Journal of Applied Pharmaceutical Research
Volume 12 Issue 5, Year of Publication 2024, Page 16 – 27
DOI: https://doi.org/10.69857/joapr.v12i5.606

Check for updates

Review Article

JOURNAL OF APPLIED PHARMACEUTICAL RESEARCH | JOAPR
www.japtronline.com ***ISSN: 2348 – 0335***

COMPREHENSIVE REVIEW OF BREAST CANCER RISK FACTORS, DIAGNOSIS, SCREENING, AND TREATMENT METHODS

Nurjamal Hoque, Ananta Choudhury*, Dhiraj Baishya, Himangshu Deka

Article Information
Received: 2nd June 2024
Revised: 10th September 2024
Accepted: 8th October 2024
Published: 31st October 2024

Keywords
Breast Cancer Treatment, Diagnosis, Stage Patients, Receptors, Endocrine therapy, Targeted Therapy

ABSTRACT
Background: Breast cancer is one of the leading causes of cancer-related deaths among women, accounting for 11.7% of all cancer cases and approximately 685,000 deaths worldwide in 2020. Its multifactorial etiology includes genetic, hormonal, and lifestyle-related risk factors with significant implications for diagnosis and treatment. Understanding these factors and the latest advancements in screening and therapeutic approaches is essential for improving patient outcomes. **Methodology:** This review synthesizes findings from peer-reviewed articles, clinical trials, and meta-analyses. The focus is on identifying key risk factors for breast cancer, evaluating the effectiveness of current diagnostic methods, and examining the latest treatment strategies, including personalized medicine. Data were collected from PubMed, Scopus, and Google Scholar databases. **Results and Discussion:** The review highlights major risk factors, including BRCA1/BRCA2 mutations, which contribute to a 45-65% lifetime risk, as well as hormonal influences and lifestyle factors like obesity and alcohol consumption. Targeted therapies, such as HER2 inhibitors (e.g., trastuzumab) and hormone therapies (e.g., tamoxifen), have significantly improved survival rates. Emerging treatments like immunotherapy and PARP inhibitors are also promising for aggressive and metastatic cases. **Conclusion:** Breast cancer continues to pose a significant health challenge, but advancements in risk assessment, early detection, and personalized treatment offer hope for better outcomes. Continued research and refining diagnostic and therapeutic approaches are essential for reducing breast cancer mortality and enhancing patient quality of life.

INTRODUCTION

Breast cancer is a medical condition characterized by the uncontrolled growth and division of abnormal cells within the breast tissue, leading to the formation of tumors. If left untreated, these cancers can metastasize, spreading to other parts of the body and potentially becoming life-threatening. It is one of the most prevalent kinds of cancer, and it is the primary global cause of cancer-related mortality for women is breast cancer [1]. Breast cancer causes approximately 25% of all cancer cases and 15% of all cancer-related deaths in women [2]. Breast cancer, on the other hand, affects men and women alike. Male breast

*Faculty of Pharmaceutical Science Assam down town university, Sankar Madhab Path, Gandhinagar, Panikhaiti, Guwahati, Assam 781026, India

***For Correspondence:** **anantachoudhury@gmail.com**

carcinomas represent 0.8% to 1% of all breast cancers [3-4]. Mortality rates vary greatly but are generally trending upward. The drastic shift in screening procedures, early diagnosis, and advancements in therapy have all contributed to greater longevity [5].

Epidemiology of breast cancer

Breast cancer originated roughly 1,500 years ago. Over 3,500 years ago, the ancient Egyptians were the first to mention the sickness [6-7]. Edwin Smith's and George Ebers' Papyri provided reasonably accurate descriptions of the state [6-7]. Around 460 B.C., Hippocrates, the father of Western medicine, categorized breast cancer as a humeral sickness [7-8]. Based on statistics from the World Health Organisation (WHO), malignant neoplasms are the primary cause of disability-adjusted life years (DALYs) among women, with breast cancer contributing to 19.6 million DALYs [9]. In 2020, there were 2.26 million new instances of breast cancer reported in women worldwide, making it one of the most often detected malignancies [10]. GLOBOCAN data from 2018 show a positive correlation between the Age-standardized incidence rates (ASIR) of breast cancer and the Human Development Index (HDI) [11].In 2020, breast cancer impacted 2.3 million women globally, resulting in 685,000 deaths [12]. The global breast cancer mortality-to-incidence ratio (MIR) in 2020, often used to assess 5-year survival rates, was 0.30 [12]. Considering the clinical severity of breast cancer, the 5-year survival rate was 89.6% for cases that were confined to a specific area and 75.4% for cases that had spread to nearby regions in countries with advanced healthcare systems (Hong Kong, Singapore, and Turkey). The survival rates for localized and regional breast cancer in less developed nations such as Costa Rica, India, the Philippines, Saudi Arabia, and Thailand were 76.3% and 47.4%, respectively [13]. Based on the latest projections, it is anticipated that by 2030, there will be around 2.7 million new instances of the disease identified worldwide each year, resulting in approximately 0.87 million deaths [14].

Types of Breast Cancer

There are two categories of breast cancer in situ: ductal carcinoma in situ (DCIS) and lobular carcinoma in situ (LCIS). DCIS cancers commonly arise in the mammary ducts [15] Main types of breast cancers are described in Figure 1. Fortunately, the terminal ductal lobular units (TDLUs) are the source of all pre-invasive lesions [16]. The two predominant types of malignant tumors that invade surrounding tissues are infiltrating/invasive lobular (ILC) and ductal (invasive ductal carcinoma [IDC]). ILC comprises around 15% of all cases [17] .In the ILC subtype, cancer cells frequently exhibit a high degree of morphological similarity [17]. Nuclei are often minuscule and have a consistent shape throughout cells. The tumor has several growth patterns[17]. A genetic subtype, Breast cancer's intricacy, has long been recognized and explored. Initially, histological characteristics classified breast tumors, but since the 1980s, HER2 and estrogen receptor expression have distinguished them. By 2000, the microarray revolution demonstrated that the phenotypic differences among breast cancers stemmed from their mRNA expression patterns. The more recent genomic revolution confirmed this. Nuclei are typically small and consistently formed throughout cells [18-19]. Different molecular subtypes of breast cancer were discovered using genetic microarrays [20].

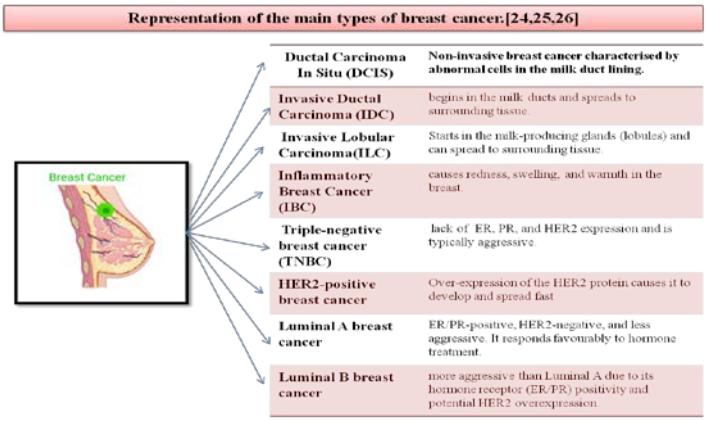

Figure 1: Breast cancer types

Stages of Breast Cancer: Stages of breast cancer are expressed on **Figure 2** [20]**.**

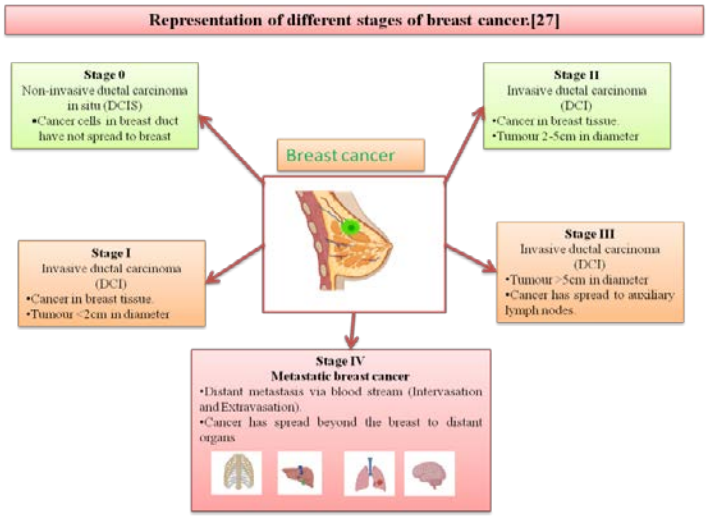

Figure 2: stages of breast cancer

Risk factors

There is a vast array of risk factors for breast cancer, encompassing both characteristics that can be changed and those that cannot be changed [**Table 1**][18].

