From Diagnosis to Remission Navigating Innovative Tumor Markers and Uncovering Hidden Risk in Breast Cancer Care, a Review Article.

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DOI: https://doi.org/10.51244/IJRSI.2024.1102018

Received: 21 January 2024; Revised: 04 February 2024; Accepted: 10 February 2024; Published: 08 March 2024

ABSTRACT

Breast cancer is a leading cause of cancer-related deaths worldwide, and its management requires a multi-disciplinary approach. This review article aims to provide an overview of the use of tumor markers in breast cancer diagnosis, prognosis, and treatment monitoring, as well as the assessment of risk for recurrence and the development of second primary tumors. The article also discusses the challenges associated with the interpretation of tumor marker results and the integration of risk assessment tools into clinical practice. Overall, the review provides a comprehensive overview of the current state of knowledge on tumor markers and risk assessment in breast cancer care, and offers insights into how these tools can be used to optimize patient outcomes.

Method: This review article was conducted by searching electronic databases such as PubMed, Medline, and Scopus, using a combination of keywords related to breast cancer, tumor markers, risk assessment, and clinical management. The search was limited to articles published in English language, and the final selection was based on the relevance and quality of the studies.Tumor markers such as estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and Ki-67 are important in breast cancer diagnosis, prognosis, and treatment. They can be used to guide treatment decisions, monitor response to therapy, and detect recurrence. Risk assessment tools such as Adjuvant! Online and PREDICT can also provide valuable information for clinicians and patients in making informed decisions regarding treatment and follow-up. However, the interpretation of tumor marker results and the integration of risk assessment tools into clinical practice requires careful consideration and collaboration

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

between the multidisciplinary team.

Conclusion: The review highlights the potential benefits and limitations of tumor markers in breast cancer care, including their ability to predict risk, monitor treatment response, and facilitate early detection of disease recurrence. However, the use of these markers must be balanced against their potential for false-positive and false-negative results, as well as the need for careful interpretation and clinical context.

Keywords: Tumor markers, Estrogen receptor, Progesterone receptor, HER2, Ki-67, Risk assessment.

INTRODUCTION

As people's lifestyle, living environment, and stress levels continue to change, malignant tumors have become a major health concern[1] .Breast cancer is a prevalent malignancy among women, with its incidence rate on the rise in recent years[1].Breast cancer has an insidious onset, with no specific symptoms during its early stages. Also Breast cancer diagnosis and its subsequent treatment can have a profound impact on a person's emotional well-being[2] As a result, the majority of cases are not detected until they have progressed to middle or late stages, resulting in missed opportunities for optimal treatment.[3]

Risk factors for breast cancer; a list of some of the risk factors for breast cancer

Age: The risk of breast cancer increases with age, with the majority of cases occurring in women over the age of 50 [4].**Gender**: Women are at higher risk for breast cancer than men [5].

Family history: Women with a first-degree relative (mother, sister, daughter) who has had breast cancer have a higher risk of developing the disease themselves [6].**Personal history**: Women who have previously had breast cancer are at higher risk of developing a new cancer in the other breast or in a different part of the same breast [7].**Hormonal factors**: Exposure to hormones, such as estrogen and progesterone, can increase the risk of breast cancer [8].**Prolactin levels and breast cancer**;

Prolactin hormone produced by the pituitary gland that stimulates breast development and milk production during lactation. There is some evidence to suggest that elevated levels of prolactin may be associated with an increased risk of breast cancer[9], although the relationship between prolactin and breast cancer risk is not fully understood and remains a subject of ongoing research.

Some studies have suggested that women with higher levels of prolactin may have a slightly increased risk of breast cancer compared to women with lower levels of prolactin [9-12]. Other studies, however, have not found a significant association between prolactin levels and breast cancer risk[13] [14].Higher circulating prolactin has been associated with increased breast cancer risk. Prolactin binding to the prolactin receptor (PRLR) can activate the transcription factor STAT5[15]

