based on three factors: The size of the primary tumor (T), spread to lymph nodes (N), and distant metastasis (M) (28). Stage 0 is non-invasive cancer, such as ductal carcinoma in situ and lobular carcinoma in situ. These cancers have not spread beyond the breast tissue.

1. Stage I BCs are small and have not spread to lymph nodes.
2. Stage II BCs are larger and may have spread to lymph nodes near the breast.
3. Stage III BCs are larger and have spread to lymph nodes farther from the breast.
4. Stage IV BCs have spread to other parts of the body, such as the bones, liver, or lungs.

Stage 0 - 3 BCs (without distant metastasis) are considered curable, while stage 4 BC (with distant metastasis) is considered incurable (29).

Classification based on molecular subtypes: Breast cancer is a complex disease that has been classified in many ways over the years. In the 2000s, DNA microarrays revealed that BCs can be divided into four molecular subtypes. The four clinically valuable subtypes of BC are luminal A-like, luminal B-like, TNBC, and HER2-positive (21). Each subtype has a different prognosis and requires a different treatment approach (6). For example, luminal A-like BC is typically treated with hormone therapy, while HER2-positive BC is typically treated with targeted therapy (5). By understanding the molecular subtypes of BC, doctors can provide the best possible care for their patients.

## 6. Breast Cancer Prognosis

The prognosis of BC, or how likely a person is to survive the disease, depends on the stage of the cancer at diagnosis and is also population-dependent. In high income countries, for example Canada, USA, and Australia, early-stage BC (stage 0 and stage I) has an excellent prognosis, with a 98% - 100% 5-year survival rate, meaning that 98 to 100 out of 100 people diagnosed with these stages will survive for at least 5 years after diagnosis. The 5-year survival rate for stage II BC is about 92% - 95%, and for stage III BC is about 70% - 75% (e.g., 74% in Canada; 67 - 89% range in Australian data depending on age). However, the prognosis for stage IV BC, which has spread to other parts of the body, is much worse, with only 20% - 30% of patients surviving their next 5 years (30-32). However, overall 5-year survival in many low- and middle-income countries is much lower, often 40 - 60%, largely because a high proportion present with stage III - IV and have limited access to systemic therapy and radiotherapy. Early detection and treatment strategies for BC in low-income and upper middle-income countries: A modelling study.

- Other factors that can affect the prognosis of BC include the patient's age, the tumor grade, the tumor type, and the presence of tumor-infiltrating lymphocytes (6). Understanding these factors aids in determining the patient's outlook and guiding treatment decisions.

- Patients who are diagnosed with BC at a younger age, especially before the age of 35, tend to have better prognoses than older patients (33). Geriatric patients with BC (older than 75 years of age) have a 17% higher risk of dying from the disease than younger patients (34).

## 7. Treatment

Treatment consists of a variety of techniques, each customized to tackle the complexities of BC (35, 36). Surgery, radiation therapy (RT), chemotherapy (CT), endocrine therapy, and targeted therapy are strong foundations of BC treatment, each adding a critical piece to the puzzle of successful intervention.

Surgery: (1) Surgery is an important part of BC treatment. In the past, mastectomy was the most common surgery for BC. But now, breast conservation is the preferred option (37). This means that the surgeon removes the tumor, but not the entire breast. The decision of whether to have breast conservation or mastectomy depends on several factors, including the size of the tumor, the patient's overall health, and the patient's preferences (38); (2) Surgery is usually the first step in BC treatment. But in some cases, it may be done after initial systemic therapy. Systemic therapy is treatment that targets cancer cells throughout the body (6); (3) Over time, BC surgery has evolved to be less aggressive. Clinical trials by the NSABP showed that lumpectomy (removing the tumor) with radiation is just as effective as mastectomy (removing the whole breast) for early-stage BC (39).

