

Breast Cancer: Complex Etiology, Early Detection, and Evolving Therapeutic Strategies for Improved Outcomes

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Abstract

Breast cancer (BC) is a major global health concern in the 21st century, influenced by complex carcinogenesis involving genetic, environmental, and ethnic factors. It is the most common cancer among women worldwide, accounting for 11.7% of all cancer cases, with over 2.2 million new diagnoses and more than half a million deaths annually. Key risk factors include age (most cases occur in women over 40), ethnicity (with African American and Hispanic women experiencing poorer survival), and genetic mutations such as BRCA1/2. Other contributors include hormonal exposure, breast density, obesity, alcohol use, and reproductive history.

Epidemiologically, breast cancer incidence and mortality rates vary widely by region and development status, with higher rates found in countries with very high Human Development Index (HDI). Survival rates are markedly better in regions with advanced healthcare systems. Common signs include breast lumps, changes in breast size or shape, skin and nipple alterations, and unexplained pain. Treatment modalities encompass surgery (breast-conserving or mastectomy), chemotherapy (adjuvant/neoadjuvant), radiation therapy, endocrinal therapy targeting hormone receptors, and emerging biological therapies focused on molecular targets like HER2 and CDK4/6.

Overall, breast cancer's complexity demands multifaceted approaches incorporating early detection, personalized treatment based on genetic and molecular profiles, and addressing socio-demographic disparities. Advances in targeted therapies and better understanding of risk factors are vital for improving prognosis and survival globally.

Keywords: Breast cancer (BC), Global health concern, Carcinogenesis, Human Development Index (HDI), BRCA1/2 mutations

Introduction

In the 21st-century global epidemiological, ethnic, and environmental milieu, breast cancer (BC) is a major concern. Cancer can develop from a complex process called carcinogenesis that affects diverse cells, tissues, and organs. The ability to spread to other parts of the body (metastasis), resistance to factors that inhibit growth, rapid cell division, increased blood vessel formation (angiogenesis), avoidance of cell death (apoptosis), and activation of growth-promoting signals are some of the key pathological mechanisms involved [1]. The process of carcinogenesis is complex and influenced by both environmental and genetic variables. Every year, the number of deaths from cancer increases, making it one of the world's top causes of death. Although a large number of malignancies may not always result in death, they frequently result in a considerable reduction in life quality and huge financial costs. With an expected 2.3 million new cases worldwide, breast cancer is the sixth most prevalent cause of cancer-related deaths and one of the most frequently diagnosed malignancies, according to GLOBOCAN 2020 estimates [2]. Breast cancer (BC) now accounts for 11.7% of all cancer cases worldwide, making it the most common cause of cancer. Globally, more than half a million women die from BC each year, and over 2.2 million are diagnosed with the condition, according to World Health Organization (WHO) and current research conducted in 2021 and 2022 [3]. This indicates that breast cancer accounts for about 20–35% of cancer cases and 15–16% of cancer deaths [2–4]. Experts worry that if this trend continues, processed foods and population expansion may cause more than 3 million more instances of cancer in British Columbia each year in 20 years [4,5]. Cancer cells share similar (but not identical) DNA and RNA with the cells of the organism from which they arose. Because of their resemblance, the immune system finds it challenging to identify them, particularly in cases where it is compromised [6].

Considering the age of incidence for BC as well as the 5-year survival, data collected from practice and multiple studies suggest that age is considered the most important risk factor in developing this disease. Up to 95% of cancer cases occur in women aged 40 or older. The median age at the time of diagnosis has been found to be 61 years old [7,8]. Ethnicity also plays an important part in this pathology. Several early studies stated that African American and Hispanic women have inferior BC survival rates compared to Caucasian women, even though non-Caucasian women have a lower incidence of developing the disease. Asian or Asian/Pacific Islander (API) ethnicity was associated with better survival outcomes in multivariable analyses. African American ethnicity is usually associated with an increased frequency of the aggressive triple-negative BC (TNBC) subtype and is considered to be an independent predictor of a poor outcome, a situation also observed in Australian aboriginal communities, Malay ethnicity, and minority immigrant populations [9]. Regarding the genetic mutations that are

