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(REVIEW ARTICLE)

Current and emerging biomarkers in breast cancer: A review

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Abstract

The second leading cause of cancer-related mortality in women is breast cancer, a complicated illness. A growing body of research suggested that a number of variables, including environmental and genetic factors, may be linked to the development and spread of breast cancer. One of the most crucial parts of treating breast cancer is early diagnosis of patients. Imaging methods are primary diagnosis approaches among a variety of diagnosis platforms that may yield important information about individuals with breast cancer. Numerous imaging modalities, including computed tomography (CT), positron-emission tomography (PET), mammography, magnetic resonance imaging (MRI), and single-photon emission computed tomography (SPECT), have been demonstrated to be useful for diagnosing and tracking patients with breast cancer at different stages of the disease. In addition to imaging methods, patients with breast cancer may benefit from the use of biochemical biomarkers such proteins, genes, DNA, mRNAs, and microRNAs as additional diagnostic and therapeutic tools. We reviewed a number of imaging modalities in this review, along with current conventional, cutting-edge, and prospective biomarkers that may be used to diagnose breast cancer in patients.

Keywords: Breast Cancer; Imaging Techniques; Biomarkers; Biosensor; PCR

1. Introduction

WHO estimates that cancer will be the primary cause of death globally in 2020, accounting for around 10 million fatalities, or roughly one in six deaths. The term "cancer" refers to a broad category of illnesses that can impact any area of the body. Neoplasms and malignant tumors are other words that are used. Rapid emergence of aberrant cells that proliferate beyond normal bounds and have the ability to infect nearby bodily regions and move to other organs is one of the characteristics that characterize cancer; this latter process is known as metastasis. The main reason why people die from cancer is because of widespread metastases.

The term "biosensor" was originally used in 1977 by Karl Cammann, a professor of analytical chemistry. After all, the International Union of Pure and Applied Chemistry (IUPAC) did not define a biosensor until 1977. It was created to combine the fields of engineering, biology, and chemistry into a single instrument for the detection of bioanalytical chemicals in a sample [1].

The United States is expected to have 1,918,030 new instances of cancer in 2022, and 609,360 cancer fatalities, with about 350 deaths per day from lung cancer, the most common cause of cancer-related mortality. The incidence of female breast cancer increased gradually (by 0.5% yearly) from 2014 to 2018.

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2. Biosensors

Researchers from all over the world have begun to create and develop biosensors that might effectively detect cancer, unpaid for the non-destructive early diagnosis of the disease. In essence, biosensors transform biological entities such as proteins, DNA, and RNA into detectable and studied electrical signals in order to identify and study a particular biological analyte [2]. The term "Bios" enters the picture because the sensor detects biological materials. Nucleic acids, enzymes, antibodies, and microorganisms are a few examples of the biological stuff. The contemporary glucose sensor is derived from the study of Prof. Leland C. Clark Jr., who is regarded as the "Father of Biosensors" [3].

Different types of biosensors cancer cell detection :

- Calorimetric Biosensors
- Fluorescence Biosensors
- SERS – Based Biosensors
- SPR – Based Biosensors
- Electrochemical Biosensors
- Electro-magnetic meta materials-based Biosensors
- Crystal Optical Refractive Index Biosensors [4].

Table 1 The Three Components of Biosensors [5]

Capture Agents	Transducers	Surface Chemistry
Antibody	Electrochemical	-Non covalent/Non-specific
Oligonucleotide	Mass change	Non-covalent/ non-specific
	Optical	Covalent/non-specific
	Others	Covalent/Site-specific

Three elements need to be taken into account when building a biosensor: a transducer to convert a biochemical response into a measurable signal, an immobilization matrix to immobilize a recognition biomolecule, and a bio-recognition element for the selective recognition of an analyte, also known as a bio receptor [5].

2.1. Classification of Biosensors

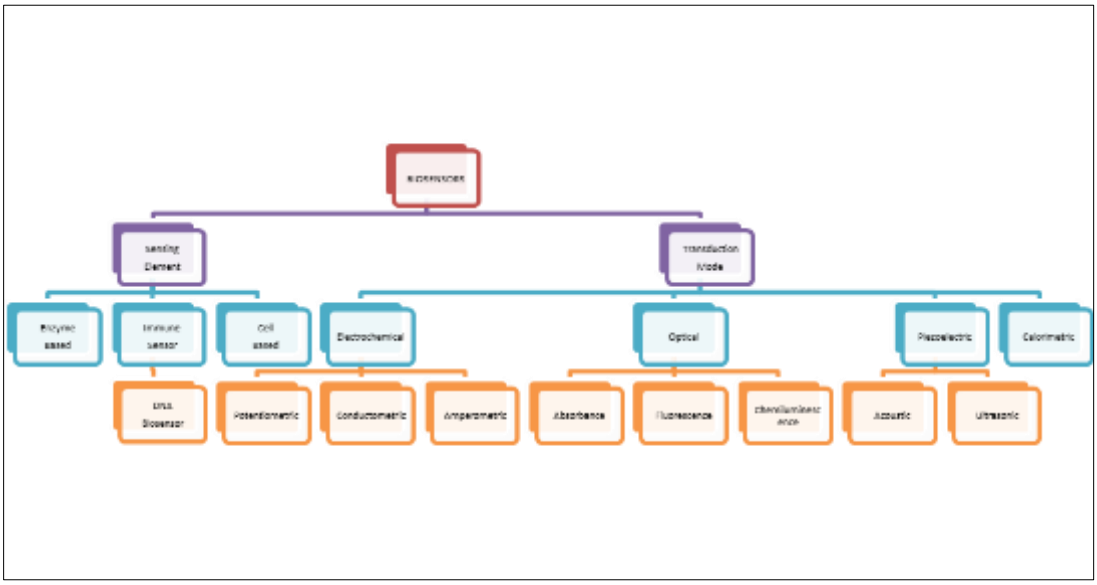

Figure 1 Types of Biosensors [6]

2.2. Advantages

Compared to conventional cancer diagnosis techniques, biosensors may offer a variety of benefits, including shorter test times, portability, high sensitivity and selectivity, simplicity, miniaturization, and adaptability. Biosensor-based diagnostics can help with cancer screening, increase early diagnosis rates, and lead to better prognoses. This technology can be especially helpful for improving healthcare delivery to the underprivileged and in public settings. Biosensors may be used for automated testing, multi-target analysis, and economical testing [7].

3. Biomarkers

Owing to a number of drawbacks associated with invasive cancer detection procedures, scientists and researchers worldwide are focusing on non-invasive cancer diagnosis through the use of cancer biomarkers. A biomarker is a biological molecule that can be found in blood or other bodily fluids or tissues that can indicate an abnormal or normal process of a disease or condition like cancer, according to the National Cancer Institute [8].

4. Breast cancer

The most frequent cause of cancer-related mortality is breast cancer [9, 10]. In addition, although women have traditionally been more susceptible to the illness [11], the prevalence of breast cancer is rising worldwide and is higher for those who live in less developed nations [12]. Early cancer diagnosis is of tremendous interest to the public because it greatly increases the likelihood of successful cancer treatment [13]. Therefore, it is essential to recognize cancer cells in order to detect cancer at an early stage [14, 15].