Radiation: (1) Radiation therapy is a cancer treatment that uses high-energy beams to kill cancer cells. It is often used after BC surgery to kill any remaining cancer cells and reduce the risk of the cancer coming back. Radiation therapy can also help to improve the chances of survival. The reduction in locoregional recurrences with radiation is about 75% (6). Radiation therapy in BC may be delivered to the whole breast or a portion of the breast (after lumpectomy), the chest wall (after mastectomy), and the regional lymph nodes (40). Postlumpectomy whole-breast radiation is a standard

component of breast-conserving therapy (41); (2) Radiation therapy after surgery can shrink the tumor in combination with CT. However, RT can also cause some side effects, such as decreased sensation in the breast tissue or under the arm, skin problems in the treated area, such as soreness, itching, peeling, and redness, and at the end of treatment, the skin may become moist and weepy (42); (3) Radiation therapy has also improved with time. Studies have shown that adding radiation after lumpectomy reduces the risk of cancer returning and improves survival (43). New techniques like partial breast irradiation have emerged, offering similar effectiveness in reducing local recurrence while causing fewer side effects (44).

Systemic therapy. Systemic therapy is a type of treatment that travels through the bloodstream to reach cancer cells throughout the body. Systemic therapies for early BC are very effective, and both adjuvant endocrine therapy and adjuvant CT can reduce BC mortality by about one-third (45).

Hormonal therapy: (1) Hormone therapy, also known as endocrine therapy, is a type of treatment that can slow or stop the growth of hormone-sensitive tumors. Hormonal therapy is a very effective treatment for BC, especially in women whose tumors are ER-positive (46). Hormones are substances produced by glands in the body and circulated in the bloodstream. Hormone-sensitive tumors are tumors that need hormones to grow. BC cells are often hormone-sensitive, meaning that they need estrogen or progesterone to grow (47); (2) The choice of medication is primarily determined by the patient's menopausal status. Other factors include differences in efficacy and side effect profile (21); (3) The first hormonal therapy for BC was the removal of the ovaries, which produce estrogen. This targeted the dependency of breast tumors on estrogen, which is secreted by the ovaries. In recent years, new drugs have been developed that target other pathways involved in BC growth, such as CDK4/6 inhibitors and mTOR inhibitors (48, 49). However, extended endocrine therapy is associated with ongoing treatment-related symptoms and risk of life-threatening toxicities (50).

Target therapy: (1) The phosphatidylinositol 3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway is often dysregulated in BC (51). Studies have shown that inhibitors of mTOR can have antitumor activity in a variety of cancer types, including hormone receptor-positive BC (52); (2) CDK targeting has emerged

as a new treatment option for hormone-positive BC in recent years. CDKs (cyclin-dependent kinases) are proteins that control the cell cycle, and targeting them can help to reestablish cell cycle control and stop cancer cells from growing (53).

Chemotherapy: (1) Chemotherapy is a systemic treatment for BC that uses drugs to kill or stop the growth of cancer cells (54). In CT, the drugs are injected into a vein or taken by mouth, and they enter the bloodstream to reach cancer cells throughout the body (55); (2) Chemotherapy can cause a number of problems. The short-term effects are: GI tract symptoms, hair loss, bone marrow suppression, and the long-term effects: Reduced muscle strength, increased lymphedema (56). Lymphedema is a condition that causes swelling in one or both arms, similar to BC. It can be caused by a number of factors, including high Body Mass Index (BMI), mastectomy, the number of lymph nodes removed, and axillary lymph node dissection (57). Symptoms of lymphedema include pain, heaviness, tightness, and decreased range of motion; (3) Despite the risks, CT is still a critical treatment for preventing recurrence in many patients with stage I-III BC. It is the only systemic therapy that has been shown to be effective in the TNBC, and it is an important addition to endocrine therapy or ERBB2-directed therapy in patients with HR+/ERBB2- or ERBB2+BC, respectively (40); (4) Chemotherapy is a standard treatment for high-risk BC. The most common CT regimens include doxorubicin and cyclophosphamide followed by paclitaxel (AC-T), weekly paclitaxel, or every 3 weekly docetaxel (58). Chemotherapy is more effective in reducing recurrence and BC mortality in patients with HR negative disease (45).

By coordinating these techniques, healthcare practitioners can improve not just patients' quality of life but also their chances of long-term recovery.

## 8. Survivorship

The incidence of BC in young women has increased over time, but the survival rate has also increased significantly. This is especially true for metastatic BC, where the survival rate has increased by more than 20% since 2005 (59). These findings suggest that early detection and improved treatment are leading to better outcomes for young women with BC. A comprehensive analysis of 130 studies on BC revealed global survival rates for women at different time frames (57). The

pooled rates of survival were 0.92 at 1 year, 0.75 at 3 years, 0.73 at 5 years, and 0.61 at 10 years. Survival rates were generally higher in developed regions compared to developing regions, and younger women had better survival outcomes than older women. Furthermore, early-stage diagnoses were associated with improved survival rates. Overall, the rates of survival in 2010 to 2017 were significantly higher than those in the 1969 to 1960 period (60).