known to increase the risk of developing BC, the European Society of Breast Cancer Specialists (EUSOMA) estimates that 3% of all BC cases are caused by an underlying deleterious mutation of the BRCA1 or BRCA2 genes [10]. BRCA genes play a very important part in the BC genetic etiology because of their role in repairing damaged DNA. Furthermore, mutations of the BRCA genes are also associated with an increased risk of ovarian cancer. In the case of clinically significant mutations, the estimated lifetime risk is about 80% for BC and 40–65% for ovarian cancer. Ovarian cancer is considered another public health problem known to have a poor prognosis, ranked as the seventh most common cancer type in women in terms of incidence and mortality worldwide [11–13]. Recent research has pointed out that BRCA1 mutation carriers with BC had more chances of developing TNBC than BRCA2 mutation carriers or non-carriers [14]. A smaller percentage of BCs are caused by TP53 mutations or, in rare cases, by moderate penetrance alleles such as CHEK2, ATM, and BRIP1 [15,16]. Other less frequent mutations or proliferation markers have been correlated with certain molecular BC subtypes. Antigen Ki-67, also known as Ki-67 or marker of proliferation Ki-67 (MKI67), is a protein whose expression reliably correlates with cancer proliferation [17]. Immunohistochemical evaluation of this marker has been used for years to indicate cancer prognosis, outcome, and treatment response. PIK3CA gene mutations can lead to the overactivity of the PI3K enzyme, promoting the growth of cancer cells. Even though changes in the PI3K gene can cause a variety of cancers, when referring to BC, PI3K mutation or amplification and other aberrations in the PI3K signaling pathway can often be observed in hormone receptor-positive (HR+) BC. In recent years, PIK3CA inhibitors, such as alpelisib, have shown significant progress in HR+/HER2-negative (HER2-) metastatic BC [18].

The cell cycle

In cancerous cells, the process of cell division is disrupted and unregulated, resulting in cell proliferation and tumor growth. The normal cell cycle is as represented in figure 1

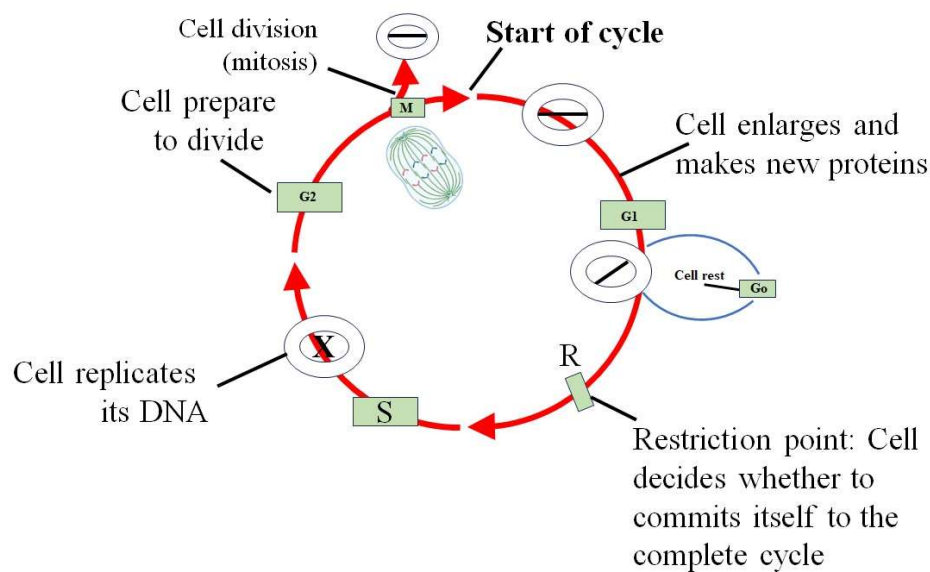


Figure 1 Stage of normal cell cycle

Epidemiology:

The World Health Organization (WHO) reports that malignant neoplasms represent the largest global health burden for women, accounting for an estimated 107.8 million Disability-Adjusted Life Years (DALYs), with 19.6 million DALYs attributed specifically to breast cancer [19]. Breast cancer is the most commonly diagnosed cancer among women globally, with 2.26 million new cases (95% UI, 2.24–2.79 million) reported in 2020. In the United States, breast cancer is projected to represent 29% of all new cancer cases in women. The 2018 GLOBOCAN data indicates a strong positive correlation between age-standardized incidence rates (ASIR) of breast cancer and the Human Development Index (HDI). In 2020, the ASIR was highest in countries with a very high HDI (75.6 per

100,000), while it was over 200% lower in countries with medium and low HDI (27.8 per 100,000 and 36.1 per 100,000, respectively) [20,21].