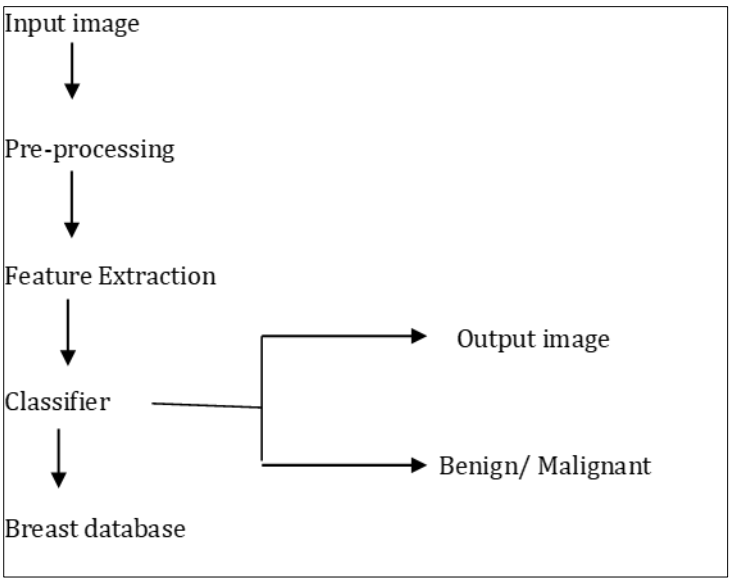

Figure 2 Breast cancer detection system[16]

In 2020, the World Health Organization reported 2.26 million new cases of breast cancer and 685,000 deaths from the disease. An electronic device known as a biosensor offers a particularly useful method for the early detection of breast cancer and the measurement of breast cancer biomarkers [17–20].

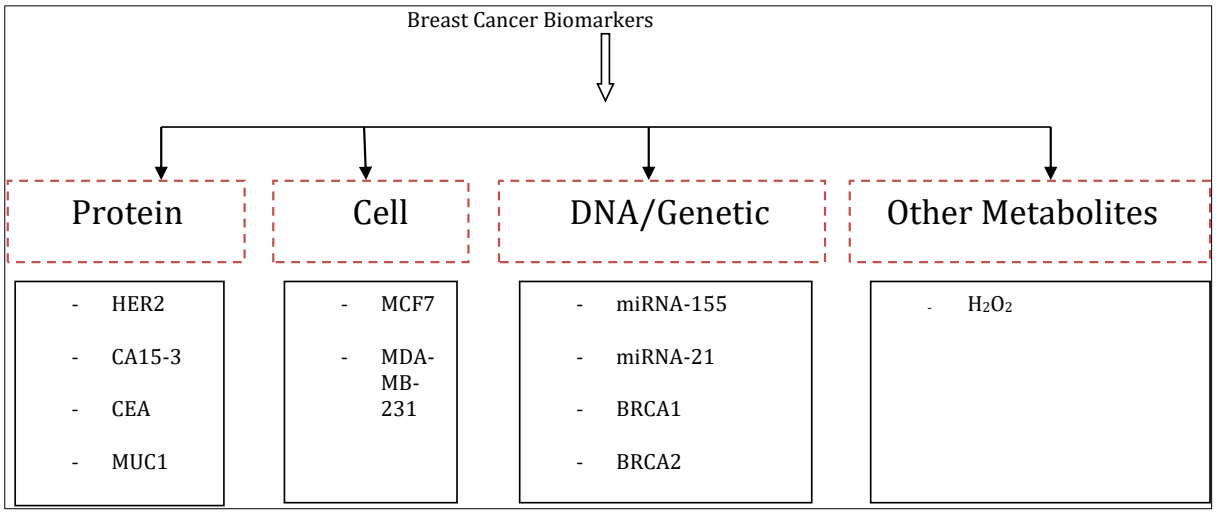

Figure 3 Breast Cancer Biomarkers

5. Imaging techniques and breast cancer

One non-communicable disease that accounts for 12% of all deaths globally and approximately 12 million new cases are diagnosed annually is cancer [21, 22]. Almost 24.2% of newly diagnosed malignancies in women are caused by this cancer [23]. With an anticipated 2.3 million new cases in women, breast cancer will account for 11.7 percent of all cancer cases in 2025, overtaking lung cancer as the leading cause of cancer incidence worldwide [24, 25]. A review of the literature indicates that 626,679 deaths and around two million new instances of breast cancer were recorded in 2018 [26]. Women who are younger may also be harmed by this cancer [27]. Iranian women have more breast density than women of other races [28, 29]. Ninety percent of females with breast cancer survive, according to surveys; however, the survival rate drops to sixty percent for women with advanced illness [30]. The high death rates from cancer have persisted in spite of the use of strong medications in recent years, which has increased research into alternative cancer treatment strategies [31, 32]. During the whole course of treating neoplasms, imaging is used [33]. The first step in detecting cancer is to use imaging technologies, which are an integral element of clinical procedures related to the condition [34]. Among the many benefits of medical imaging are long-term use, less invasive procedures, and real-time monitoring without tissue loss [31]. Leonard Fass (2008) and Safarpour Lima and colleagues (2019) discovered in a review of the literature that imaging through screening is essential to cancer care [31, 34]. Imaging techniques can be used to identify breast cancer early [26]. However, different approaches have different levels of sensitivity and specificity [35, 36]. Assessments state that integrated imaging methods can offer extra information for the management of the illness [31]. Ultrasonography, screening mammography, and combinations of these techniques are examples of complementary imaging [34]. Because of the rise in false-negative mammograms, women with thick breast tissue are advised to undergo additional screening modalities, such as ultrasonography [37]. Berg et al. (2008) found that combining screening ultrasonography with mammography will reduce the number of cases diagnosed, but it will also increase the frequency of false positives significantly [38].

Table 2 Imaging Techniques

Techniques	**Model**	**Samples**	**Sensitivity and Specificity**	**References**
Mammography Ultrasonography			Sensitivity 86% Specificity 56% Sensitivity 89 % Specificity 22 %	Olubukola A.T. Omidiji et al., 2017
Mammography			Sensitivity 53% Specificity	Wendie A. Berg et al., 2016

Ultrasonography			90% Sensitivity 52% Specificity 86%	
B7-H3–targeted ultrasound	Mice			Bachawal et al., 2015
18 F-FES-PET	Human	100	Sensitivity 100%	van Kruchten et al., 2015
PSOWNN	Human	54		Dheeba, Singh, & Selvi, 2014
Film-screen mammography	Human	738		Michell et al., 2012
Full-field digital mammography	Human	738		Michell et al., 2012
Digital breast tomosynthesis	Human	738		Michell et al., 2012
The NHS Breast Screening Programme (NHSBSP)	Human	26,475		Bennett, Sellars, & Moss, 2011
Ultrasonography	Human	241	Sensitivity 100% Specificity 89.1%	Zanello et al., 2011
MR mammography	Human	36	Sensitivity 94%	Chan et al., 2010
Digital breast tomosynthesis (DBT)			Sensitivity 69.8% Specificity 88.9%	Gennaro et al., 2010
Full-field digital mammography (FFDM)			Sensitivity 74.3% Specificity 84.8%	Gennaro et al., 2010
Computed tomographic (CT)	Human	29000		de González et al., 2009
SPECT imaging (MIBI)	Human	146	Sensitivity 96% Specificity 59%	Brem et al., 2008
MR imaging	Human	70	Sensitivity 97%	Kuroki-Suzuki et al., 2007
BMRI	Human	116		Trecate et al., 2006
Scintimammography	Human	59	Sensitivity 85% Specificity 90%	Das, Biswal, & Bhavaraju, 2006
X-ray mammography	Human	59	Sensitivity 89% Specificity 14%	Das et al., 2006
FDG-PET	Human	80	Sensitivity 44% Specificity 95%	Kumar et al., 2006
FDG-PET	Human	125	Sensitivity 84.5% Specificity 98.5%	Gil-Rendo et al., 2006
Digital mammography	Human	49,528	Sensitivity 0.70 ± 0.03 Specificity 0.92 ± 0.001	(Pisano et al., 2005)
Film mammography	Human	49,528	Sensitivity 0.66 ± 0.03 Specificity 0.92 ± 0.001	Pisano et al., 2005
Positron emission tomography (PET)	Human	360	Sensitivity 61%	Wahl, Siegel, Coleman, & Gatsonis, 2004
MR mammography	Human	7	Sensitivity 81%	Kinkel & Vlastos, 2001