Table 1: Modifiable and non-modifiable risk factors for breast cancer

Non- modifiable risk factors	Modifiable risk factors
Female sex	Hormone replacement treatment
Older age	Physical activity
Family history	Overweight obesity
Genetic mutations	Alcohol consumption
Ethnicity	Smoking
Pregnancy and breast feeding	Insufficient vitamin supplementation
Density of breast tissue	Excessive exposure to artificial light
Prior medical record of breast cancer	Exposure to chemicals
Prior radiation treatments	Other drugs

2. Diagnosis Methods:

Imaging tests and biopsies are essential for identifying cancer of the breast and informing surgical selections on tumor management, axillary staging, and treatment sequencing, which are expressed in **Figure 3** [21].

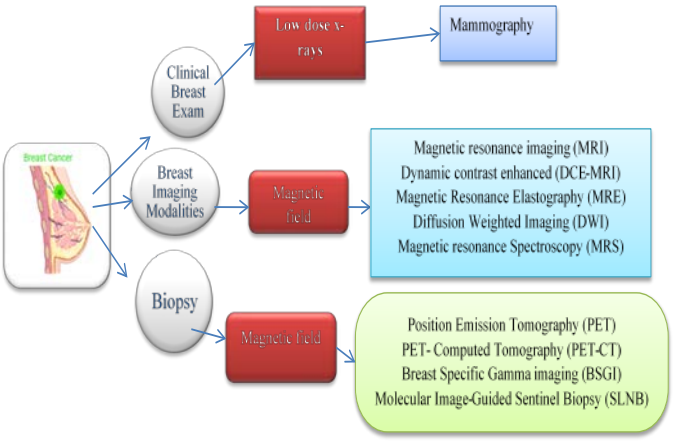

Figure 3: Representation of diagnostics and screening techniques for breast cancer

Mammography

Mammography, also called breast radiography, can identify benign and malignant abnormalities. A minimal radiation dose is applied to the compressed breast, positioned between two distinct plates, to provide an X-ray image [22]. Mammogram screening is utilized to detect early indicators of breast cancer before symptoms appear, aiming to lower mortality rates through early detection. Diagnostic mammography is a medical procedure that helps diagnose breast cancer in women who show symptoms, such as a lump in the breast [23][24][25]. For example, patients may have diverse mammograms, each producing a markedly different result despite delivering the exact breast density measurement. Previous studies used mammography outcomes to calculate the quantity of glandular tissue. However, these automated techniques for assessing breast density are insufficient for predicting breast cancer occurrence [26].

Magnetic Resonance Mammography (MRI)

Magnetic resonance imaging (MRI) of the breast is a non-invasive and non-ionizing diagnostic imaging technique. It uses low-energy radiofrequency radiation and a magnetic field to produce detailed images of the internal breast tissues[27]. MRI is utilized to assess the extent of malignancy and detect the existence of metastatic tumors in women previously diagnosed with breast cancer. It accurately detects tumors up to 2 cm in size. Nonetheless, bigger breast tumors are often exaggerated because the aberrant breast tissue surrounding the disease may result in a greater mastectomy rate [27][28][29]. To mitigate the risk of unforeseen adverse reactions and enhance breast cancer selectivity, it is possible to encapsulate these contrast agents into polymeric carriers that specifically target breast cancer cells.[30][31].Conducting tests resulted in a rise in unintended outcomes. Before any surgical intervention, it is essential to do a histological examination of these results [32][33].

Dynamic Contrast-Enhanced MRI (DCE-MRI)

Enhanced breast imaging using a dynamic contrast agent or an intravenous injection of a magnetic contrast agent allows an MRI to examine the tissue's temporal enhancement pattern. This imaging technology, which does not require any invasion of the body, quantifies the blood vessel formation in tissues, analyzes the makeup of the interstitial space, and detects any abnormalities or lesions present [34]. This imaging technique is very effective in viewing the process of tumor angiogenesis and evaluating the overall rates of tumor recurrence and patient survival in individuals with breast cancer [35][36][37]. DCE-MRI is a sophisticated imaging technique that enables the

assessment of disease severity in a non-invasive and three-dimensional manner, even before any noticeable structural changes occur. This technology helps predict the overall treatment response before starting therapy or in the early stages of treatment [38][39].

Diffusion - Weighted Imaging (DWI)

Diffusion-weighted imaging (DWI) is an MRI technique that does not require contrast agents. Instead, it uses water molecules' motion to create contrast in magnetic resonance (MR) images. This technique effectively addresses numerous constraints associated with traditional breast MRI [40][41][42]. Technological advancements are resolving various picture quality challenges that have hindered the widespread use of DWI for breast imaging [43].

Magnetic Resonance Elastography MRI

Breast MRE is a medical imaging technology that generates cross-sectional images without invasive procedures or exposure to ionizing radiation [44][45]. It is common for breast tumors to be stiffer than the normal tissues and noncancerous growths nearby because they have more cells, more collagen, and higher levels of proteoglycans [46]. Manual examination, commonly employed in routine breast screening, possesses specificity and sensitivity. Magnetic resonance imaging (MRI) of the breast can overcome the limitations of physical examination [47][48]. Remarkably, the initial findings indicate significant promise. The primary limitation in the application of magnetic resonance elastography (MRE) for breast cancer is the challenge of achieving a significant degree of spatial resolution and accurately identifying minute focal lesions. The issue arises from the comparable amounts of rigidity seen in both soft malignant tumors and rigid benign tumors [49].

Magnetic Resonance Spectroscopy (MRS):

Incorporating an MRI technique into the in vivo 1H MRS methodology results in a total acquisition time increase of about 10 minutes. This approach has the benefit of enhancing the diagnostic capabilities compared to clinical breast examinations [50][51]. MRS has a specificity of around 88%. However, one disadvantage of this imaging technique is that it requires somewhat more significant lesions and has limited sensitivity in identifying the total choline (Cho) signal. The phosphocholine metabolite, elevated in breast cancer, is a diagnostic marker [52][53].

Positron Emission Tomography (PET) scanning and PET combined with computer-aided tomography (CT)

The most widely used and authorized PET radiotracer by the US FDA is 2-deoxy-2-(18F) fluoro-D-glucose (FDG). FDG targets the enhanced glucose metabolism of cancer cells[54]. Cells with cancer are more proliferative and have a faster glucose utilization rate than normal ones. FDG PET radiotracers enter cells via the glucose carrier; therefore, tumor cells take them up at higher levels than normal cells [55]. FDG uptake is negatively correlated with prognosis [53][54][56]. PET-CT combines PET, a nuclear medical procedure, and CT, generating accurate body images. PET scanners designed for breast imaging, particularly positron emission mammography (PEM), have greatly enhanced their capacity to capture intricate features and identify minute irregularities. As a result, they are currently used in clinical settings to examine primary malignancies [57][58]. Multiple studies have demonstrated that 18F-FDG PET/CT hybrid imaging sheds light on the increased cellular uptake of glucose in malignant tumors [59][60][61]. Jorgensen et al. determined that nanoparticle-assisted photothermal therapy (PT) dramatically decreased tumor cell absorption of 18F-FDG, making it a valuable marker for assessing treatment outcomes [62].