In 2020, the breast cancer mortality-to-incidence ratio (MIR), which reflects 5-year survival rates, was 0.30 worldwide. In regions with advanced healthcare systems (such as Hong Kong, Singapore, and Turkey), the 5-year survival rates were 89.6% for localized breast cancer and 75.4% for regional cancer. In contrast, in less developed countries (including Costa Rica, India, the Philippines, Saudi Arabia, and Thailand), the survival rates were lower, at 76.3% for localized and 47.4% for regional breast cancer [22,23].

Risk factor for developing breast cancer among women:

➤ **Previous diagnosis of breast cancer:**

Women who have previously had breast cancer face a higher risk of it returning. The second occurrence can develop in the same breast or in the other one. While most women with ductal carcinoma in situ or lobular carcinoma in situ do not experience a recurrence, they are still at an elevated risk of it happening [24].

➤ **A family history of breast cancer and other types of cancer:**

When breast cancer is present in one or more close blood relatives, it suggests that the disease may be hereditary. In some families, there are more cases of breast cancer than would be expected by chance. Determining whether this pattern is due to coincidence, shared lifestyle factors, inherited genes, or a combination of these elements can be challenging.[25]

➤ **Breasts of large sizes:**

Dense breasts contain more milk ducts, glands, and connective tissue than fatty tissue. Breast density is inherited, and women with denser breasts have a higher risk of developing breast cancer compared to those with little or no dense tissue. Mammograms are the only way to detect breast density, but dense tissue can make the images harder to read. On a mammogram, dense tissue appears white, similar to tumors, while fatty tissue appears dark, which can hide a tumor.[26]

➤ **The late menopause:**

Menopause occurs when the ovaries stop producing hormones, particularly estrogen and progesterone, leading to a decline in hormone levels and the cessation of the menstrual cycle. If menopause happens later in life (after age 55), the body is exposed to estrogen and other hormones for a longer time, which increases the risk of breast cancer. In contrast, if menopause occurs earlier, the exposure to these hormones is shorter, which is linked to a lower risk of breast cancer.[27]

➤ **Whether a woman has delayed or no pregnancies:**

Pregnancy interrupts the exposure of breast cells to circulating estrogen and also decreases the total number of menstrual cycles a woman has over her lifetime. A woman's risk of breast cancer is slightly higher if she has no pregnancies or if her first full-term pregnancy occurs after the age of 30. Early pregnancy is linked to a reduced breast cancer risk, and having more children offers greater protection. Conversely, a woman who never becomes pregnant faces an increased risk of breast cancer [28].

Causes of breast cancer:

The detailed description of causes of breast cancer is given in table 1

Table 1: Causes of breast cancer

Sr.no.	Causes	Description
1	Genetic factors	Inherited mutations in genes like BRCA1 and BRCA2 significantly increase the risk of breast cancer [29].
2	Hormonal factors	Hormones like estrogen and progesterone influence breast cancer development. Longer exposure to these hormones increases risk [30].

3	Obesity and diet	Overweight and obesity, especially after menopause, are linked to higher estrogen levels, increasing risk [31].
4	Alcohol consumption	Regular alcohol consumption is linked to an increased risk of breast cancer, even with moderate intake [31].
5	Physical activity	Sedentary lifestyle contributes to an increased risk of developing breast cancer [31].

Sign and symptoms:

The detailed description of sign and symptoms of breast cancer is given in table 2.

Table 2: Sign and Symptoms of breast cancer

Sr.no.	Symptoms	Description
1	Lump in the Breast	A new lump or mass in the breast, often felt during self-examination. It can be painless or painful and may have irregular edges [32].
2	Change in Breasts Size and shape	Noticeable changes in size, shape or symmetry of the breast. The breast may appear swollen or asymmetrical [33].
3	Skin changes	Skin over the breast may become red, dimpled, or resemble the texture of an orange peel [34].
4	Nipple changes	Nipple inversion, itching, scaling, or unusual discharge (not breast milk) may occur [32].
5	Unexplained pain	Persistent pain in the breast or nipple, especially if it doesn't correlate with the menstrual cycle [33].

Treatment of Breast cancer:

➤ Surgery

Breast-conserving surgery (BCS) and mastectomy are the two main surgical procedures that allow the removal of breast cancerous tissues. BCS, sometimes known as a quadrantectomy, lumpectomy, wide local excision, or partial/segmental mastectomy, allows for the removal of cancerous tissue while simultaneously preserving healthy breast tissue. It is frequently used in conjunction with oncoplastic, a type of plastic surgery. A mastectomy is the total removal of the breast, and it is frequently followed right away by breast reconstruction. Both axillary lymph node dissection (ALND) and sentinel lymph node biopsy (SLNB) are used to remove the afflicted lymph nodes. Although BCS appears to be much more advantageous for patients, patients who receive this treatment frequently exhibit a propensity to require a full mastectomy in the future [35]. But the use of BCS is primarily linked to far superior cosmetic results, less psychological strain on the patient, and less postoperative problems [36]. According to the European Society for Medical Oncology's (ESMO) guidelines, the size of the tumor, the patient's desire to save their breast, the clinical phenotype, and the practicality of surgery all influence the therapy option for patients with early-stage breast cancer [37].