Spectroscopic Reconstructed Near Infrared Tomographic Imaging	Human	5		McBride, 2001
Computer-aided diagnosis	Human	1,083	Sensitivity 81%	Birdwell, Ikeda, O'Shaughnessy, & Sickles, 2001
MR mammography	Human	50	Sensitivity 96%	Viehweg, Lampe, Buchmann, & Heywang-Köbrunner, 2000
MR mammography	Human	50	Sensitivity 58%	Fischer, Kopka, & Grabbe, 1999
MR mammography	Human	33	Sensitivity 67%	Westerhof, Fischer, Moritz, & Oestmann, 1998
MR mammography	Human	19	Sensitivity 100%	Boetes et al., 1997
MR mammography	Human	13	Sensitivity 77%	Orel et al., 1997
MR mammography	Human	58	Sensitivity 96.5%	Gilles et al., 1996
MR mammography	Human	11	Sensitivity 100%	Soderstrom et al., 1996
MR mammography	Human	17	Sensitivity 82%	Bone et al., 1996
MR mammography	Human	8	Sensitivity 87%	Boetes et al., 1995
18 F-FES-PET	Human	86	Sensitivity 69% Specificity 100%	Dehdashti et al., 1995
MR mammography	Human	7	Sensitivity 100%	Harms et al., 1993
18 F-FES-PET	Human	100	Sensitivity 100%	Mintun et al., 1988
Computed tomographic (CT)	Human	1,625		Chang et al., 1980

Imaging tools provide images with varying contrast due to physical quality variations. X-ray-based cancer imaging approaches are not receiving as much attention as digital imaging technologies. To identify cancer, stage it, evaluate the effectiveness of therapy, and direct biopsy procedures, a magnetic resonance system is employed [34].

5.1. Digital Imaging Technology

One often used screening method is mammography [39]. To identify the illness, mammography screening for malignancy is frequently utilized [27]. Numerous studies have indicated that it can lower the death rate from cancer [27, 40]. Mammography can be used to image young, compact breasts, but because the surrounding fibro glandular tissue masks the appearance of lesions, it is not sensitive enough to identify abnormalities [31]. The "gold standard" for identifying breast cancer is film mammography [41]. Screen-film mammography has certain intrinsic limitations, such as poor contrast features [42], even if it can also be utilized for early tumor diagnosis and follow-up [27]. Compared to conventional film-based procedures, full-field digital mammography (FFDM) is a helpful imaging technique for breast screening that has several advantages. A few benefits include reduced dosage, telemedicine, softcopy review, tomosynthesis, and digital archiving [34]. It's important to remember that classic film-screen mammography has advantages in terms of availability and affordability [43].

Skaane and Skjennald (2004) discovered that mammography outperformed screen-film mammography in the 50–69 age group for cancer detection. The study was titled "Screen-Film Mammography versus Full-Field Digital Mammography with Soft-Copy Reading." In the 45–49 age range, the detection rates for the two systems were almost the same [44]. Obenauer and associates discovered in a study that screen film is inferior than digital mammography in terms of image quality [45]. One of the possible drawbacks of 2D mammography is the normal tissues, like glandular tissue, that can cover up and obscure tumors [31]. Breast tightness may be reduced by using X-ray technology [34]. In contrast-enhanced mammography, iodinated agents are utilized as a preliminary method [46]. The theory underlying this experimental technology is that angiogenesis, a process that causes rapid tumor growth, requires an increased blood supply [33]. If the compression tool is not in use, contrast has to be provided. Angiogenesis sites will see an accumulation of the contrast agent [46]. Tomosynthesis has potential use in therapy monitoring and primary and secondary lesion diagnosis [31, 47].

5.2. Ultrasonography

A routine imaging procedure called ultrasonography is used to diagnose breast cancer. It has progressed to the point where breast imaging is now possible in recent years [27]. A follow-up examination using ultrasound technology can help to clarify unclear findings [48]. Ultrasonography can be used to evaluate the orientation and shape of breasts, particularly fatty and thick breasts [49]. Extended field of view imaging provides a panoramic high-resolution image of the breast [50,51]. Using ultrasonic detection, elastic sonography is a common method for finding breast lesions [52]. To identify and track the effectiveness of local therapy, contrast-enhanced ultrasound is utilized [53]. This method makes use of intravenously administered gas microbubbles [54]. 3D ultrasonography can be used to determine the volume of a lesion [55].

Despite the fact that some studies thought there would be a rise in false-positive masses if ultrasonography was used to identify cases that mammography missed [56]. The accuracy of diagnosis was reported to be increased by using ultrasonography in addition to mammography by Berg and colleagues (2008) [38]. One study found that mammography is indicated for breast cancer when comparing the results of ultrasonography with mammography [57]. Tiny, node-negative breast cancers can be found with screening ultrasonography, according to a 2008 publication [38]. Ultimately, the researchers discovered that breast neoplasm could be predicted by mammography, ultrasonography, and clinical diagnosis [58]. In a different survey, Devolli-Disha and associates assessed 546 women who had breast complaints and found that, in comparison to mammography, ultrasonography had a statistically significant higher rate in patients with breast complaints [59].

5.3. Magnetic Resonance Imaging (MRI)

As a supplementary technique, breast MRI is performed in conjunction with mammography [31]. Breast neoplasm was examined using MRI by Ross and colleagues (1982) [60]. Breast MR is becoming more and more popular as an adjunctive modality. MRI is not commonly used as a breast cancer monitoring test because of high false positives and high costs, despite its superior sensitivity than mammography [61]. For women with thick breast tissue, breast MRI is a useful screening technique [31]. The ability of MRI to identify contralateral breast neoplasm expansion has been confirmed by the American Cancer Society [31]. These problems suggest that MRI is preferable to mammography [62]. This disparity implies that using magnetic resonance imaging to guide the decision between surgery and a breast-conserving mastectomy can be beneficial. More precise anatomical delineation and cancer detection have been made possible by recent developments in MRI technology [63, 64]. A variety of methods may be used in conjunction with one another to identify breast cancer early [35]. A study found that mammography is insufficient for an early diagnosis, as is mammography combined with ultrasonography [65].

6. Biochemical markers and breast cancer

Table 3 Biomarkers used in Breast Cancer

Biomarkers	Description	Reference
Classical Markers		
Ki-67	Protein expression is related to cell proliferation and higher protein levels to biological aggressiveness.	Rakha et al., 2022 Menon et al.,2019
P53	Tumor suppressor protein involved in cell cycle arrest, differentiation, senescence, apoptosis, cell growth, and DNA repair. Its degradation is linked to tumor formation, progression, and metastasis.	Xu et al.,2021 Shahbandi et al.,2020
ER	Nuclear receptor that acts as a ligand-activated transcription factor. The main isoform is ERα that is associated with cell survival and proliferation.	Fuentes and Silveyra et al.,2019 Mills et al.,2018
PR	Nuclear receptor that acts as a ligand-activated transcription factor. It is associated with the expression of genes related to the cell cycle, cell differentiation, and proliferation.	Cenciarini and Proietti et al., 2019 Hilton et al.,2018
HER2	Receptor signaling leads to tumor growth and proliferation, adhesion, cell survival, and metastasis	Harbeck et al.,2019 Nicolini et al.,2018