Despite examining plasma prolactin levels in relation to PRLR or pJAK2 tumor expression, we did not detect distinct differences in their association with breast cancer risk. However, in premenopausal women, we did observe associations only for pSTAT5 positive tumors. This indicates that prolactin may play a role in breast tumor development through other pathways, although further research is required.[15] Overall, while there is some evidence to suggest that high levels of prolactin may be a risk factor for breast cancer, more research is needed to fully understand the relationship between prolactin and breast cancer risk. **Lifestyle factors:** Lifestyle factors such as alcohol consumption, lack of physical activity, and obesity have been associated with an increased risk of breast cancer[16].**Genetic mutations**: Inherited mutations in certain genes, such as BRCA1 and BRCA2, can increase the risk of breast cancer [17].BRCA1 and BRCA2: Mutations in the BRCA1 and BRCA2 genes are associated with an increased risk of developing breast and

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

ovarian cancer. Testing for BRCA mutations is recommended for individuals with a family history of breast or ovarian cancer or other risk factors. The sensitivity and specificity of BRCA testing can vary depending on the specific test used and the population being tested [18]**Radiation exposure**: Exposure to ionizing radiation, such as during radiation therapy for another cancer, can increase the risk of breast cancer [19]. **Dense breast tissue**: Women with dense breast tissue, as seen on mammograms, may have a higher risk of breast cancer [20].**Environmental factors:** Exposure to certain environmental factors, such as certain chemicals or pollutants, may increase the risk of breast cancer [21].**Hormone replacement therapy (HRT):** Hormone replacement therapy, which is used to relieve symptoms of menopause, can increase the risk of breast cancer, especially if it's used for an extended period of time [22].

Alcohol consumption: Drinking alcohol, even in moderate amounts, can increase the risk of breast cancer [23].**Obesity**: Being overweight or obese, especially after menopause, can increase the risk of breast cancer [24].**Lack of physical activity**: Not getting enough physical activity can increase the risk of breast cancer [25].**It's important to note** that having one or more of these risk factors doesn't necessarily mean that someone will develop breast cancer, and many women who develop breast cancer have no known risk factors. Nonetheless, understanding these risk factors can help inform decisions about screening and prevention strategies.

TUMOR MARKERS OF BREAST CANCER

Tumor markers are substances that can be found in blood, urine, or tissue samples that may indicate the presence of cancer. Although there are several tumor markers that have been studied for breast cancer, none of them are currently recommended for routine screening or diagnosis of breast cancer. Nonetheless, the following is a list of some of the most commonly studied tumor markers for breast cancer:**it's important to note** that none of these markers are currently recommended for routine screening or diagnosis of breast cancer, and their usefulness as prognostic or predictive tools is still being studied.

- **Circulating tumor cells (CTCs):** CTCs are tumor cells that have detached from the primary tumor and entered the bloodstream. They have the potential to provide information on the progression and metastasis of breast cancer.[26]
- **MicroRNAs:** MicroRNAs are small RNA molecules that play a role in gene expression. They have been found to be deregulated in breast cancer and have potential as prognostic and diagnostic biomarkers [27] miRNAs hold promise as useful biomarkers for breast cancer detection and management. However, further research is needed to validate their clinical utility and to develop reliable assays for their detection in patient samples.
- **Exosomes:** Exosomes are small vesicles that are secreted by cells and contain various molecules including proteins, RNA, and DNA. They have been found to be involved in cancer development and progression and have potential as diagnostic and prognostic biomarkers [28] Exosomes released by cancer cells can have several effects that contribute to cancer development and progression, including:
- Promotion of tumor growth: Exosomes can carry growth factors, cytokines, and other molecules that stimulate the proliferation of cancer cells.
- Induction of angiogenesis: Exosomes can contain pro-angiogenic factors that promote the formation of new blood vessels, which is necessary for the growth and metastasis of tumors.
- Facilitation of invasion and metastasis: Exosomes can promote the invasion of cancer cells into surrounding tissues and their dissemination to distant sites by carrying factors that increase cell motility and extracellular matrix degradation.
- Modulation of immune response: Exosomes can influence the immune response by carrying immunosuppressive molecules that prevent immune cells from recognizing and attacking cancer cells [29].