➤ Chemotherapy

One systemic treatment for BC is chemotherapy, which can be either adjuvant or neoadjuvant. Each person's choice is unique based on the characteristics of the breast tumor; chemotherapy may also be utilized for the secondary breast cancer. In order to downstage large tumors to allow for BCS or in small tumors with worse prognostic molecular subtypes (such as HER2 or TNBC), neoadjuvant chemotherapy is used for locally advanced BC and inflammatory breast cancers. It can be administered intravenously or orally and can be used to determine prognostics and predictive factors of response. Drugs such as carboplatin, cyclophosphamide, 5-

fluorouracil/capecitabine, taxanes (paclitaxel, docetaxel), and anthracyclines (doxorubicin, epirubicin) are being used in combination as part of treatment schemes 2-4. Given that many genetic breast cancer subtypes react differently to preoperative chemotherapy, selecting the right medication is crucial [38]. Chemotherapy before and after surgery is equally effective [39].

➤ **Radiation Therapy**

After surgery and/or chemotherapy, radiotherapy is usually used to treat BC locally. It is done to reduce the chance of breast cancer returning by ensuring that all of the malignant cells are eliminated. Furthermore, when breast cancer is metastatic or incurable, radiation therapy is beneficial [40]. The type of radiation therapy used depends on the type of surgery that was done previously or on the particular clinical situation. The most common techniques are breast radiotherapy, which is always applied after breast cancer surgery, chest-wall radiotherapy, which is typically applied after mastectomy, and "breast boost," which is a boost of high-dose radiation to the location of the tumor bed as a complement to breast radiotherapy after breast cancer surgery. Particularly speaking, there are various forms of breast radiation, including as

1. intraoperative radiation therapy (IORT)
2. 3D-conformal radiotherapy (3D-CRT)
3. intensity-modulated radiotherapy (IMRT)
4. brachytherapy—which refers to internal radiation in contrast to other above-mentioned techniques.

Fatigue, lymphoedema, and skin irritation and darkening from radiation exposure are some of the most frequent adverse effects of radiation therapy for women with breast cancer. Nevertheless, radiation treatment is strongly linked to increased patient survival rates overall and decreased recurrence risk [41].

➤ **Endocrinal (Hormonal) Therapy**

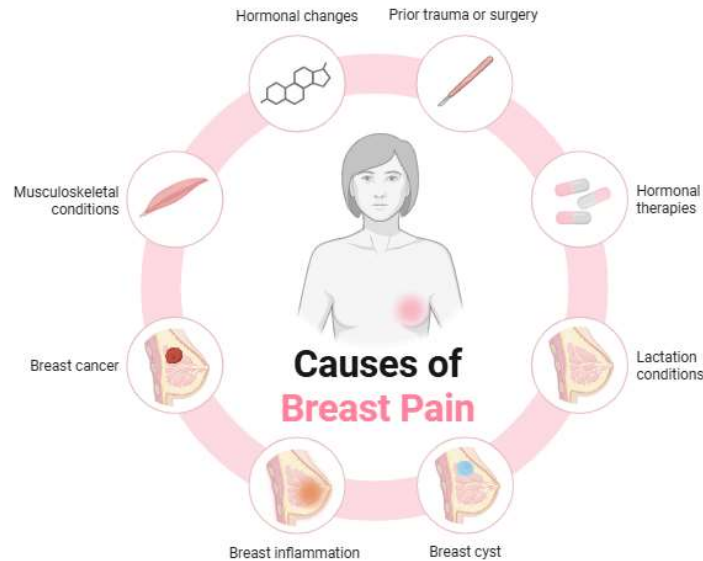
Endocrine therapy is useful in cases of breast cancer metastasis or recurrence and can be utilized as an adjuvant or neoadjuvant treatment for individuals with the Luminal-molecular subtype of BC. Since the expression of ERs is a regular occurrence in individuals with breast cancer, blocking it with hormone therapy is frequently employed as a possible therapeutic approach. Lowering estrogen levels or stopping estrogen from stimulating breast cancer cells are the goals of endocrine therapy. Selective estrogen receptor degraders (SERDs) like fulvestrant and selective estrogen receptor modulators (SERMs) like tamoxifen and toremifene are medications that block ERs, while aromatase inhibitors (AIs) like letrozole, anastrozole, and exemestane are therapies that try to reduce estrogen levels [42,43]. Lowered estrogen levels in premenopausal women can also be achieved through ovarian suppression brought on by oophorectomy, luteinizing hormone-releasing hormone analogs, or a number of chemotherapy medications [44]. However, with such treatment, about 50% of hormone-receptor-positive breast cancers develop increasing resistance to hormonal therapy [45]. Chemotherapy and endocrine therapy together have been linked to lower death rates for people with breast cancer [46].