Gene Aleterations		
PTEN	Tumor suppressor gene related to cell cycle progression, cell growth, and survival. Deletions or mutations are related to proliferation, invasion, and metastasis.	Chen et al.,2022 Carbognin et al.,2019
CHEK2	Tumor suppressor gene related to cell cycle regulation, inhibition of cell proliferation, activation of DNA repair, and apoptosis. It encodes the protein serine/threonine CHK2 kinase, which is involved in DNA damage repair	Boonen et al.,2022 Greville-Heygate et al.,2020 Kleiblova et al.,2019
CDH1	Tumor suppressor gene that encodes the E-cadherin cell–cell adhesion protein, that prevents migration of tumor cells, avoiding cancer progression and metastases.	Bücker and Lehmann et al.,2022
PIK3CA	Gene involved in regulation of proliferation and apoptosis. PI3K protein is involved in several cellular processes, such as protein synthesis, cell proliferation, survival, glucose homeostasis, and DNA repair.	Reinhardt et al.,2022 Venetis et al.,2020 Thorpe et al.,2015
BRCA1 / BRCA2	Tumor suppressor genes fundamental to DNA repair. Loss of function generates inefficient DNA repair, increasing mutation rates, and contributing to tumor development.	Ayed-Guerfali et al.,2021
ATM	Gene associated with the DNA double-strand break repair mechanism. It encodes proteins that participate in DNA repair and cell cycle regulation.	Toss et al.,2021 Cunha et al.,2021 Moslemi et al.,2021
BRIP1	Tumor suppressor gene that encodes a protein belonging to the RecQ DEAH helicase family that helps repair damaged DNA by interacting with BRCA1.	Khan et al.,2021 Moyer et al.,2020
BARD1	BRCA1-binding partner protein that is related to DNA damage repair. Higher expression is associated with worse prognosis.	Zheng et al.,2021 Zhu et al.,2018
PALB2	Tumor suppressor gene that encodes PALB2, responsible for BRCA2 nuclear localization and DNA damage repair	Nepomuceno et al.,2017
Protein		
Ki-67	Ki-67 plays an important function in cell division, but its exact role is still unknown. The clinical significance of Ki-67 index as a prognostic marker and predictor of recurrence in different molecular subtypes of breast cancer.	Soliman & Yussif, 2016
ErbB2	The ErbB2 receptor tyrosine kinase 2 in human serum and raw cancer lysates.	Eletxigerra et al., 2015
CA15-3 CA125 CEA TSGF	Univariate analysis revealed that combined detection of CA15-3, CA125, CEA, and TSGF in nipple discharge served as novel biomarkers for the diagnosis and prognosis of breast cancer	Wang et al., 2014
SPAG9	An association of the cancer testis antigen sperm-associated antigen 9 (SPAG9) in ovarian carcinomas.	Kanojia, Garg, Gupta, Gupta, & Suri, 2009
AHSG anti-AHSG autoantibody	Used as a tumor antigen.	Yi et al., 2009
EFEMP1	Antagonist of angiogenesis	Sadr-Nabavi et al., 2009

Matrix metalloproteinases (MMP)	Angiogenic factor	Pories et al., 2008
ADAM 12	Can be detected in the urine of breast cancer patients and provide independent prediction of disease status.	Pories et al., 2008
PDGF IGF-I	Prognostic factor for breast cancer. Synergistically promote cell proliferation and the transformation of several types of cells.	Pasanisi et al., 2008
CA 15-3	One of the most import reliable for metastatic breast cancer monitoring	Toth et al., 2008
LG3 fragment	An antiangiogenesis factor, was decreased in the cancer cell line.	Chang et al., 2008
TBX3	Transcription factor of the T-box gene family	Yarosh et al., 2008
Ki-67	Prognostic factor used to evaluate the proliferative activity of breast cancer	De Azambuja et al., 2007
caPCNA isoform	Highly effective detector of malignany.	Malkas et al., 2006
Metallothionein	A family of low molecular weight metal binding proteins encoded by at least 10 functional MT genes that are associated with cell proliferation in breast cancer.	Bay, Jin, Huang, & Tan, 2006
Leptin and ObR	A product of obese gene. The activities of leptin are mediated through the transmembrane leptin receptor	Garofalo et al., 2006
BC1	Serum Biomarker.	Mathelin, Cromer, Wendling, Tomasetto, & Rio, 2006
BC3	Serum Biomarker.	Mathelin et al., 2006
HNP1	Have a potential role in the biosynthetic and tissue remodeling responses of conjunctival fibroblasts.	Li et al., 2005
Protein kinase Cε (PKCε)	A member of a family of serine/threonine protein kinases, is a transforming oncogene that has been reported to be involved in cell invasion and motility. The role of PKCε in breast cancer development and progression.	Pan et al., 2005
GATA3	Is a transcriptional activator highly expressed by the luminal epithelial cells in the breast.	Mehra et al., 2005
HCCR	Oncoprotein is reported to be related to tumorigenesis, in breast cancer, functioning as a negative regulator of p53.	Jung et al., 2005
EZH2	Is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells.	Kleer et al., 2003
HSP27 (u) 14-3-3 sigma (d)	HSP27 was found up-regulated while14-3-3 sigma was down-regulated in the serum of breast cancer patients.	Rui, Jian-Guo, Yuan-Peng, Hai, & Bing-Gen, 2003
ERα ERβ	In vivo observations, ERβ may have the potential to become a therapeutic target in the specific subcohort of ERα-negative breast cancers.	Fuqua et al., 2003
HER2	Have prognostic significance in breast cancer.	Yamashita et al., 2003

CD24	Expressed in hematological malignancies as well as in a large variety of solid tumors including breast cancer.	Kristiansen et al., 2003
Cox-2	Can induce mammary tumorigenesis.	Ristimäki et al., 2002
NMP66	Involved in malignant transformation	Lüftner & Possinger, 2002
c-erbB-2 and p53	Prognostic significance in breast cancer.	Beenken et al., 2001
BAG-1	Is a multifunctional protein that interacts with a wide range of target molecules to regulate apoptosis, proliferation, transcription, metastasis and motility.	Turner et al., 2001
mRNA		
SPAG9	A member ofcancer testis (CT) antigen family, is associated with ovarian carcinomas.	Kanojia et al., 2009
ERR	The importance of estrogen-related receptors (ERRs) in human breast cancer was assessed by comparing their mRNA profiles with established clinicopathological indicators and mRNA profiles of estrogen receptors (ERs) and ErbB family members.	Ariazi, Clark, & Mertz, 2002
Her-2/neu	Signaling leads to tumor growth and proliferation, adhesion, cell survival and metastasis,	Pawlowski, Révillion, Hebbar, Hornez, & Peyrat, 2000
Gene		
NANOG	Cell inducing factor.	Nagata et al., 2017
KLF4	Cell inducing factor	Nagata et al., 2017
HOTAIR	As an androgen-repressed lncRNA	Zhang et al., 2015
KLK10 exon 3 methylation	*KLK10* exon 3 methylation provides important prognostic information in early breast cancer patients.	Kioulafa et al., 2009
EFEMP1	Down regulated factor.	Sadr-Nabavi et al., 2009
mtDNA	mtDNA replication can result in diminished mitochondrial biogenesis, decreased energy output, and organ dysfunction.	Kohler et al., 2009
ccf nDNA	Detected by Multiplex Real- Time PCR	Kohler et al., 2009
Free Circulating Tumor DNA	Detected by Real- Time PCR	Catarino et al., 2008
14-3-3-σ gene	Detected by Methylation specific PCR	Martínez-Galán et al., 2008
ESR1	Detected by Methylation specific PCR	Martínez-Galán et al., 2008
LINE1	Detected by Real-Time PCR	Sunami, Vu, Nguyen, Giuliano, & Hoon, 2008
Phosphocholine	Phosphocholine cytidylyltransferase (CCT) assay	Eliyahu, Kreizman, & Degani, 2007
C35 (C17orf37)	Northern blot and Real-Time PCR	Evans et al., 2006
microRNA		