Molecular Image-Guided Sentinel Node Biopsy (MIGSNB)

Sentinel lymph node biopsy (SLNB) is a minimally invasive procedure used to determine whether early-stage breast cancer has spread to nearby lymph nodes. This technique is often performed to assess the extent of cancer dissemination's determine the most effective treatment approach by assessing the presence of nodal metastases[63]. The SLNB technique is well-known for its markedly decreased post-operative complications compared to standard axillary lymph node dissection [64][65]. Implementing accurate SLNB protocols might reduce the need for invasive surgeries and identify the occurrence of multiple-basin draining by precisely locating sentinel lymph nodes. This would ultimately improve the accuracy of staging in women diagnosed with invasive breast cancer [66].

Breast Specific-Gamma imaging (BSGI)

During Breast-Specific Gamma Imaging (BSGI), a radioactive tracer such as Technetium Tc99m Sestamibi is injected into the patient's bloodstream, and a specialized device is used to image the breast [67][68][69][70]. Unlike mammography, BSGI is not impacted by the density of the breasts [71][72]. The new BSGI

offers better sensitivity for identifying sub-centimeter lesions when compared with scintimammography [73]. The primary drawback of this method is that it is unsuitable for routine breast cancer screening due to the extensive radiation exposure to the entire body [74].

Treatment Approaches

The available treatment modalities for breast cancer encompass surgical intervention, radiation therapy (RT), chemotherapy (CT), endocrine (hormone) therapy (ET), and targeted therapy [75].

Surgery

Treatments for surgical mastectomy and breast-conserving surgery (BCS) are available for patients with early-stage invasive breast cancer. Within ten years following radiation treatment (RT) and breast-conserving surgery (BCS), the local recurrence rate (LRR) for human epidermal growth factor receptor-2 (HER-2) and estrogen receptor (ER)-positive breast cancer is roughly 2-3. For triple-negative breast cancer (TNBC), it is 5%. This is similar to what has been observed after mastectomy in early-stage breast cancer instances [76][77]. Furthermore, as compared to mastectomy, individuals who received BCS+RT had superior aesthetic results and higher life satisfaction [78]. Therefore, the planned surgical standard of care for the majority of breast cancers involves combining breast-conserving surgery (BCS) with radiation therapy. However, we must handle the decision to choose breast-conserving surgery (BCS) cautiously when treating patients who have significant worries about micro-calcifications, many malignant areas, the difficulty of achieving complete tumor removal, and restrictions on radiation therapy [79]. BCS is not contraindicated for younger patients, those with lobular carcinoma, or those with aggressive subtypes such as triple-negative and HER2-positive illnesses. Patients with big tumors may benefit from neo-adjuvant chemotherapy (NAC) to downstage the tumor for BCS [80]. The use of axillary treatment is a debated topic among patients with surgically node-negative (cN0) breast cancer [81]. Surgery is also an essential component in the treatment of local and regional recurring breast cancer. For recurrent patients following BCS, total mastectomy is the mainstay of therapy. Recovery mastectomy combined with axillary lymph node dissection (ALND) may result in 85-95% control of the illness in the local and regional areas. The user's text is incomplete and lacks information [82]. Patients who experienced chest-wall recurrence after initial mastectomy had a greater risk of metastasis than those who were first treated with BCS [82]. Moreover, previous research has indicated that incomplete tissue removal was linked to a 60–70% rise in the likelihood of a second local recurrence. Therefore, experts widely recommend comprehensive excision of reoccurring lesions for patients who initially underwent mastectomy [83].

Radiation Therapy

WBI is recommended for the treatment of early breast cancer that does not require nodal therapy [84][85]. Additionally, partial breast irradiation (PBI) has demonstrated similar local control rates [85][86]. Despite having a similar recurrence rate of 4.4% over 5 years, brachytherapy should be approached carefully owing to the lack of extensive supporting data [87][88]. The quantity of affected axillary lymph nodes (ALNs) plays a crucial role in assessing the necessity of radiation therapy following a mastectomy. Patients with a diagnosis of four or more positive axillary lymph nodes (ALNs) commonly receive post-mastectomy radiation treatment (PMRT). However, there are uncertainties about administering PMRT to individuals with between one and three afflicted axillary lymph nodes [89]. Recent investigations have shown that persons with one to three axillary lymph nodes (ALNs) do not experience any additional survival benefits while receiving contemporary systemic therapy [90][91]. So, it is important to find people more likely to respond well to post-mastectomy radiation therapy (PMRT) by looking at their younger age, larger breast and axilla loads, and unique biological traits. New research suggests that the 8th American Joint Committee on Cancer (AJCC) pathological prognostic staging, which uses molecular markers, can help doctors figure out how best to treat women with N1 breast cancer with radiation therapy [92][93]. The MA.20 study randomly allocated 1832 patients with positive lymph nodes to either breast irradiation or comprehensive regional nodal irradiation, which included internal mammary nodes (IMNs) [94].

Chemotherapy

N-acetylcysteine (NAC) can reduce the degree of breast and axillary involvement in operable breast cancer, convert inoperable breast cancer into a state amenable to surgical treatment, and eradicate tiny, disseminated cancer cells[95]. N-acetylcysteine (NAC) is advised for individuals who have a large tumor, Significant involvement of axillary lymph nodes, and aggressive subtypes of breast cancer, such as triple-negative and HER2-positive, often necessitate chemotherapy as part of the

treatment regimen. Chemotherapy strategies commonly employed include neoadjuvant chemotherapy (NAC), adjuvant chemotherapy (AC), and salvage chemotherapy. Chemotherapy can decrease the probability of early breast cancer recurrence by around 30%. The user's text is incomplete and lacks information [95]. Utilizing NAC in aggressive subtypes of breast cancer may aid in assessing the effectiveness of treatment, forecasting the prognosis of the illness, and informing future treatment choices. Prior research has demonstrated that neoadjuvant chemotherapy. However, patients who received NAC experienced a 17% reduction in mastectomy rates [96][97]. In addition, multigene assays and molecular classifications can be used to categorize and distinguish persons who would derive advantages from chemotherapy, particularly in cases where there is no involvement of lymph nodes. Still, there is the presence of estrogen receptors, the absence of three specific receptors, or the presence of HER2 receptors [98]. The use of anthracyclines is the subject of discussion. However, chemotherapy appears crucial for individuals at high risk, particularly those with triple-negative and HER2-positive subtypes of breast cancer [99][100].

Endocrine Therapy

Endocrine treatment is commonly used as an adjunct therapy for individuals with hormone receptor-positive malignancies (with at least 1% staining for estrogen receptor or progesterone receptor) for 5-10 years. The efficacy of endocrine treatment is directly correlated with the hormone receptor expression level [100]. Administering a daily dose of 20 mg of Tamoxifen for 5 years in premenopausal persons led to a nearly 50% decrease in the chance of recurrence during the initial 4 years and a reduction of over 30% in the 5-9 year period. Prolonged treatment with Tamoxifen resulted in significant decreases in both recurrence rates and mortality from breast cancer[101]. Additional analysis of the ATLAS trial showed that extending Tamoxifen to 10 years led to a 2% decrease in breast cancer mortality (9.6% vs 11.6%) compared to a 5-year treatment with Tamoxifen [102]. Treatment options for postmenopausal women include Tamoxifen or AI immunotherapy for 5 years, either alone or in combination. Patients at high risk or with lobular histology are more likely to get AI immunotherapy as an adjuvant treatment for breast cancer since it reduced death rates for more than five years compared to Tamoxifen [103][104]. However, patients who received AI medication experienced a greater occurrence of bone-related adverse effects, including fractures and osteoporosis. Hence, Tamoxifen can be a viable option for those who experience significant negative effects from AI therapy. Additional assessment is required to determine the optimal time for administering Tamoxifen and AI to postmenopausal women while considering the trade-off between potential hazards and advantages. Multigame tests can aid in estimating the optimal duration of treatment [105].

Targeted Therapy

As a second-line medical treatment, lapatinib is authorized for the treatment of metastatic HER2-positive breast carcinoma. The small-molecule blocker neratinib, which targets HER1/2, has effectively prevented HER2 activity. Compared to the combination of lapatinib and capecitabine, the stage III NALA studies showed that combining neratinib with capecitabine enhanced progression-free survival (PFS). They decreased the incidence of central nervous system illnesses [106].