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

- **Human epidermal growth factor receptor 2 (HER2/neu)**: HER2/neu is a protein that is often overexpressed in breast cancer, particularly in aggressive forms of the disease. It is not considered a tumor marker per se, but it is used to guide treatment decisions in breast cancer patients HER2/neu status is routinely tested in breast cancer patients to guide treatment decisions [30]. HER2/neu is over expressed in about 20% of breast cancers. It is an important biomarker for guiding treatment decisions in patients with breast cancer. The sensitivity and specificity of HER2 testing vary depending on the assay and cutoff values used. In general, immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) are considered the gold standards for HER2 testing. The reported sensitivity and specificity of HER2 IHC and FISH vary widely depending on the study and assay used, but in general, they are reported to be high. For example, a meta-analysis of 25 studies reported a pooled sensitivity of 95.4% and specificity of 95.5% for HER2 IHC in breast cancer [31].
- **Estrogen receptor (ER), progesterone receptor (PR),**
  estrogen receptor (ER) and progesterone receptor (PR) are two important biomarkers in breast cancer. ER and PR are both nuclear receptors that are expressed in normal breast tissue and are responsible for regulating the growth and differentiation of breast cells. In breast cancer, the expression of ER and PRcan help determine the aggressiveness of the tumor and guide treatment decisions [32].Tumors that are ER- positive and/or PR-positive are more likely to respond to hormonal therapies, such as tamoxifen or aromatase inhibitors, which block the effects of estrogen in the body. Tumors that are ER-negative and PR- negative are less likely to respond to these therapies and may require other treatments, such as chemotherapy[33]
- ER, PR, and HER2 are not technically considered tumor markers, but they are important biomarkers in breast cancer that guide treatment decisions. ER and PR are hormone receptors that are expressed in a significant proportion of breast cancers, and their presence can influence the choice of endocrine therapy. HER2 is a protein that is overexpressed in some types of breast cancer, and it can be targeted with specific therapies such as trastuzumab [34]. ER and PR are nuclear proteins that are expressed in about 75% and 65% of breast cancers, respectively.. The sensitivity and specificity of ER and PR testing vary depending on the assay and cutoff values used. In general, immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) are considered the gold standards for ER, PR testing. The reported sensitivity and specificity of ER and PR IHC and FISH vary widely depending on the study and assay used, but in general, they are reported to be high. For example, a meta-analysis of 44 studies reported a pooled sensitivity of 96.6% and specificity of 98.5% for ER IHC in breast cancer [31], sensitivity and specificity of progesterone receptor testing were 94.8 and 92.6%, respectively [35]. .It's worth noting that there are many other potential tumor markers for breast cancer that have been studied, but their usefulness in clinical practice is still uncertain. More research is needed to determine whether any of these markers could be useful for screening, diagnosis, or treatment of breast cancer.
- **Glycans:** Glycans are complex sugar molecules that are attached to proteins and lipids. They have been found to be deregulated in breast cancer and have potential as biomarkers for early detection and diagnosis.[26]. Glycosylation patterns were among the earliest identified biomarkers for cancer, and they still serve as valuable indicators for identifying cells with stem-cell-like characteristics, both in cancerous and healthy tissues[36]. The glycosylation of specific proteins in serum and/or tumor tissues can be used as a diagnostic biomarker and to assess patient prognosis and responses to treatment
- **Carcinoembryonic antigen (CEA)**: CEA is a protein that is often elevated in breast cancer patients. However, its usefulness as a screening or diagnostic tool for breast cancer is limited due to its low sensitivity and specificity [37]. Clinical value of serum biomarkers CEA predicting sentinel lymph node metastasis of breast cancer sensitivity of sensitivity 67.9%, specificity 73.8% [38].
- **Cancer antigen 27.29 (CA 27.29)**: CA 27.29 is a carbohydrate antigen that is often elevated in breast cancer patients, particularly those with metastatic disease. However, it is not recommended for routine screening or diagnosis of breast cancer due to its low sensitivity and specificity [39].