miR-183/182/96 cluster	Detected By qRT-PCR	Song et al., 2016
miR-197	Detected By qRT-PCR	Shaker, Maher, Nassar, Morcos, & Gad, 2015
miR-205	Detected By qRT-PCR	Shaker et al., 2015
miRNA-10b	Detected By qRT-PCR	Eissa et al., 2015
miR-181b (d)	Detected By qRT-PCR	Sochor et al., 2014
miR-148b	Detected By qRT-PCR	Shen et al., 2014
miR-133a	Detected By qRT-PCR	Shen et al., 2014
miR-19a	Detected By qRT-PCR	Sochor et al., 2014
miR-24 (d)	Detected By qRT-PCR	Sochor et al., 2014
miR-1280	Detected by Microarray	Park et al., 2014
miR-1260	Detected by Microarray	Park et al., 2014
miR-720	Detected by Microarray	Park et al., 2014
miR-195	Detected By qRT-PCR	Heneghan et al., 2010
let-7a	Detected By qRT-PCR	Heneghan et al., 2010
miR-595 (u)	Detected By qRT-PCR	Zhao et al., 2010
miR-589 (u)	Detected By qRT-PCR	Zhao et al., 2010
miR-425 (u)	Detected By qRT-PCR	Zhao et al., 2010
miR-155 (d)	Detected By qRT-PCR	Zhao et al., 2010
miR-340 (d)	Detected By qRT-PCR	Zhao et al., 2010
miR-181a (d)	Detected By qRT-PCR	Zhao et al., 2010
miR-151-5p (d)	Detected By qRT-PCR	Zhao et al., 2010
miR-1275 (d)	Detected By qRT-PCR	Zhao et al., 2010
miR-1304 (d)	Detected By qRT-PCR	Zhao et al., 2010
miR-10b	Detected by Microarray and qRT-PCR	Mattie et al., 2006
miR-27b	Detected by Microarray and qRT-PCR	Mattie et al., 2006
miR-17-5p	Detected by Microarray and qRT-PCR	Mattie et al., 2006
miR-29b-2	Detected by Microarray and qRT-PCR	Mattie et al., 2006
miR-155	Detected by Microarray and Northern Blot	Iorio et al., 2005
miR-21	Detected by Microarray and Northern Blot	Iorio et al., 2005
miR-145	Detected by Microarray and Northern Blot	Iorio et al., 2005
miR-125b	Detected by Microarray and Northern Blot	Iorio et al., 2005

There are a number of drawbacks to using different imaging modalities, including cost, low sensitivity, and poor specificity [66]. Therefore, it appears that the introduction of novel biomarkers capable of circumventing the associated constraints of imaging techniques is necessary. One of the most crucial parts of diagnosing and tracking patients with breast cancer is the use of several biomarkers. A deeper comprehension of the cellular and molecular mechanisms involved in the etiology of breast cancer may be possible with the use of the appropriate biomarkers [67]. These results

may be useful in developing therapeutic strategies and tracking how well breast cancer patients are responding to their care.

Humans' MKI-67 gene, which is located on chromosome 10q26.2, encodes the nonhistone protein Ki-67, which is found in the nucleus and nucleoli [68]. Cell proliferation is correlated with Ki-67 expression, and biological aggressiveness in BC is correlated with greater protein levels [68,69]. When paired with additional markers, the predictive value of Ki-67 staining can be utilized to classify primary tumors and their metastases in addition to providing useful information on survival and recurrence rates [70]. Its application in clinical practice as a discriminator between luminal A and B types—Luminal B typically being more proliferative and having a higher Ki-67 detection than luminal A—has garnered a great deal of attention, particularly in cases where hormone receptors (HR) are positive [69,71]. The most common metric for assessing the efficacy of neoadjuvant endocrine therapy (NET) is the measurement of Ki-67 following a brief course of treatment, which indicates a biological response to the therapy [69]. Shifting Ki-67 levels were one of the primary outcome biomarkers in the IMPACT study, which compared the risk of mortality and recurrence of HR-positive BC patients on three different NET regimens [72]. Ki-67 suppression was higher with anastrozole (76% and 82%) than with tamoxifen (60% and 62%) and the combination of anastrozole and tamoxifen (64% and 61%) in this trial after 2 and 12 weeks of use [73]. It is possible to assess the efficacy of particular medicines by utilizing short-term Ki-67 alterations to forecast long-term benefits and consequences [69, 72, 73]. Ki-67 is still not commonly employed in clinical routines due to uncertainties regarding its analytical validity [72]. This is because different antibodies have varying degrees of reliability and interlaboratory scoring methodologies are highly variable, leading to a lack of agreement regarding scoring methods and cutoff values [69,74]. To ensure scoring uniformity, standardization, and subsequent clinical validation, recommendations are currently required for the use of Ki-67 in clinical practice [72].

Encoded by the TP53 gene, p53 is a tumor suppressor protein that plays a role in transcriptional regulation of processes including cell cycle arrest, differentiation, senescence, apoptosis, proliferation, and DNA repair [75,76]. Its degeneration is closely associated with the initiation, spread, and metastasis of tumors, making it a significant tumor suppressor [76]. The most commonly altered gene in British Columbia is TP53, which is seen in roughly 30–35% of primary invasive cases [77]. According to BC subtypes, TP53 mutations differ; they are present in 70% of HER2-positive cases and 80% of triple-negative breast tumors (TNBC) [77]. TP53 mutations are a significant biomarker in clinical practice and a possible therapeutic target because of the high occurrence of TNBC [77]. Immunohistochemistry (IHC) and DNA sequencing are used to detect the status of TP53 mutations [75]. Drugs had no effect on TP53-mutated tumors for a very long time. On the other hand, novel anticancer therapeutic approaches have been presented by recent preclinical investigations that have introduced drugs capable of restoring wild p53 characteristics [75,77]. COTI-2, PRIMA-1, APR-246, PK11007, and 3-quinuclidinone derivatives are a few of them [77]. Synnott et al. [78] reported that COTI-2 was able to reactivate mutant p53 and cause TNBC cells to undergo a therapeutic apoptotic response. PRIMA-1 and the production of apoptotic proteins in MDA-231 cells with mutant p53 protein were found to be related by Lee et al. [79]. Moreover, like BRCA1, TP53 holds considerable promise as a cancer molecular risk marker. As therapeutic targets for chemoprevention and targeted therapeutics, both tumor suppressor genes have the potential to be biomarkers for monitoring, early risk assessment, and propensity to BC [80]. Because of the aggressiveness, complexity, and frequency of tumors, breast cancer continues to be one of the primary cancer types studied in clinical trials.