Recent advancement and future prospective

Recent advancements in breast cancer diagnosis have transformed the accuracy and efficacy of detection methods. Digital breast tomosynthesis (DBT), also known as 3D mammography, has enhanced traditional imaging by reducing tissue overlap, improving the visibility of small tumors in dense breast tissue, and lowering false positive rates [107]. Liquid biopsy, which detects circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs), is another emerging diagnostic tool that offers a non-invasive alternative to tissue biopsies and allows real-time monitoring of tumor progression [104]. Additionally, AI-powered algorithms have improved diagnostic accuracy by assisting in mammogram interpretation, reducing the rates of false positives and negatives, and providing more precise and earlier detection [105]. Screening advancements have also evolved to become more personalized and effective. Risk-based screening incorporating genetic, environmental, and lifestyle factors is becoming the norm, particularly for high-risk groups like those with BRCA1/BRCA2 mutations [108]. Advances in genetic testing have made it easier to detect individuals at higher risk for breast cancer, allowing for earlier interventions such as preventive surgeries or more frequent monitoring [109]. Moreover, emerging imaging technologies like photoacoustic imaging, which combines laser-induced ultrasound, offer a promising approach for detecting early-stage tumors with high precision, potentially surpassing the capabilities of conventional mammography [110]. Treatment approaches have shifted towards precision medicine and

targeted therapies, improving patient outcomes. Immunotherapy, especially checkpoint inhibitors like Atezolizumab, has shown significant promise in treating aggressive subtypes such as triple-negative breast cancer [111]. Additionally, targeted therapies like PARP inhibitors for BRCA-mutated cancers and CDK4/6 inhibitors for hormone receptor-positive cancers have revolutionized treatment strategies by offering more personalized approaches that minimize side effects and increase efficacy [112]. Nanotechnology-based drug delivery systems, such as solid lipid nanoparticles, are being explored to improve drug targeting and reduce systemic toxicity, indicating a promising future for more effective and less invasive treatment options [110][112].

CONCLUSION

The present review aims to consolidate and update the knowledge on breast cancer, particularly emphasizing its current epidemiology, risk factors, categorization, prognostic biomarkers, and therapeutic choices. It is critical to give top priority to the development of efficient preventive strategies, with a focus on modifiable risk factors that have the potential to significantly lower the incidence of breast cancer, given the marked increase in the disease's incidence and mortality rates recorded in recent years. The two main screening methods used now to enable early identification of breast cancer are mammography and tomography. The continuous quest for predictive biomarkers and possible targets for biological therapy has greatly enhanced breast cancer treatment and clinical results.

FINANCIAL ASSISTANCE

NIL

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Nurjamal Hoque contributed to the review's conceptualization, editing, and design. Ananta Choudhury contributed to the analysis and interpretation of data, visualization, and formatting. Dhiraj Baishya was involved in the literature search and data collection. Himangshu Deka wrote the original draft, researched the literature, and collected data.

REFERENCES

[1] Sartaj A, Qamar Z, Qizilbash FF, Annu, Md S, Alhakamy NA, Baboota S, Ali J. Polymeric Nanoparticles: Exploring the Current Drug Development and Therapeutic Insight of Breast Cancer Treatment and Recommendations. *Polymers (Basel).*, **13**, (2021) https://doi.org/10.3390/polym13244400

[2] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA. Cancer J. Clin.*, **65**, 87–108 (2015) https://doi.org/10.3322/caac.21262

[3] Gómez-Raposo C, Zambrana Tévar F, Sereno Moyano M, López Gómez M, Casado E. Male breast cancer. *Cancer Treat. Rev.*, **36**, 451–7 (2010) https://doi.org/10.1016/j.ctrv.2010.02.002

[4] Giordano SH, Buzdar AU, Hortobagyi GN. Breast cancer in men. *Ann. Intern. Med.*, **137**, 678–87 (2002) https://doi.org/10.7326/0003-4819-137-8-200210150-00013

[5] Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int. J. cancer*, **136**, E359-86 (2015) https://doi.org/10.1002/ijc.29210

[6] Akram M, Siddiqui S. Breast cancer management: Past, present and evolving. *Indian J. Cancer*, **49**, 277 (2012) https://doi.org/10.4103/0019-509X.104486

[7] Papavramidou N, Papavramidis T, Demetriou T. Ancient Greek and Greco-Roman methods in modern surgical treatment of cancer. *Ann. Surg. Oncol.*, **17**, 665–7 (2010) https://doi.org/10.1245/s10434-009-0886-6

[8] GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet (London, England)*, **392**, 1736–88 (2018) https://doi.org/10.1016/S0140-6736(18)32203-7

[9] Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdela J, , Zhang K, Zhou M, Zodpey S, Zuhlke LJ, Naghavi M, Murray CJL. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet*, **392**, 1736–88 (2018) https://doi.org/10.7326/0003-4819-137-8-200210150-00013

[10] Ferlay J, Colombet M, Soerjomataram I, Parkin DM, Piñeros M, Znaor A, Bray F. Cancer statistics for the year 2020: An overview. *Int. J. Cancer*, **149**, 778–89 (2021) https://doi.org/10.1002/ijc.29210

[11] Sharma R. Global, regional, national burden of breast cancer in 185 countries: evidence from GLOBOCAN 2018. *Breast Cancer Res. Treat.*, **187**, 557–67 (2021) https://doi.org/10.1007/s10549-020-06083-6

[12] Sung H, Ferlay J, Siegel RL, 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.*, **71**, 209–49 (2021) https://doi.org/10.3322/caac.21660

[13] Sankaranarayanan R, Swaminathan R, Brenner H, Chen K, Chia KS, Chen JG, Law SC, Ahn Y-O, Xiang YB, Yeole BB, Shin HR, Shanta V, Woo ZH, Martin N, Sumitsawan Y, Sriplung H, Barboza AO, Eser S, Nene BM, Suwanrungruang K, Jayalekshmi P, Dikshit R, Wabinga H, Esteban DB, Laudico A, Bhurgri Y, Bah E, Al-Hamdan N. Cancer survival in Africa, Asia, and Central America: a population-based study. *Lancet Oncol.*, **11**, 165–73 (2010) https://doi.org/10.1016/S1470-2045(09)70335-3

[14] Sathishkumar K, Chaturvedi M, Das P, Stephen S, Mathur P. Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. *Indian J. Med. Res.*, **156**, 598 (2022) https://doi.org/10.4103/ijmr.ijmr_1821_22

[15] Logan GJ, Dabbs DJ, Lucas PC, Jankowitz RC, Brown DD, Clark BZ, Oesterreich S, McAuliffe PF. Molecular drivers of lobular carcinoma in situ. *Breast Cancer Res.*, **17**, 76 (2015) https://doi.org/10.1186/s13058-015-0580-5

[16] Wellings SR. A hypothesis of the origin of human breast cancer from the terminal ductal lobular unit. *Pathol. Res. Pract.*, **166**, 515–35 (1980) https://doi.org/10.1016/S0344-0338(80)80248-2

[17] Reed AEM, Kutasovic JR, Lakhani SR, Simpson PT. Invasive lobular carcinoma of the breast: morphology, biomarkers and 'omics. *Breast Cancer Res.*, **17**, 12 (2015) https://doi.org/10.1186/s13058-015-0519-x

[18] Łukasiewicz S, Czeczelewski 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 (Basel).*, **13**, 4287 (2021) https://doi.org/10.3390/cancers13174287

[19] Nounou MI, ElAmrawy F, Ahmed N, Abdelraouf K, Goda S, Syed-Sha-Qhattal H. Breast Cancer: Conventional Diagnosis and Treatment Modalities and Recent Patents and Technologies. *Breast Cancer Basic Clin. Res.*, **9s2**, BCBCR.S29420 (2015) https://doi.org/10.4137/BCBCR.S29420