The fight against BC presents a challenging landscape. According to a study, the overall mortality rate of BC stood at 16.9 per 100 person-years observation. The median survival time was found to be 38.3 months (with an interquartile range of 26.23 to 49.4 months) as reported in the study (61).

Another research highlights that the survival of BC patients is influenced by a multitude of factors, spanning socio-demographic variables such as age, educational level, financial status, and family history (59). Moreover, pathological and clinical features of the tumor – such as its size, lymph node involvement, presence of metastasis, clinical stage, anatomical location, and histological grade – are key factors influencing patient outcomes (59). Moreover, the presence of co-morbidities and the type of treatment received by patients also impact their survival prospects (62).

## 9. Breast Cancer Survivors' Needs and Cares

Breast cancer survivors (BCSs) have a variety of needs that extend beyond medical therapy. These requirements include mental health, physical wellness, and long-term issues. Understanding and satisfying these needs is critical to assisting survivors on their path.

- Psychological/emotional needs: (1) The most frequently reported psychological and emotional needs of BCSs were depression, anxiety, and stress (63), as well as fears about cancer spread and recurrence (64). Other needs included fear of disclosure, uncertainty about the future, stigma associated with cancer, frustration, low mood, and isolation (65). Another study found that psychosocial interventions for patients with BC in South Korea have a large effect on reducing negative emotions and enhancing quality of life (66); (2) Breast cancer survivors have a wide range of psychological needs, including spiritual, communication, interpersonal, social, and family-related needs (67). It is important to

be flexible and responsive to the changing needs of BCSs. BCSs may not always be comfortable talking about their needs, so it is crucial to generate a safe and supportive space where they feel comfortable sharing their thoughts and feelings.

- Health/physical needs: (1) The most common physical symptoms reported by BCSs were fatigue and pain (68). Pain, fatigue, and depressive symptoms are often found together in cancer patients, both those receiving curative and palliative care. This cluster of symptoms is often accompanied by sleep disturbances (69).

Long-term health issues: In addition to the physical and emotional challenges of BC, survivors may also face a number of long-term health issues.

- Cardiotoxicity after Adjuvant Therapy: (1) Cardiac toxicity is a serious side effect of BC adjuvant treatments. It can occur years after treatment, and is most commonly associated with the use of anthracyclines and trastuzumab. Endocrine therapy and chest wall radiotherapy, especially when the left breast is involved, can also increase the risk of cardiac toxicity (70); (2) Cardiac toxicity is caused by a direct effect on heart muscle cells, which can lead to cell death and a decrease in the pumping ability of the heart. This can result in a reduction in left ventricular ejection fraction (LVEF), which is a factor of how well the heart is pumping. In some cases, this can lead to symptomatic congestive heart failure (71).

- Fertility impairment: (1) The risk of fertility impairment is a growing concern for younger women with BC who are candidates for systemic adjuvant therapies. This is because the incidence of BC in European women in their 20 s and 30 s is increasing, and CT drugs can cause premature ovarian failure, which is the loss of ovarian function before the age of 40 (72).

## 10. Conclusions

Advances in the diagnosis and treatment of BC have improved the ability to stratify patients by risk and allowed clinicians to recommend therapy based on cancer prognosis and patient preference. Breast cancer treatment is complex and involves a combination of different modalities, including surgery, radiotherapy, CT, hormonal therapy, and targeted therapy. Treatment plans are customized to address the complexities of

each individual case. Most women with early-stage BC are treated with surgery, often followed by RT, and many also get some kind of systemic drug therapy. The more the BC has spread, the more treatment is needed.

## Footnotes

**AI Use Disclosure:** The authors declare that no generative AI tools were used in the creation of this article.

**Authors' Contribution:** Study concept and design: T. T. N. and H. G.; Analysis and interpretation of data: M. N. and H. G.; Drafting of the manuscript: M. N.; Critical revision of the manuscript for important intellectual content: M. N., H. G., and R. S.

**Conflict of Interests Statement:** The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

**Funding/Support:** No funding was received for this research.

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