➤ **Biological Therapy**

Targeted therapy, or biological therapy, can be administered at any point throughout breast therapy, either as adjuvant therapy following surgery or as neoadjuvant therapy prior to surgery. Among the main medications used in biological therapy for individuals with HER2-positive breast cancer are trastuzumab, pertuzumab, trastuzumab deruxtecan, lapatinib, and neratinib [47-51]. The effectiveness of angiogenesis inhibitors, such as bevacizumab or a recombinant humanized monoclonal anti-VEGF antibody (rhuMAb VEGF), is also being regularly studied [52].

For Luminal, HER2-negative breast cancer, postmenopausal women frequently take CDK4-6 inhibitor palbociclib or ribociclib concurrently with hormonal therapy, but premenopausal women are more likely to receive everolimus-TOR inhibitor with exemestane [53-55]. Abemaciclib, everolimus, and two penultimate medications can also be utilized to treat HER2-negative and estrogen-positive breast cancers [56,57]. Denosumab is authorized in cases of bone metastases, whereas atezolizumab is authorized for triple-negative breast cancer [58-60].

Causes of Breast cancer [61]



Conclusion

Breast cancer remains a major global health challenge, characterized by complex interactions between genetic, environmental, hormonal, and lifestyle factors. Its incidence and mortality vary significantly across different regions and ethnic groups, underscoring the impact of socio-demographic disparities and healthcare access. Genetic mutations such as BRCA1/2 play a critical role, alongside modifiable risk factors like obesity, alcohol consumption, and reproductive history.

Early detection and accurate diagnosis are essential to improving survival, as breast cancer can present with diverse signs such as lumps, changes in breast size or skin texture, and nipple alterations. Treatment strategies are multifaceted, including surgery, chemotherapy, radiation, endocrine therapy, and advanced targeted biological therapies tailored to the tumour's molecular profile. These interventions aim to maximize efficacy while minimizing adverse effects and preserving quality of life.

To reduce the global burden of breast cancer, comprehensive approaches integrating prevention, personalized treatment, and equity in healthcare delivery are vital. Continued research into genetic markers and novel therapies, alongside public health efforts targeting lifestyle risk factors and early screening, will enhance outcomes and survival rates worldwide.