[20] Inic Z, Zegarac M, Inic M, Markovic I, Kozomara Z, Djurisic I, Inic I, Pupic G, Jancic S. Difference between Luminal A and Luminal B Subtypes According to Ki-67, Tumor Size, and Progesterone Receptor Negativity Providing Prognostic Information. *Clin. Med. Insights Oncol.*, **8**, CMO.S18006 (2014) https://doi.org/10.4137/CMO.S18006

[21] Moo T-A, Sanford R, Dang C, Morrow M. Overview of Breast Cancer Therapy. *PET Clin.*, **13**, 339–54 (2018) https://doi.org/10.1016/j.cpet.2018.02.006

[22] Bhushan A, Gonsalves A, Menon JU. Current State of Breast Cancer Diagnosis, Treatment, and Theranostics. *Pharmaceutics*, **13**, 723 (2021) https://doi.org/10.3390/pharmaceutics13050723

[23] Avcı H, Karakaya J. A Novel Medical Image Enhancement Algorithm for Breast Cancer Detection on Mammography Images Using Machine Learning. *Diagnostics*, **13**, 348 (2023) https://doi.org/10.3390/diagnostics13030348

[24] Mandelblatt JS, Cronin KA, Bailey S, Berry DA, de Koning HJ, Draisma G, Huang H, Lee SJ, Munsell M, Plevritis SK, Ravdin P, Schechter CB, Sigal B, Stoto MA, Stout NK, van Ravesteyn NT, Venier J, Zelen M, Feuer EJ, Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network. Effects of mammography screening under different screening schedules: model estimates of potential benefits and harms. *Ann Intern Med.*, **151**,738-47(2009) https://doi.org/10.1059/0003-4819-151-10-200911170-00010

[25] Nelson HD. Screening for Breast Cancer: An Update for the U.S. Preventive Services Task Force. *Ann. Intern. Med.*, **151**, 727 (2009) https://doi.org/10.7326/0003-4819-151-10-200911170-00009

[26] Yala A, Lehman C, Schuster T, Portnoi T, Barzilay R. A Deep Learning Mammography-based Model for Improved Breast Cancer Risk Prediction. *Radiology*, **292**, 60–6 (2019) https://doi.org/10.1148/radiol.2019182716

[27] Jain PK, Dubey A, Saba L, Khanna NN, Laird JR, Nicolaides A, Fouda MM, Suri JS, Sharma N. Attention-Based UNet Deep Learning Model for Plaque Segmentation in Carotid Ultrasound for Stroke Risk Stratification: An Artificial Intelligence Paradigm. *J. Cardiovasc. Dev. Dis.*, **9**, 326 (2022),https://doi.org/10.3390/jcdd9100326

[28] Jethava A, Ali S, Wakefield D, Crowell R, Sporn J, Vrendenburgh J. Diagnostic Accuracy of MRI in Predicting Breast Tumor Size: Comparative Analysis of MRI vs Histopathological Assessed Breast Tumor Size. *Conn. Med.*, **79**, 261–7 (2015) https://doi.org/10.1186/s12957-017-1197-1

[29] Grimsby GM, Gray R, Dueck A, Carpenter S, Stucky C-C, Aspey H, Giurescu ME, Pockaj B. Is there concordance of invasive breast cancer pathologic tumor size with magnetic resonance imaging? *Am. J. Surg.*, **198**, 500–4 (2009) https://doi.org/10.1016/j.amjsurg.2009.07.012

[30] Ayat NR, Vaidya A, Yeung GA, Buford MN, Hall RC, Qiao PL, Yu X, Lu Z-R. Effective MR Molecular Imaging of Triple Negative Breast Cancer With an EDB-Fibronectin-Specific Contrast Agent at Reduced Doses. *Front. Oncol.*, **9**, (2019) https://doi.org/10.3389/fonc.2019.01351

[31] Leithner D, Moy L, Morris EA, Marino MA, Helbich TH, Pinker K. Abbreviated MRI of the Breast: Does It Provide Value? *J. Magn. Reson. Imaging*, **49**, (2019) https://doi.org/10.1002/jmri.26291

[32] Peters NHGM, Borel Rinkes IHM, Zuithoff NPA, Mali WPTM, Moons KGM, Peeters PHM. Meta-Analysis of MR Imaging in the Diagnosis of Breast Lesions. *Radiology*, **246**, 116–24 (2008) https://doi.org/10.1148/radiol.2461061298

[33] Metcalfe KA, Finch A, Poll A, Horsman D, Kim-Sing C, Scott J, Royer R, Sun P, Narod SA. Breast cancer risks in women with a

family history of breast or ovarian cancer who have tested negative for a BRCA1 or BRCA2 mutation. *Br. J. Cancer*, **100**, 421–5 (2009) https://doi.org/10.1038/sj.bjc.6604830

[34] Rahbar H, Partridge SC. Multiparametric MR Imaging of Breast Cancer. *Magn. Reson. Imaging Clin. N. Am.*, **24**, 223–38 (2016) https://doi.org/10.1016/j.mric.2015.08.012

[35] Teifke A, Behr O, Schmidt M, Victor A, Vomweg TW, Thelen M, Lehr H-A. Dynamic MR Imaging of Breast Lesions: Correlation with Microvessel Distribution Pattern and Histologic Characteristics of Prognosis. *Radiology*, **239**, 351–60 (2006) https://doi.org/10.1148/radiol.2392050205

[36] Lee SH, Cho N, Kim SJ, Cha JH, Cho KS, Ko ES, Moon WK. Correlation between High Resolution Dynamic MR Features and Prognostic Factors in Breast Cancer. *Korean J. Radiol.*, **9**, 10 (2008) https://doi.org/10.3348/kjr.2008.9.1.10

[37] Lee J, Kim SH, Kim Y, Park J, Park GE, Kang BJ. Radiomics Nomogram: Prediction of 2-Year Disease-Free Survival in Young Age Breast Cancer. *Cancers (Basel).*, **14**, (2022) https://doi.org/10.3390/cancers14184461

[38] Gillman J, Toth HK, Moy L. The Role of Dynamic Contrast-Enhanced Screening Breast MRI in Populations at Increased Risk for Breast Cancer. *Women's Heal.*, **10**, 609–22 (2014) https://doi.org/10.2217/whe.14.61

[39] Malayeri AA, El Khouli RH, Zaheer A, Jacobs MA, Corona-Villalobos CP, Kamel IR, Macura KJ. Principles and Applications of Diffusion-weighted Imaging in Cancer Detection, Staging, and Treatment Follow-up. *RadioGraphics*, **31**, 1773–91 (2011) https://doi.org/10.1148/rg.316115515

[40] Petralia G, Bonello L, Priolo F, Summers P, Bellomi M. Breast MR with special focus on DW-MRI and DCE-MRI. *Cancer Imaging*, **11**, 76–90 (2011) https://doi.org/10.1102/1470-7330.2011.0014

[41] Baron P, Dorrius MD, Kappert P, Oudkerk M, Sijens PE. Diffusion-weighted imaging of normal fibroglandular breast tissue: influence of microperfusion and fat suppression technique on the apparent diffusion coefficient. *NMR Biomed.*, n/a-n/a (2010) https://doi.org/10.1002/nbm.1475

[42] Baltzer P, Mann RM, Iima M, Sigmund EE, Clauser P, Gilbert FJ, Martincich L, Partridge SC, Patterson A, Pinker K, Thibault F, Camps-Herrero J, Le Bihan D. Diffusion-weighted imaging of the breast—a consensus and mission statement from the EUSOBI International Breast Diffusion-Weighted Imaging working group. *Eur. Radiol.*, **30**, 1436–50 (2020) https://doi.org/10.1007/s00330-019-06510-3

[43] Glaser KJ, Manduca A, Ehman RL. Review of MR elastography applications and recent developments. *J. Magn. Reson. Imaging*, **36**, 757–74 (2012) https://doi.org/10.1002/jmri.23597