The nuclear receptor known as the estrogen receptor (ER) functions as a transcription factor that is activated by ligands [81]. The nucleus has two isoforms of ER, ERα and ERβ [82]. ERα is the predominant form of ER in BC and it has a transcriptional role in genes related to cell survival and proliferation [83]. Divergent functions are linked to this isoform, ERβ, whose involvement is yet not entirely known [71]. ER is used in relation to ERα/ESR1 in this review. The most widely utilized predictive marker in BC is ER, which is primarily used for endocrine therapy (ET)-based treatment options and classification [69]. In situations with BC that have just been diagnosed, ER measurement is both required and advised [84]. When compared to ER-negative instances, ER expression is acknowledged as a BC biomarker of good prognosis [69,71]. The degree of ER tumor expression determines the response to ET, which is contingent upon ER positive [69]. ER antagonists are used in estrogen suppression therapies to eradicate ER-positive BC cells [85]. For the adjuvant therapy of ER-positive BC patients, a number of authorized ETs are often utilized and have been shown to increase survival and the time to disease recurrence [82,85]. Adjuvant ET is standard and advised for at least 5 years following surgery in luminal-type BC, which expresses both the progesterone and ER receptors [86]. Aromatase inhibitors (AIs), which include anastrozole, letrozole, and exemestane, are among the several forms of ET. They work by preventing the manufacture of estrogen, which lowers the amount of estrogen that is circulating in postmenopausal individuals [82,84,85]. Conversely, selective estrogen receptor modulators (SERMs), including tamoxifen, which may have antagonistic effect in breast tissue, compete with estrogen for ER binding and are recommended for premenopausal women [82,85]. Fulvestrant is one example of a selective estrogen receptor degrader (SERD) that has antagonistic and ER-degrading activities in addition to anti-estrogenic effects in the breast [87]. However, ET resistance may affect how well a treatment works. Estrogen-independent ER reactivation, caused by certain mutations in the ESR1

gene, is the most common cause of acquired resistance. It is uncommon to find in original BC patients and more common in recurrent and metastatic instances, particularly following long-term AI treatment [82,84,85,87]. Other types of ET can be employed sequentially to treat ERpositive instances, circumventing developed resistance to a particular medication because they work through different mechanisms [84]. Currently, CDK4/6, PI3K, and mTORC1 are among the other molecules that several ET therapies target [88].

Similar to ER, the progesterone receptor (PR) is a ligand-activated transcription factor and belongs to the nuclear receptor family [71]. PR attaches to DNA when it is active and controls the expression of many genes involved in the cell cycle, as well as cell differentiation and proliferation [89]. About 80–90% of ER-positive BC cases have positive PR results [69]. PR measurement is typically carried out in conjunction with ER; it is required and advised in cases that are initially diagnosed as well as in lesions that are recurring or metastatic [84]. Immunohistochemistry (IHC) is the suggested test for PR assessment, similar to ER [69]. Because this receptor can be activated by estrogen, the value of monitoring PR is still debatable [89] and not entirely understood [84]. This happens as a result of crosstalk between these two receptors caused by ER's regulation of the PGR gene, which is an ER-dependent gene product [69]. In light of this, PR serves as a biomarker for an intact and functional ER system [84,89], which has a direct bearing on a tumor's capacity to respond to endocrine treatments (ETs). PR positivity not only indicates a greater response to ETs but also indicates a functioning ER pathway, and patients with PR-positive tumors typically experience better clinical outcomes [90]. Longer disease-free longevity, a decreased recurrence rate, and an improved tamoxifen response may all be associated with high PR expression [89]. Tests like PAM50 yield semi-quantitative PR scores, which are useful in differentiating between BC types such luminal A and B [91]. As Luminal A subtypes have a better prognosis than Luminal B, elevated PR expression is thus more frequently detected in them [91]. According to Mohammed et al. [92], PR can bind to chromatin and modulate the expression of ERα when it is in the presence of an agonist ligand. A favorable prognosis is linked to this regulation of gene expression [92]. Research has demonstrated that ER and PR can interact negatively or positively, and a greater knowledge of this crosstalk can help to create more effective treatments [89]. Clinical trials are being conducted to investigate the potential of selective progesterone receptor modulators (SPRMs) to induce and modulate agonist, antagonist, or mixed PR responses in a tissue-specific way [93]. Mifepristone, telapristone acetate, and onapristone are a few of these modulators [94]. Antiprogestogens such as mifepristone and onapristone have shown promising results in treating patients who had not responded to other forms of treatment [94Mifepristone, either by itself or in conjunction with 4-hydroxytamoxifen (4-OHT), induced cell death and growth arrest in ER/PR-positive MCF7 cells that were resistant to antiestrogens, as shown by Gaddy et al. [95].

Along with HER1, HER3, and HER4, HER2 (human epidermal growth factor receptor 2) is a member of the human epidermal growth factor receptor family and is encoded by the ERBB2 gene [86,96]. Since HER2-positive cancers have a significant propensity for metastasis, ERBB2 amplification and overexpression in BC occur in 13–15% of cases and are associated with a poorer prognosis [86,69,97]. Immunohistochemistry (IHC) and/or in situ hybridization (ISH) are used to assess HER2 status [31]. Though the precise ligand for HER2 is unknown, dimerization follows ligand binding to activate HER2 [86]. Tumor growth and proliferation, adhesion, cell survival, and metastasis are all caused by HER2 signaling and are linked to the activation of pathways such PI3K/AKT/MAPK and RAS [86,84]. Aggressive histological features brought on by HER2 overexpression are linked to a shortened survival period [69]. Measuring the HER2 status is advised in cases of metastasis and recurrence and required in situations of invasive BC [86,84]. When it comes to HER2 assessment, IHC yields a result based on HER2 overexpression in a score that ranges from 0 to 3+, where 0/1+ is regarded as negative, 3+ as positive, and 2+ as equivocal, necessitating further testing with FISH [69]. Increased cell proliferation and invasion activity are seen in tumors scoring 3+ [97]. In cases of BC characterized by ERBB2 amplification or the overexpression of the HER protein, anti-HER-2 targeted treatments have demonstrated effectiveness [86]. Drugs based on anti-HER2 monoclonal antibodies, including margetuximab, trastuzumab, and tucatinib; tyrosine kinase inhibitors (TKIS), including lapatinib, tucatinib, and neratinib; and antibody-drug conjugates (ADCs), which bind a cytotoxic agent to a monoclonal antibody, like ado-trastuzumab emtansine (T-DM1) and trastuzumab deruxtecan (T-DXd) [69,98]. Pertuzumab and trastuzumab, together with a taxane, are the two HER2 antibodies used in combination as the first line of treatment for metastatic HER-2 malignancies [99]. Intra- and intertumoral HER2 heterogeneity appears to have an adverse effect on the response to anti-HER2 therapy, resulting in larger tumor size, poorer histology, more lymph node metastases, shorter recurrence time, and lower patient survival [98]. Additionally, treatment approaches are impacted by changes in HER2 status following metastasis. Loss of HER2 is more common in metastatic cancers [86]. Patients with brain metastases typically do not qualify for anti-HER2 clinical trials because tumor resistance in these circumstances is caused by the tumor's inability to cross the blood-brain barrier [86,98]. Patients with brain metastases would benefit more from lapatinib, tucatinib, and neratinib since TKIs are notably smaller and have a higher penetration capacity [98].

One of the most commonly changed genes in human cancer, including BC, is phosphohatase and tensin homolog (PTEN), a tumor suppressor whose function is inextricably linked to the advancement of the cell cycle, cell proliferation, and

survival [100]. PTEN mutations or deletions in tumor cells have been shown to dramatically boost migration and invasion activity, which in turn promotes invasion, metastasis, and proliferation. PTEN levels are significantly lower in metastatic BC cells than in localized cancer cells [101]. The PI3K/Akt oncogenic pathway, which promotes cell growth and survival, is excessively activated when PTEN function is lost [102]. Almost half of all BC cases have been shown to have PTEN activity loss as a result of protein, genetic, or epigenetic changes [100]. Somatic mutations are the primary cause of PTEN inactivation [101]. While the majority of research has not yet shown a connection between PTEN loss and prognosis in BC patients participating in treatment trials, new data indicates that BC HR+/HER2− or HER2+ patients may have worse results if PTEN expression is downregulated [100]. PTEN loss alters the function of BRAF, EGFR, and immunological "checkpoint" inhibitors, which can be a mechanism of resistance to different treatments. It also adversely impacts sensitivity to CDK4/6 inhibitors, starting signaling cascades that hyperactivate cyclins/CDKs [103]. In both HER2-positive and -negative BC, certain phase II and III clinical studies including translational analyses are investigating the predictive function of PTEN in response to various anticancer drugs. However, due to the variability of treatment regimens in patient cohorts, it is challenging to evaluate the true significance of PTEN loss due to the lack of consistency and reproducibility between clinical investigations [100]. Therefore, strong data are needed to fully prove PTEN's predictive/prognostic role in BC, even though there is some indication of a relationship between PTEN functional status, clinical outcome, and responsiveness to different treatments [100].