REFERENCES

1. Łukasiewicz, S.; Czezelewski, M.; Forma, A.; Baj, J.; Sitarz, R.; Stanisławek, A. Breast cancer—Epidemiology, risk factors, classification, prognostic markers, and current treatment strategies—An updated review. *Cancers* 2021, 13, 4287.
2. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J. Clin.* 2021, 71, 209–249.
3. Sharma, R. Global, regional, national burden of breast cancer in 185 countries: Evidence from GLOBOCAN 2018. *Breast Cancer Res. Treat.* 2021, 187, 557–567.
4. Arnold, M.; Morgan, E.; Rumgay, H.; Mafra, A.; Singh, D.; Laversanne, M.; Vignat, J.; Gralow, J.R.; Cardoso, F.; Siesling, S.; et al. Current and future burden of breast cancer: Global statistics for 2020 and 2040. *Breast* 2022, 66, 15–23.
5. Smolarz, B.; Zadrozna Nowak, A.; Romanowicz, H. Breast Cancer—Epidemiology, Classification, Pathogenesis and Treatment (Review of Literature). *Cancers* 2022, 14, 2569.
6. Cancer-Its various types along with causes, symptoms, treatments and stages, in: cancer info guide, 2009. <http://www.cancer-info-guide.com/> (15 Mar. 2010).
7. Loibl, S.; Poortmans, P.; Morrow, M.; Denkert, C.; Curigliano, G. Breast cancer. *Lancet* 2021, 397, 1750–1769.
8. VanderWalde, A.; Hurria, A. Early breast cancer in the older woman. *Clin. Geriatr. Med.* 2012, 28, 73–91.
9. Yap, Y.S. Outcomes in breast cancer—Does ethnicity matter? *ESMO Open* 2023, 8, 101564.
10. Yoshida, R. Hereditary breast and ovarian cancer (HBOC): Review of its molecular characteristics, screening, treatment, and prognosis. *Breast Cancer* 2021, 28, 1167–1180.
11. Fu, X.; Tan, W.; Song, Q.; Pei, H.; Li, J. BRCA1 and Breast Cancer: Molecular Mechanisms and Therapeutic Strategies. *Front. Cell Dev. Biol.* 2022, 10, 813457.
12. Cobec, I.; Sas, I.; Moatar, A.; Moleriu, L.; Rempen, A. Ovarian cancer health politics in Romania and Germany: A comparative study. *Exp. Ther. Med.* 2021, 22, 1217.
13. Cobec, I.M.; Popescu, R.; Moatar, A.E.; Verdes, D. Ovarian Cancer under the Magnifying Glass. *August Rom. J. Mil. Med.* 2021, 124, 291–296.
14. Chen, H.; Wu, J.; Zhang, Z.; Tang, Y.; Li, X.; Liu, S.; Cao, S.; Li, X. Association between BRCA status and triple-negative breast cancer: A meta-analysis. *Front. Pharmacol.* 2018, 9, 909.
15. Breast Cancer Association Consortium. Breast Cancer Risk Genes—Association Analysis in More than 113,000 Women. *N. Engl. J. Med.* 2021, 384, 428–439.
16. Shahbandi, A.; Nguyen, H.D.; Jackson, J.G. TP53 Mutations and Outcomes in Breast Cancer: Reading beyond the Headlines. *Trends Cancer* 2020, 6, 98–110.
17. Davey, M.G.; Hynes, S.O.; Kerin, M.J.; Miller, N.; Lowery, A.J. Ki-67 as a prognostic biomarker in invasive breast cancer. *Cancers* 2021, 13, 4455.
18. Fusco, N.; Malapelle, U.; Fassan, M.; Marchiò, C.; Buglioni, S.; Zupo, S.; Criscitiello, C.; Vigneri, P.; Dei Tos, A.P.; Maiorano, E.; et al. PIK3CA Mutations as a Molecular Target for Hormone Receptor-Positive, HER2-Negative Metastatic Breast Cancer. *Front. Oncol.* 2021, 11, 644737.
19. World Health Organization. Global Health Estimates 2016: Disease Burden by Cause, Age, Sex, by Country and by Region, 2000–2016; World Health Organization: Geneva, Switzerland, 2018; Available online: https://www.who.int/healthinfo/global_burden_disease/estimates/en/index1.html (accessed on 9 July 2021).
20. Ferlay J., Ervik M., Lam F., Colombet M., Mery L., Piñeros M., Znaor A., Soerjomataram I., Bray F. Global Cancer Observer: Cancer Today. International Agency for Research on Cancer, Lyon, France: 2020. [(accessed on 9 July 2021)]. Available online: <https://gco.iarc.fr/today>. [Google Scholar]
21. Sharma R. Global, regional, national burden of breast cancer in 185 countries: Evidence from GLOBOCAN 2018. *Breast Cancer Res. Treat.* 2021;187:557–567. doi: 10.1007/s10549-020-06083-6. [DOI] [PubMed] [Google Scholar]
22. Vostakolaei F.A., Karim-Kos H.E., Janssen-Heijnen M.L.G., Visser O., Verbeek A.L.M., Kiemeny L. The validity of the mortality to incidence ratio as a proxy for site-specific cancer survival. *Eur. J. Public Health.* 2010;21:573–577. doi: 10.1093/eurpub/ckq120. [DOI] [PubMed] [Google Scholar]
23. Sankaranarayanan R., Swaminathan R., Brenner H., Chen K., Chia K.S., Chen J.-G., Law S.C., Ahn Y.-O., Xiang Y.B., Yeole B.B., et al. Cancer survival in Africa, Asia, and Central America: A population-based study. *Lancet Oncol.* 2010;11:165–173. doi: 10.1016/S1470-2045(09)70335-3. [DOI] [PubMed] [Google Scholar]
24. Buist DSM, Abraham L, Lee CI, et al. Breast biopsy intensity and findings following breast cancer screening in women with and without a personal history of breast cancer. *JAMA Intern Med.* 2018;178:458–68.
25. Maio F, Tari DU, Granata V, et al. Breast cancer screening during COVID-19 emergency: patients and department management in a local experience. *J Pers Med.* 2021;11:380.
26. Thigpen D, Kappler A, Brem R. The role of ultrasound in screening dense breasts—a review of the literature and practical solutions for implementation. *Diagnostics.* 2018;8:20.