[44] Patel BK, Samreen N, Zhou Y, Chen J, Brandt K, Ehman R, Pepin K. MR Elastography of the Breast: Evolution of Technique, Case Examples, and Future Directions. *Clin. Breast Cancer*, **21**, e102–11 (2021) https://doi.org/10.1016/j.clbc.2020.08.005

[45] Hawley JR, Kalra P, Mo X, Raterman B, Yee LD, Kolipaka A. Quantification of breast stiffness using MR elastography at 3 Tesla with a soft sternal driver: A reproducibility study. *J. Magn. Reson. Imaging*, **45**, 1379–84 (2017) https://doi.org/10.1002/jmri.25511

[46] Pepin KM, Ehman RL, McGee KP. Magnetic resonance elastography (MRE) in cancer: Technique, analysis, and applications. *Prog. Nucl. Magn. Reson. Spectrosc.*, **90**–**91**, 32–48 (2015) https://doi.org/10.1016/j.pnmrs.2015.06.001

[47] Sinkus R, Siegmann K, Xydeas T, Tanter M, Claussen C, Fink M. MR elastography of breast lesions: Understanding the solid/liquid duality can improve the specificity of contrast-enhanced MR mammography. *Magn. Reson. Med.*, **58**, 1135–44 (2007) https://doi.org/10.1002/mrm.21404

[48] Manduca A, Oliphant TE, Dresner MA, Mahowald JL, Kruse SA, Amromin E, Felmlee JP, Greenleaf JF, Ehman RL. Magnetic resonance elastography: Non-invasive mapping of tissue elasticity. *Med. Image Anal.*, **5**, 237–54 (2001) https://doi.org/10.1016/s1361-8415(00)00039-6

[49] Lorenzen J, Sinkus R, Lorenzen M, Dargatz M, Leussler C, Röschmann P, Adam G. MR elastography of the breast:preliminary clinical results. *RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der Bildgeb. Verfahren*, **174**, 830–4 (2002) https://doi.org/10.1055/s-2002-32690

[50] Haddadin IS, McIntosh A, Meisamy S, Corum C, Snyder ALS, Powell NJ, Nelson MT, Yee D, Garwood M, Bolan PJ. Metabolite quantification and high-field MRS in breast cancer. *NMR Biomed.*, **22**, 65–76 (2009) https://doi.org/10.1002/nbm.1217

[51] Stanwell P, Mountford C. In Vivo Proton MR Spectroscopy of the Breast. *RadioGraphics*, **27**, S253–66 (2007) https://doi.org/10.1148/rg.27si075519

[52] Fardanesh R, Marino MA, Avendano D, Leithner D, Pinker K, Thakur SB. Proton MR spectroscopy in the breast: Technical innovations and clinical applications. *J. Magn. Reson. Imaging*, **50**, 1033–46 (2019) https://doi.org/10.1002/jmri.26700

[53] Liberti M V., Locasale JW. The Warburg Effect: How Does it Benefit Cancer Cells? *Trends Biochem. Sci.*, **41**, 211–8 (2016) https://doi.org/10.1016/j.tibs.2015.12.001

[54] Flavell RR, Naeger DM, Mari Aparici C, Hawkins RA, Pampaloni MH, Behr SC. Malignancies with Low Fluorodeoxyglucose Uptake at PET/CT: Pitfalls and Prognostic Importance: Resident and Fellow Education Feature. *RadioGraphics*, **36**, 293–4 (2016) https://doi.org/10.1148/rg.2016150073

[55] Kawada K, Iwamoto M, Sakai Y. Mechanisms underlying 18 F-fluorodeoxyglucose accumulation in colorectal cancer. *World J. Radiol.*, **8**, 880 (2016) https://doi.org/10.4329/wjr.v8.i11.880

[56] Kadoya T, Aogi K, Kiyoto S, Masumoto N, Sugawara Y, Okada M. Role of maximum standardized uptake value in fluorodeoxyglucose positron emission tomography/computed tomography predicts malignancy grade and prognosis of operable breast cancer: a multi-institute study. *Breast Cancer Res. Treat.*, **141**, 269–75 (2013) https://doi.org/10.1007/s10549-013-2687-7

[57] Jin S, Kim S, Ahn J, Jung KH, Ahn SH, Son BH, Lee JW, Gong G, Kim HO, Moon DH. 18 F-fluorodeoxyglucose uptake predicts pathological complete response after neoadjuvant chemotherapy for breast cancer: A retrospective cohort study. *J. Surg. Oncol.*, **107**, 180–7 (2013) https://doi.org/10.1002/jso.23255

[58] Narayanan D, Madsen KS, Kalinyak JE, Berg WA. Interpretation of Positron Emission Mammography and MRI by Experienced Breast Imaging Radiologists: Performance and Observer Reproducibility. *Am. J. Roentgenol.*, **196**, 971–81 (2011) https://doi.org/10.2214/AJR.10.5081

[59] 59] Hsu DFC, Freese DL, Levin CS. Breast-Dedicated Radionuclide Imaging Systems. *J. Nucl. Med.*, **57**, 40S-45S (2016) https://doi.org/10.2967/jnumed.115.157883

[60] Giammarile F, Castellucci P, Dierckx R, Estrada Lobato E, Farsad M, Hustinx R, Jalilian A, Pellet O, Rossi S, Paez D. Non-FDG PET/CT in Diagnostic Oncology: a pictorial review. *Eur. J. Hybrid Imaging*, **3**, 20 (2019) https://doi.org/10.1186/s41824-019-0066-2

[61] Blanchet EM, Millo C, Martucci V, Maass-Moreno R, Bluemke DA, Pacak K. Integrated Whole-Body PET/MRI With 18F-FDG, 18F-FDOPA, and 18F-FDA in Paragangliomas in Comparison With PET/CT. *Clin. Nucl. Med.*, **39**, 243–50 (2014) https://doi.org/10.1097/RLU.0000000000000289

[62] Wibmer AG, Hricak H, Ulaner GA, Weber W. Trends in oncologic hybrid imaging. *Eur. J. Hybrid Imaging*, **2**, 1 (2018) https://doi.org/10.1186/s41824-017-0019-6

[63] Escalona S, Blasco JA, Reza MM, Andradas E, Gómez N. A systematic review of FDG-PET in breast cancer. *Med. Oncol.*, **27**, 114–29 (2010) https://doi.org/10.1007/s12032-009-9182-3

[64] Jørgensen JT, Norregaard K, Martín MS, Oddershede LB, Kjaer A. Non-invasive Early Response Monitoring of Nanoparticle-assisted Photothermal Cancer Therapy Using 18 F-FDG, 18 F-FLT, and 18 F-FET PET/CT Imaging. *Nanotheranostics*, **2**, 201–10 (2018) https://doi.org/10.7150/ntno.24478

[65] Lyman GH, Somerfield MR, Bosserman LD, Perkins CL, Weaver DL, Giuliano AE. Sentinel Lymph Node Biopsy for Patients With Early-Stage Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J. Clin. Oncol.*, **35**, 561–4 (2017) https://doi.org/10.1200/JCO.2016.71.0947

[66] Cox CE, Kiluk J V., Riker AI, Cox JM, Allred N, Ramos DC, Dupont EL, Vrcel V, Diaz N, Boulware D. Significance of Sentinel Lymph Node Micrometastases in Human Breast Cancer. *J. Am. Coll. Surg.*, **206**, 261–8 (2008) https://doi.org/10.1016/j.jamcollsurg.2007.08.024

[67] Kang J, Chang JH, Kim SM, Lee HJ, Kim H, Wilson BC, Song T-K. Real-time sentinel lymph node biopsy guidance using combined ultrasound, photoacoustic, fluorescence imaging: in vivo proof-of-principle and validation with nodal obstruction. *Sci. Rep.*, **7**, 45008 (2017) https://doi.org/10.1038/srep45008

[68] Brem RF, Ruda RC, Yang JL, Coffey CM, Rapelyea JA. Breast-Specific γ-Imaging for the Detection of Mammographically Occult Breast Cancer in Women at Increased Risk. *J. Nucl. Med.*, **57**, 678–84 (2016) https://doi.org/10.2967/jnumed.115.168385