The protein serine/threonine CHK2 kinase, which is involved in DNA damage repair, is encoded by the Checkpoint Kinase 2 (CHEK2) gene [104,105]. It serves as a crucial tumor suppressor gene for controlling the cell cycle, inhibiting the growth of cells, activating DNA repair, and inducing apoptosis [106]. Cancer may result from aberrant CHEK2 expression [107]. CHEK2 germline mutations have been linked to an increased risk of developing various cancers [104], with a frequency of 1.08% in BC patients [108]. Protein kinase activity is lost in CHEK2 pathogenic mutations, which also result in a modest relative risk increase (2-4) of developing BC [106]. BC subtypes luminal A or luminal B are developed in the majority of patients with pathogenic or likely pathogenic mutations [108]. Since CHEK2 mutations and ER-positive BC have been linked in a number of studies [109–111], it seems sense to treat individuals with CHEK2-related BC with tamoxifen [106]. Mutations in the CHK2 kinase domain have the potential to cause apoptosis and alter a cell's susceptibility to chemotherapy [112]. While certain CHEK2 mutations have been linked to a higher risk of BC and better response to chemotherapy, more research is required to produce more precise results [107].

The E-cadherin cell adhesion molecule, which inhibits tumor cell metastasis, is encoded by the CDH1 gene [113]. Cancer metastasis is linked to decreased E-cadherin function and expression because it causes a lack of cell adhesion, which increases cell motility and enables cancer cells to pass through the basement membrane and infiltrate surrounding tissues [114]. Individuals who have hypermethylation of the CDH1 promoter are 5.83 times more likely to develop BC [115]. A reduced survival rate and a worse prognosis can result from CDH1 malfunction [116]. In HER2- and ER-negative BC, CDH1 hypermethylation is often elevated and is not correlated with PR status [115]. In support of the links between CDH1 hypermethylation and metastasis, Shinozaki et al. [117] showed that CDH1 was the most often methylated gene (90%) in cases with sentinel lymph node metastasis. According to Sebova et al. [118], CDH1 hypermethylation may be utilized as a biomarker for the possibility of tumor metastasis. DNA methylation inhibitors (DNMTs) such as 5-AzaCdR and 5-fluoro-20-deoxycytidine, which have been used in human lung cancer and BC cells, and 5-fluoro-20-deoxycytidine, which is currently in clinical trials for the treatment of BC and other solid tumors, can demethylate CDH1, thereby reversing its hypermethylation, making it a potential new drug target [115].

Proliferation and apoptosis are regulated by phosphatidylinositol-3-kinase (PI3K), gene symbol (PIK3CA); somatic mutations in PIK3CA can trigger both processes [119]. Protein synthesis, cell division, survival, glucose homeostasis, and DNA repair are only a few of the biological functions that PI3Ks are involved in [120,121]. One of the most prevalent BC alterations is PIK3CA mutations [122], and activating PIK3CA mutations, which cause the α-PI3K isoform to become hyperactivated, are present in about 30–40% of cancer patients [123, 124]. These mutations are linked to poor prognosis and chemoresistance, with a lower overall survival rate (19.6 months compared to 23.5 months) [125,126]. Mutations in the PIK3CA gene have been demonstrated to be carcinogenic, indicating a part in the development and spread of tumors [122,127]. Compared to other isoforms, alpelisib is 50 times more effective as an α-selective PI3K inhibitor when taken orally [128]. According to Reinhardt et al. [119], adjuvant therapy with aromatase inhibitors was not effective in treating early BC patients with PIK3CA somatic mutations. Tamoxifen was recommended as the preferable treatment for these individuals.

Tumor suppressor genes BRCA1 and BRCA2 are essential for DNA repair via the homologous recombination pathway [129]. The BRCA1 and BRCA2 genes had a mean cumulative breast cancer risk of 72% and 69%, respectively, at 80 years of age. Germline mutations in these genes are linked to an elevated risk of developing ovarian and breast cancer [130]. When these genes are not functioning properly, ineffective DNA repair results, which raises the rate of mutations and aids in the growth of tumors [129]. While the presence of pathogenic or likely pathogenic variants in BRCA2 is linked to

ER-positive malignancies, patients with pathogenic or likely pathogenic variations in BRCA1 are predisposed to TNBC [131]. There are conflicting findings about the predictive and prognostic significance of BRCA mutations in non-metastatic breast cancer patient survival [132]. Bilateral mastectomy is advised for women with BRCA mutations since they have an increased risk of developing secondary cancer. Research indicates that women who receive a bilateral mastectomy and have BRCA1/BRCA2 mutations are less likely to pass away from breast cancer than those who receive a unilateral mastectomy [133DNA-damaging medicines, such as topoisomerase II inhibitors (anthracyclines), PARP inhibitors, and interchain cross-linking agents (platinum or alkylating agents), are more effective against tumors with detrimental BRCA1/BRCA2 mutations [132]. When compared to conventional chemotherapies, treatment with PARP inhibitors (olaparib and talazoparib) was found to improve quality of life, prolong progression-free survival, and decrease side effects in metastatic BC with germline pathogenic or probably pathogenic BRCA1 or BRCA2 variants [131].

Ataxia-telangiectasia mutated (ATM), a gene with pathogenic or likely pathogenic variants of moderate penetrance linked to the DNA double-strand break repair mechanism and with a mutation frequency of 0.78% in BC patients, is one of the most frequently occurring genes associated with BC susceptibility [108]. When there is cell stress and a DNA damage response, the ATM gene produces proteins that are involved in DNA repair and cell cycle regulation [108,134,135]. The modest penetrance of ATM gene mutations increases the 2-to 5-fold relative risk of developing BC in heterozygous carriers, primarily in those who are HER2- or hormone-receptor-positive [134, 135]. A worse prognosis, increased risk of lymph node metastasis, more aggressive tumors, and an intermediate and high-grade illness are experienced by many BC patients with ATM mutations [136]. Due to its function as one of the DNA damage response junction points, which are implicated in significant signaling cascades like PI3K-AKT and MEK-ERK, ATM is a useful target for BC treatment [137]. According to Gilardini et al. [138], BC cell lines can become more sensitive to PARP inhibitors when ATM levels in cancer cells are decreased [138]. Changes in this gene can make cancer cells more susceptible to medications derived from platinum. However, following radiation therapy, ATM mutations raise the chance of a second tumor [136].

Repairing DNA cross-links is essential for maintaining genome stability and is facilitated by the BRIP1 gene (breast cancer 1 interacting helicase 1). BRIP1 is a good candidate for tumor progression and is linked to the development of BC when it is either mutated or overexpressed [139, 140]. BRIP1 is a gene found on chromosome 17's long arm that codes for a RecQ DEAH helicase family protein that interacts with BRCA1 to aid in the repair of damaged DNA [139,141–143]. Consequently, BRIP1 does not interact with BRCA1 and cannot repair damaged DNA if it is deleted or incomplete [139]. Thus, BRIP1 functions as a tumor suppressor and is essential for maintaining the genetic information of cells [139,141,142]. Families without BRCA1/BRCA2 mutations may be at risk for BC onset due to a gene called BRIP1 [143]. According to a recent study, this gene has prognostic significance due to its relationship with rare missense BRIP1 alleles and two SNPs with BC [140,144]. The survival rate of BC patients, promoter methylation status, and breast tumor subtypes have all been linked to BRIP1 overexpression. These results imply that BRIP1 may serve as a latent therapeutic target in addition to being a predictive molecular biomarker for BC development and prognosis [139]. The usage of PARP1 inhibitors is one of the treatment approaches being investigated for cancers with BRIP1 mutations. Moreover, cells lacking in BRIP1 or BRCA are more susceptible to cisplatin treatment [145].