27. Vatankhah H, Khalili P, Vatanparast M, et al. Prevalence of early and late menopause and its determinants in Rafsanjan cohort study. *Sci Rep.* 2023;13:1847.
28. Garnæs KK, Elvebakk T, Salvesen O, et al. Dietary intake in early pregnancy and glycemia in late pregnancy among women with obesity. *Nutrients.* 2022;14:105.
29. Miki, Y., et al. (1994). "BRCA1 Gene." *Science*, 266(5182), 66-71. DOI: 10.1126/science.7915170
30. Collaborative Group on Hormonal Factors in Breast Cancer (2019). "Menarche, Menopause, and Breast Cancer Risk." *Lancet*, 393(10175), 308-318. DOI: 10.1016/S0140-6736(18)31955-4
31. World Cancer Research Fund/American Institute for Cancer Research (2018). "Diet, Nutrition, Physical Activity and Breast Cancer." [AICR Report](#)
32. American Cancer Society (2024). "Signs and Symptoms of Breast Cancer." [American Cancer Society](#)
33. National Cancer Institute (2023). "Breast Cancer Symptoms." [NCI](#)
34. Mayo Clinic (2023). "Breast Cancer Symptoms and Causes." [Mayo Clinic](#)
35. Morrow, M.; White, J.; Moughan, J.; Owen, J.; Pajack, T.; Sylvester, J.; Wilson, J.F.; Winchester, D. Factors Predicting the Use of Breast-Conserving Therapy in Stage I and II Breast Carcinoma. *J. Clin. Oncol.* 2001, 19, 2254–2262. [CrossRef].
36. Rahman, G.A. Breast conserving therapy: A surgical technique where little can mean more. *J. Surg. Tech. Case Rep.* 2011, 3, 1–4. [CrossRef].
37. Cardoso, F.; Kyriakides, S.; Ohno, S.; Penault-Llorca, F.; Poortmans, P.; Rubio, I.; Zackrisson, S.; Senkus, E. Early breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* 2019, 30, 1194–1220. [CrossRef].
38. Rouzier, R.; Perou, C.; Symmans, W.F.; Ibrahim, N.; Cristofanilli, M.; Anderson, K.; Hess, K.R.; Stec, J.; Ayers, M.; Wagner, P.; et al. Breast Cancer Molecular Subtypes Respond Differently to Preoperative Chemotherapy. *Clin. Cancer Res.* 2005, 11, 5678–5685. [CrossRef].
39. Fisher, B.; Bryant, J.; Wolmark, N.; Mamounas, E.; Brown, A.; Fisher, E.R.; Wickerham, D.L.; Begovic, M.; DeCillis, A.; Robidoux, A.; et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J. Clin. Oncol.* 1998, 16, 2672–2685. [CrossRef] [PubMed].
40. Yang, T.J.; Ho, A.Y. Radiation Therapy in the Management of Breast Cancer. *Surg. Clin. N. Am.* 2013, 93, 455–471. [CrossRef] [PubMed]
41. Joshi, S.C.; Khan, F.A.; Pant, I.; Shukla, A. Role of Radiotherapy in Early Breast Cancer: An Overview. *Int. J. Health Sci.* 2007, 1, 259–264.
42. Lumachi, F.; Luisetto, G.; Basso, S.M.M.; Basso, U.; Brunello, A.; Camozzi, V. Endocrine Therapy of Breast Cancer. *Curr. Med. Chem.* 2011, 18, 513–522. [CrossRef] [PubMed]
43. Tremont, A.; Lu, J.; Cole, J.T. Endocrine Therapy for Early Breast Cancer: Updated Review. *Ochsner J.* 2017, 17, 405–411. [PubMed]
44. Jones, K.L.; Buzdar, A.U. A review of adjuvant hormonal therapy in breast cancer. *Endocr.-Related Cancer* 2004, 11, 391–406. [CrossRef] [PubMed]
45. Drăgănescu, M.; Carmocan, C. Hormone Therapy in Breast Cancer. *Chirurgia* 2017, 112, 413–417. [CrossRef] [PubMed]
46. Abe, O.; Abe, R.; Enomoto, K.; Kikuchi, K.; Koyama, H.; Masuda, H.; Nomura, Y.; Sakai, K.; Sugimachi, K.; Tominaga, T.; et al. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. *Lancet* 2005, 365, 1687–1717. [CrossRef]
47. Maximiano, S.; Magalhães, P.; Guerreiro, M.P.; Morgado, M. Trastuzumab in the Treatment of Breast Cancer. *Bio. Drugs* 2016, 30, 75–86. [CrossRef]
48. Ishii, K.; Morii, N.; Yamashiro, H. Pertuzumab in the treatment of HER2-positive breast cancer: An evidence-based review of its safety, efficacy, and place in therapy. *Core Evid.* 2019, 14, 51–70. [CrossRef]
49. Nguyen, X.; Hooper, M.; Borlagdan, J.P.; Palumbo, A. A Review of Fam-Trastuzumab Deruxtecan-nxki in HER2-Positive Breast Cancer. *Ann. Pharmacother.* 2021. [CrossRef]
50. Moreira, C.; Kaklamani, V. Lapatinib and breast cancer: Current indications and outlook for the future. *Expert Rev. Anticancer. Ther.* 2010, 10, 1171–1182. [CrossRef]
51. Park, J.W.; Liu, M.C.; Yee, D.; Yau, C.; Veer, L.J.V.; Symmans, W.F.; Paoloni, M.; Perlmutter, J.; Hylton, N.M.; Hogarth, M.; et al. Adaptive Randomization of Neratinib in Early Breast Cancer. *N. Engl. J. Med.* 2016, 375, 11–22. [CrossRef]
52. Pegram, M.D.; Reese, D.M. Combined biological therapy of breast cancer using monoclonal antibodies directed against HER2/protein and vascular endothelial growth factor. *Semin. Oncol.* 2002, 29, 29–37. [CrossRef]
53. Riccardi, F.; Colantuoni, G.; Diana, A.; Mocerino, C.; Lauria, R.; Febbraro, A.; Nuzzo, F.; Addeo, R.; Marano, O.; Incoronato, P.; et al. Exemestane and Everolimus combination treatment of hormone receptor positive, HER2 negative metastatic breast cancer: A retrospective study of 9 cancer centers in the Campania Region