[69] Karger E, Kureljusic M. Artificial Intelligence for Cancer Detection—A Bibliometric Analysis and Avenues for Future Research. *Curr. Oncol.*, **30**, 1626–47 (2023) https://doi.org/10.3390/curroncol30020125

[70] Liu H, Zhan H, Sun D. Comparison of 99mTc-MIBI scintigraphy, ultrasound, and mammography for the diagnosis of BI-RADS 4 category lesions. *BMC Cancer*, **20**, 463 (2020) https://doi.org/10.1186/s12885-020-06938-7

[71] Gong Z, Williams MB. Comparison of breast specific gamma imaging and molecular breast tomosynthesis in breast cancer detection: Evaluation in phantoms. *Med. Phys.*, **42**, 4250–9 (2015) https://doi.org/10.1118/1.4922398

[72] Rechtman LR, Lenihan MJ, Lieberman JH, Teal CB, Torrente J, Rapelyea JA, Brem RF. Breast-Specific Gamma Imaging for the Detection of Breast Cancer in Dense Versus Nondense Breasts. *Am. J. Roentgenol.*, **202**, 293–8 (2014) https://doi.org/10.2214/AJR.13.11585

[73] Zhang Z, Wang W, Wang X, Yu X, Zhu Y, Zhan H, Chen Z, Li B, Huang J. Breast-specific gamma imaging or ultrasonography as adjunct imaging diagnostics in women with mammographically dense breasts. *Eur. Radiol.*, **30**, 6062–71 (2020) https://doi.org/10.1007/s00330-020-06950-2

[74] Surti S. Radionuclide Methods and Instrumentation for Breast Cancer Detection and Diagnosis. *Semin. Nucl. Med.*, **43**, 271–80 (2013) https://doi.org/10.1053/j.semnuclmed.2013.03.003

[75] Urbano N, Scimeca M, Tancredi V, Bonanno E, Schillaci O. 99mTC-sestamibi breast imaging: Current status, new ideas and future perspectives. *Semin. Cancer Biol.*, **84**, 302–9 (2022) https://doi.org/10.1016/j.semcancer.2020.01.007

[76] Dhankhar R, Vyas SP, Jain AK, Arora S, Rath G, Goyal AK. Advances in Novel Drug Delivery Strategies for Breast Cancer Therapy. *Artif. Cells, Blood Substitutes, Biotechnol.*, **38**, 230–49 (2010) https://doi.org/10.3109/10731199.2010.494578

[77] Zumsteg ZS, Morrow M, Arnold B, Zheng J, Zhang Z, Robson M, Traina T, McCormick B, Powell S, Ho AY. Breast-Conserving Therapy Achieves Locoregional Outcomes Comparable to Mastectomy in Women with T1-2N0 Triple-Negative Breast Cancer. *Ann. Surg. Oncol.*, **20**, 3469–76 (2013) https://doi.org/10.1245/s10434-013-3011-9

[78] van Maaren MC, de Munck L, Strobbe LJA, Sonke GS, Westenend PJ, Smidt ML, Poortmans PMP, Siesling S. Ten-year recurrence rates for breast cancer subtypes in the Netherlands: A large population-based study. *Int. J. Cancer*, **144**, 263–72 (2019) https://doi.org/10.1002/ijc.31914

[79] Cipora E, Konieczny M, Karwat I, Roczniak W, Babuśka-Roczniak M. Surgical method of treatment and level of satisfaction with life among women diagnosed with breast cancer, according to time elapsed since performance of surgery. *Ann. Agric. Environ. Med.*, **25**, 453–9 (2018) https://doi.org/10.26444/aaem/91586

[80] Waks AG, Winer EP. Breast Cancer Treatment. *JAMA*, **321**, 288 (2019) https://doi.org/10.1001/jama.2018.19323

[81] Gradishar WJ, Moran MS, Abraham J, Aft R, Agnese D, Allison KH, Anderson B, Burstein HJ, Chew H, Dang C, Elias AD, Giordano SH, Goetz MP, Goldstein LJ, Hurvitz SA, Isakoff SJ, Jankowitz RC, Javid SH, Krishnamurthy J, Leitch M, Lyons J, Mortimer J, Patel SA, Pierce LJ, Rosenberger LH, Rugo HS, Sitapati A, Smith KL, Smith M Lou, Soliman H, Stringer-Reasor EM, Telli ML, Ward JH, Wisinski KB, Young JS, Burns J, Kumar R. Breast Cancer, Version 3.2022, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.*, **20**, 691–722 (2022) https://doi.org/10.6004/jnccn.2020.0016

[82] Özdemir A, Mayir B, Demirbakan K, Oygür N. Efficacy of Methylene Blue in Sentinel Lymph Node Biopsy for Early Breast Cancer. *J. breast Heal.*, **10**, 88–91 (2014) https://doi.org/10.5152/tjbh.2014.1914

[83] Wilson RE. Surgical management of locally advanced and recurrent breast cancer. *Cancer*, **53**, 752–7 (1984) https://doi.org/10.1002/1097-0142(19840201)53:3+<752::aid-cncr2820531324>3.0.co;2-2

[84] Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomised trials. Early Breast Cancer Trialists' Collaborative Group. *Lancet (London, England)*, **355**, 1757–70 (2000) https://doi.org/10.1016/S0140-6736(11)61629-2

[85] Donegan WL, Perez-Mesa CM, Watson FR. A biostatistical study of locally recurrent breast carcinoma. *Surg. Gynecol. Obstet.*, **122**, 529–40 (1966) https://doi.org/10.1111/j.1075-122X.2006.00240.x

[86] Halverson KJ, Perez CA, Kuske RR, Garcia DM, Simpson JR, Fineberg B. Isolated local-regional recurrence of breast cancer following mastectomy: Radiotherapeutic management. *Int. J. Radiat. Oncol.*, **19**, 851–8 (1990) https://doi.org/10.1016/0360-3016(90)90004-4

[87] Whelan TJ, Pignol J-P, Levine MN, Julian JA, MacKenzie R, Parpia S, Shelley W, Grimard L, Bowen J, Lukka H, Perera F, Fyles A, Schneider K, Gulavita S, Freeman C. Long-Term Results of Hypofractionated Radiation Therapy for Breast Cancer. *N. Engl. J. Med.*, **362**, 513–20 (2010) https://doi.org/10.1056/NEJMoa0906260

[88] Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, Dobbs HJ, Hopwood P, Lawton PA, Magee BJ, Mills J, Simmons S, Sydenham MA, Venables K, Bliss JM, Yarnold JR. The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol.*, **14**, 1086–94 (2013) https://doi.org/10.1016/S1470-2045(13)70386-3

[89] Polgár C, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, Lyczek J, Guinot JL, Dunst J, Miguelez CG, Slampa P, Allgäuer M, Lössl K, Polat B, Kovács G, Fischedick A-R, Fietkau R, Resch A, Kulik A, Arribas L, Niehoff P, Guedea F, Schlamann A, Pötter R, Gall C, Uter W, Strnad V. Late side-effects and cosmetic results of accelerated partial breast irradiation with interstitial brachytherapy versus whole-breast irradiation after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: 5-year resul. *Lancet Oncol.*, **18**, 259–68 (2017) https://doi.org/10.1016/S1470-2045(17)30011-6

[90] Ciabattoni A, Gregucci F, Fastner G, Cavuto S, Spera A, Drago S, Ziegler I, Mirri MA, Consorti R, Sedlmayer F. IOERT versus external beam electrons for boost radiotherapy in stage I/II breast cancer: 10-year results of a phase III randomized study. *Breast Cancer Res.*, **23**, 46 (2021) https://doi.org/10.1186/s13058-021-01424-9

[91] Swain, S. M., Baselga, J., Kim, S. B., Ro, J., Semiglazov, V., Campone, M., Ciruelos, E., Ferrero, J. M., Schneeweiss, A., Heeson, S., Clark, E., Ross, G., Benyunes, M. C., Cortés, J., & CLEOPATRA Study Group. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *The New England Journal of Medicine*, **372**(8), 724–734. (2015) https://doi.org/10.1056/NEJMoa1413513