A BRCA-binding partner protein required for DNA damage repair linked to BC vulnerability is called BARD1 (BRCA1-associated ring domain 1) [146]. Interestingly, partial inhibition of Bard1 in animals using antisense RNAs led in the formation of early malignancy stages phenotypic in murine mammary epithelial cell lines, suggesting a function for BARD1 in carcinogenesis [147]. According to Zhu et al. [148], BC cells that are resistant to tamoxifen exhibit a substantial increase in the expression of BARD1 and BRCA1. This results in resistance to chemotherapy that damages DNA, such as cisplatin and adriamycin, but not paclitaxel. Moreover, patients with early BC who express higher levels of BARD1 and BRCA1 have a poorer prognosis, particularly if they underwent radiation therapy. This suggests that PI3K inhibitors may be used to reverse chemoresistance and radioresistance in ER-positive BC patients [148]. BARD1 might be crucial to the pathophysiology of BC and the mechanisms of chemoresistance. According to certain research, TNBC is mostly connected to BARD1's function in BC [149]. Studies conducted in vivo and in vitro suggest that patients with BARD1 mutations may benefit clinically from PARP inhibitors [146].

The tumor suppressor PALB2 (partner and localizer of BRCA2) contributes to the preservation of genomic integrity. A 2–30 relative chance of developing BC is associated with pathogenic mutations [150]. individuals with a hereditary PALB2 mutation up to age 70 had a cumulative BC risk of 35%, and their 10-year survival is poorer than that of individuals without PALB2 mutations [151]. Among the eight genes that are commonly mutated in metastatic BC, PALB2 is one [152]. An examination of around 3000 BC patients in China revealed that pathogenic variations of PALB2 led to a decreased overall survival rate [153]. According to Heikkinen et al. [154], patients with PALB2 BC also had a higher propensity to display the triple-negative phenotype, higher levels of Ki67, and a poorer survival rate. According to

recent research, patients with PALB2 germline mutations may benefit greatly from platinum-based treatment regimens combined with PARP inhibitors [155,156].

According to a number of studies, a wide range of biochemical biomarkers, such as proteins (such as Her2, ER, and Ki67), mRNAs (such as ERα, ERβ, and ERRγ), enzymes (such as TSGF and CEA), and microRNAs (such as miR-21, miR-10b, miR-155, and miR-145), can be used as diagnostic biomarkers for the identification and follow-up of patients with breast cancer [67, 157]. One of the key proteins implicated in the pathophysiology of breast cancer is the human epidermal growth factor receptor 2 (HER2) [158]. Tyrosine kinase activity is seen by HER2, a member of the epidermal growth factor receptor family [159]. This receptor targets several signal transduction pathways, which may be involved in the regulation of cell growth, survival, and differentiation. It has been demonstrated that tyrosine residues in the cytoplasmic domain of the receptors may undergo auto-phosphorylation as a result of dimerization [158]. These occurrences may start a number of molecular and cellular signaling pathways that promote cancer and cell division [160]. In 10-15% of cases of gastric/esophageal cancers and 15-30% of cases of breast tumors, HER2 has been found to be upregulated and amplified [158]. Therefore, HER2 may be employed as a prognostic biomarker for breast cancer patients. Another significant protein that is essential to the pathophysiology of breast cancer is ki-67. This protein is referred to as a nuclear protein and is connected to the growth of cells [161]. Research has demonstrated that the Ki-67 nuclear antigen is absent in G0 but can be expressed in the S, G1, G2, and M stages of the cell cycle [162,161]. Numerous investigations suggested that Ki-67 might play a role in the etiology of breast cancer. Soliman and Yussif (2016a) evaluated the use of Ki-67 as diagnostic and prognostic indicators for 107 breast cancer patients under observation. They also looked into HER2, the progesterone receptor, and the estrogen receptor in breast cancer patients. According to their findings, the participants were categorized as triple-negative (TN), luminal A, luminal B, HER2 subtype, and 44, 23, 15, and 25 accordingly. It was demonstrated that the recurrence rate was 20% and that none of the luminal A patients had Ki-67 levels greater than 15%. Ki-67 levels were greater than 15% in the luminal B group, and 39% of patients experienced recurrence. Ki-67 levels were greater than 15% in 34% of HER2 subtype cases, and recurrence was 40%. Lastly, among triple-negative people, recurrence was noted in 32% of patients, and in 60% of instances, Ki-67 levels were greater than 15%. According to these results, Ki-67 levels may be used as prognostic biomarkers to track breast cancer patients [163]. In addition to HER2, other potential biomarkers for breast tumor subtyping include estrogen receptor (ER) and progesterone receptor (PR) [164]. Estradiol, a steroid hormone, is essential for the development and spread of breast cancer. Research has demonstrated that a variety of breast tumors may first express the ER and be estrogen-dependent [164]. Of the several ER subtypes found in the mammary epithelium, ERα is recognized as the primary subtype and plays a crucial role in the biology of the mammary glands and the advancement of breast cancer [165]. Once estrogen binds to ERα, ligand-activated ERα may go to the nucleus and attach itself to the responsive region in the promoter. These activities, which involve encouraging gene transcription, may be linked to the initiation of several cellular and molecular pathways that aid in the development of breast cancer [166]. Breast cancer metastasis may be facilitated by estrogen and ER, according to several lines of evidence. The epithelial-to-mesenchymal transition (EMT) may be impacted by estrogen signaling, and ERα signaling interacts with a number of EMT regulators, including Snail and Slug [167]. The promoter of metastatic tumor antigen (MTA) 3 may bind to ERα, inhibiting Snail. One gene that may have an impact on the EMT transition is the snail [168]. By forming a co-repressor complex with HDAC1 (histone deacetylase 1) and N-CoR (nuclear receptor co-repressor), ERα can control the transcription of Slug [169]. Like ERα, ERβ may play a role in estrogen signaling. Growing data suggested that upregulating ERβ could have anti-proliferative (tumor suppressor) effects and reduce cell proliferation [170, 171]. Metastatic breast cancer was found to have downregulated ERβ, whereas proliferating tumors and less metastatic conditions may be associated with upregulated ERβ expression [172, 173]. According to these results, different ER subtypes, such as ERα and ERβ, may be used as useful prognostic biomarkers for breast cancer patient identification and follow-up.

7. Conclusion

As the second most frequent disease globally, breast cancer is one of the major tumors that affect women. One of the most important components of breast cancer treatment is the diagnosis. Numerous lines of evidence suggested that a range of techniques and biomarkers may be employed as diagnostic techniques for the identification and follow-up of breast cancer patients. Mammography, MRI, SPECT, PET, CT, and other imaging modalities, as well as their development, may be used to diagnose and track patients with breast cancer. Even with continued advancements in imaging techniques, their use is hampered by a number of issues, including cost and sensitivity. Therefore, it appears that finding new instruments is necessary for the diagnosis of patients with breast cancer. Research has demonstrated that the use of novel biomarkers, such as measuring the expression levels of different proteins (such as ER, Ki67, PR, and HER2) and molecules (such as exosomes and miRNAs), has created new avenues for the diagnosis and follow-up of breast cancer patients.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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