- (Southern Italy) focused on activity, efficacy and safety. *Mol. Clin. Oncol.* 2018, 9, 255–263. [CrossRef] [PubMed]
54. Steger, G.G.; Gnant, M.; Bartsch, R. Palbociclib for the treatment of postmenopausal breast cancer—An update. *Expert Opin. Pharmacother.* 2016, 17, 255–263. [CrossRef]
 55. Shah, A.; Bloomquist, E.; Tang, S.; Fu, W.; Bi, Y.; Liu, Q.; Yu, J.; Zhao, P.; Palmby, T.R.; Goldberg, K.B.; et al. FDA Approval: Ribociclib for the Treatment of Postmenopausal Women with Hormone Receptor–Positive, HER2–Negative Advanced or Metastatic Breast Cancer. *Clin. Cancer Res.* 2018, 24, 2999–3004. [CrossRef]
 56. Kwapisz, D. Cyclin-dependent kinase 4/6 inhibitors in breast cancer: Palbociclib, ribociclib, and abemaciclib. *Breast Cancer Res. Treat.* 2017, 166, 41–54. [CrossRef]
 57. *Cancers* 2021, 13, 4287 30 of 30 305. Royce, M.E.; Osman, D. Everolimus in the Treatment of Metastatic Breast Cancer. *Breast Cancer Basic Clin. Res.* 2015, 9, 73–79. [CrossRef]
 58. Heimes, A.-S.; Schmidt, M. Atezolizumab for the treatment of triple-negative breast cancer. *Expert Opin. Investig. Drugs* 2018, 28, 1–5. [CrossRef].
 59. Steger, G.G.; Bartsch, R. Denosumab for the treatment of bone metastases in breast cancer: Evidence and opinion. *Ther. Adv. Med. Oncol.* 2011, 3, 233–243. [CrossRef] [PubMed]
 60. Tarantino, P.; Morganti, S.; Curigliano, G. Biologic therapy for advanced breast cancer: Recent advances and future directions. *Expert Opin. Biol. Ther.* 2020, 20, 1009–1024. [CrossRef] [PubMed]
 61. Groen JW, Grosfeld S, Wilschut JA, Bramer WM, Ernst MF, Mullender MM. Cyclic and non-cyclic breast-pain: A systematic review on pain reduction, side effects, and quality of life for various treatments. *Eur J Obstet Gynecol Reprod Biol.* 2017 Dec; 219:74-93. doi: 10.1016/j.ejogrb.2017.10.018.