[92] Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, Luini A, Veronesi P, Galimberti V, Zurrida S, Leonardi MC, Lazzari R, Cattani F, Gentilini O, Intra M, Caldarella P, Ballardini B. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): *a randomised controlled equivalence trial*. *Lancet Oncol.*, **14**, 1269–77 (2013) https://doi.org/10.1016/S1470-2045(13)70497-2

[93] McBride A, Allen P, Woodward W, Kim M, Kuerer HM, Drinka EK, Sahin A, Strom EA, Buzdar A, Valero V, Hortobagyi GN, Hunt KK, Buchholz TA. Locoregional Recurrence Risk for Patients With T1,2 Breast Cancer With 1-3 Positive Lymph Nodes Treated With Mastectomy and Systemic Treatment. *Int. J. Radiat. Oncol.*, **89**, 392–8 (2014) https://doi.org/10.1016/j.ijrobp.2014.02.013

[94] Muhsen S, Moo T-A, Patil S, Stempel M, Powell S, Morrow M, El-Tamer M. Most Breast Cancer Patients with T1-2 Tumors and

One to Three Positive Lymph Nodes Do Not Need Postmastectomy Radiotherapy. *Ann. Surg. Oncol.*, **25**, 1912–20 (2018) https://doi.org/10.1245/s10434-018-6422-9

[95] Wu S-G, Wang J, Lian C-L, Lei J, Hua L, Lin Q, Chen Y-X, He Z-Y.Evaluation of the 8th edition of the American joint committee on cancer's pathological staging system in prognosis assessment and treatment decision making for stage T1-2N1 breast cancer after mastectomy. *The Breast*, **51**, 2–10 (2020) https://doi.org/10.1016/j.breast.2020.02.012

[96] Verma, S., Miles, D., Gianni, L., Krop, I. E., Welslau, M., Baselga, J., Pegram, M., Oh, D. Y., Diéras, V., Guardino, E., Fang, L., Lu, M. W., Olsen, S., Blackwell, K., & EMILIA Study Group Trastuzumab emtansine for HER2-positive advanced breast cancer. *The New England Journal of Medicine*, **367**(19), 1783–1791. (2012) https://doi.org/10.1056/NEJMoa1209124

[97] Mieog JSD, van der Hage JA, van de Velde CJH. Neoadjuvant chemotherapy for operable breast cancer. *Br. J. Surg.*, **94**, 1189–200 (2007) https://doi.org/10.1002/bjs.5894

[98] Takada M, Imoto S, Ishida T, Ito Y, Iwata H, Masuda N, Mukai H, Saji S, Ikeda T, Haga H, Saeki T, Aogi K, Sugie T, Ueno T, Ohno S, Ishiguro H, Kanbayashi C, Miyamoto T, Hagiwara Y, Toi M. A risk-based subgroup analysis of the effect of adjuvant S-1 in estrogen receptor-positive, HER2-negative early breast cancer. *Breast Cancer Res. Treat.*, **202**, 485–96 (2023) https://doi.org/10.1007/s10549-023-07099-4

[99] Walsh EM, Keane MM, Wink DA, Callagy G, Glynn SA. Review of Triple Negative Breast Cancer and the Impact of Inducible Nitric Oxide Synthase on Tumor Biology and Patient Outcomes. *Crit. Rev. Oncog.*, **21**, 333–51 (2016) https://doi.org/10.1615/CritRevOncog.2017021307

[100] Suman VJ, Du L, Hoskin T, Anurag M, Ma C, Bedrosian I, Hunt KK, Ellis MJ, Symmans WF. Evaluation of Sensitivity to Endocrine Therapy Index (SET2,3) for Response to Neoadjuvant Endocrine Therapy and Longer-Term Breast Cancer Patient Outcomes (Alliance Z1031). *Clin. Cancer Res.*, **28**, 3287–95 (2022) https://doi.org/10.1158/1078-0432.CCR-22-0068

[101] Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. *Lancet*, **378**, 771–84 (2011) https://doi.org/10.1016/S0140-6736(11)60993-8

[102] Cole KM, Clemons M, Alzahrani M, Liu M, Larocque G, MacDonald F, Hutton B, Piper A, Fernandes R, Pond GR, Vandermeer L, Emam K El, McGee SF. Vasomotor symptoms in early breast cancer-a "real world" exploration of the patient experience. *Support. Care Cancer*, **30**, 4437–46 (2022) https://doi.org/10.1007/s00520-022-06848-3

[103] Aromatase inhibitors versus tamoxifen in early breast cancer: patient-level meta-analysis of the randomised trials. *Lancet*, **386**, 1341–52 (2015) https://doi.org/10.1016/S0140-6736(15)61074-1

[104] Knauer M, Filipits M, Dubsky P. Late Recurrences in Early Breast Cancer: For Whom and How Long Is Endocrine Therapy Beneficial? *Breast Care*, **9**, 97–97 (2014) https://doi.org/10.1159/000362482

[105] Mazzeo, R., Sears, J., Palmero, L., Bolzonello, S., Davis, A. A., Gerratana, L., & Puglisi, F. (2024). Liquid biopsy in triple-negative breast cancer: unlocking the potential of precision oncology. *ESMOOpen*, *9*, 103700(2024) https://doi.org/10.1016/j.esmoop.2024.103700

[106] Mann RM, Hooley R, Barr RG, Moy L. Novel Approaches to Screening for Breast Cancer. *Radiology*, **297**, 266–85 (2020) ,https://doi.org/10.1148/radiol.2020200172

[107] Verma S, Miles D, Gianni L, Krop IE, Welslau M, Baselga J, Pegram M, Oh D-Y, Diéras V, Guardino E, Fang L, Lu MW, Olsen S, Blackwell K. Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer. *N. Engl. J. Med.*, **367**, 1783–91 (2012) https://doi.org/10.1056/NEJMoa1209124

[108] Daly MB, Pal T, Berry MP, Buys SS, Dickson P, Domchek SM, Elkhanany A, Friedman S, Goggins M, Hutton ML, Karlan BY, Khan S, Klein C, Kohlmann W, Kurian AW, Laronga C, Litton JK, Mak JS, Menendez CS, Merajver SD, Norquist BS, Offit K, Pederson HJ, Reiser G, Senter-Jamieson L, Shannon KM, Shatsky R, Visvanathan K, Weitzel JN, Wick MJ, Wisinski KB, Yurgelun MB, Darlow SD, Dwyer MA. Genetic/Familial High-Risk Assessment: Breast, Ovarian, and Pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. *J. Natl. Compr. Cancer Netw.*, **19**, 77–102 (2021) https://doi.org/10.6004/jnccn.2021.0001

[109] Patterson SK, Noroozian M. Update on Emerging Technologies in Breast Imaging. *J. Natl. Compr. Cancer Netw.*, **10**, 1355–62 (2012) https://doi.org/10.6004/jnccn.2012.0141

[110] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Hegg R, Im S-A, Shaw Wright G, Henschel V, Molinero L, Chui SY, Funke R, Husain A, Winer EP, Loi S, Emens LA. Atezolizumab and Nab-Paclitaxel in Advanced Triple-Negative Breast Cancer. *N. Engl. J. Med.*, **379**, 2108–21 (2018) https://doi.org/10.1056/NEJMoa1809615

[111] Finn RS, Martin M, Rugo HS, Jones S, Im S-A, Gelmon K, Harbeck N, Lipatov ON, Walshe JM, Moulder S, Gauthier E, Lu DR, Randolph S, Diéras V, Slamon DJ. Palbociclib and Letrozole in Advanced Breast Cancer. *N. Engl. J. Med.*, **375**, 1925–36 (2016) https://doi.org/10.1056/NEJMoa1607303

[112] Tang X, Loc WS, Dong C, Matters GL, Butler PJ, Kester M, Meyers C, Jiang Y, Adair JH. The use of nanoparticulates to treat breast cancer. *Nanomedicine (Lond).*, **12**, 2367–88 (2017) https://doi.org/10.2217/nnm-2017-0202