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

- **Ki-67: Ki-67** is a protein that is used as a marker of cellular proliferation, and it has been studied as a potential prognostic marker in breast cancer. High levels of Ki-67 expression have been associated with poorer outcomes in some studies, but its usefulness as a prognostic tool is still being investigated [40].. The reported sensitivity and specificity of Ki-67 staining vary widely depending on the study and cutoff values used. In general, higher Ki-67 expression is associated with poorer prognosis in breast cancer. For example, a meta-analysis of 34 studies reported a pooled hazard ratio of 2.01 (95% confidence interval, 1.71-2.35) for disease-free survival and 1.77 (95% confidence interval, 1.48-2.12) for overall survival in patients with high Ki-67 expression [41].
- **Cancer antigen 125 (CA 125):** CA 125 is a carbohydrate antigen that has been studied as a potential tumor marker for breast cancer, particularly in patients with advanced disease. However, its usefulness in breast cancer diagnosis and management is limited due to its low sensitivity and specificity [42].
- **Human epididymis protein 4 (HE4)**: HE4 is a glycoprotein that has been studied as a potential biomarker for breast cancer, particularly in patients with advanced disease. However, its usefulness in breast cancer diagnosis and management is limited due to its low sensitivity and specificity, The cutoff value of HE4 levels for predicting breast cancer is >54.5 pmol/l with a sensitivity of 73.3%, specificity 65.3% [43].
- **Sex-determining region Y-box protein 2 (Sox2),** an embryonic transcription factor located at chromosome 3q26.33, has been frequently demonstrated to be an important prognostic marker for various tumors, including breast cancer. However, its clinicopathological role in breast cancer has not been fully elucidated [44]
- **Cancer antigen 19-9 (CA 19-9):** CA 19-9 is a carbohydrate antigen that has been studied as a potential tumor marker for metastatic breast cancer , particularly in patients with advanced disease. However, its usefulness in breast cancer diagnosis and management is limited due to its low sensitivity and specificity [45].
- **CK 19 and CK20;**Cytokeratin 19 (CK 19) and cytokeratin 20 (CK 20) are two additional tumor markers that have been studied in breast cancer:
- Cytokeratin 19 (CK 19): CK 19 is a type of cytokeratin protein that is commonly expressed in breast cancer cells. Its expression has been studied as a potential prognostic marker in breast cancer, with higher levels of expression associated with poorer outcomes in some studies [46]
- Cytokeratin 20 (CK 20): CK 20 is a type of cytokeratin protein that is not normally expressed in breast tissue, but it can be expressed in some types of breast cancer. Its expression has been studied as a potential diagnostic and prognostic marker in breast cancer, with higher levels of expression associated with more aggressive disease in some studies [47].It's important to note that the usefulness of CK 19 and CK 20 as diagnostic or prognostic markers in breast cancer is still being investigated, and their routine use in clinical practice is not currently recommended.
- **CA 15-3:** Carbohydrate antigen 15-3 (CA 15-3) is a protein that is found on the surface of some breast cancer cells. Its levels in the blood can be used to monitor the response to treatment and detect disease recurrence in some cases. However, it is not recommended as a screening test for breast cancer, as it can also be elevated in other non-cancerous conditions [48]. The reported sensitivity and specificity of CA 15-3 vary widely depending on the study and assay used. A meta-analysis of 37 studies reported a pooled sensitivity of 70.5% and specificity of 80.5% for CA 15-3 in patients with metastatic breast cancer [49].
- **CA-62; in vitro diagnostic chemiluminescent immunoassay (IVD CLIA-CA-62)** is a novel assay e for early-stage breast cancer detection[50], Human CLIA-CA-62 immunoassay is based on the novel marker for epithelial carcinomas CA-62, which is a carcinoma-specific mesenchymal marker, expressed on the epithelial cell surface prove useful as a supplement to current mammography screening and other imaging methods, thus increasing the diagnostic sensitivity in DCIS and Stage I breast cancer detection. The CLIA-CA-62 overall sensitivity for BC was 92% (100% for DCIS) at 93% specificity and it decreased in invasive stages (Stage I=97%, Stage II=85% and Stage

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

III=83%)[51], a combination of CA15-3 with CA-62 yields 75% Sensitivity at 100% Specificity for DCIS and Stage I breast cancer detection[52]

- **CA 27.29:** Carbohydrate antigen 27.29 (CA 27.29) is another protein that is found on the surface of some breast cancer cells. Like CA 15-3, its levels in the blood can be used to monitor treatment response and detect disease recurrence in some cases [49]. It is used to monitor treatment response in patients with advanced or metastatic breast cancer. However, it is not recommended for breast cancer screening or diagnosis. The reported sensitivity and specificity of CA 27.29 vary widely depending on the study and assay used. A meta-analysis of 24 studies reported a pooled sensitivity of 60.6% and specificity of 83.6% for CA 27.29 in patients with breast cancer [49].
- **UPA and PAI-1**: Urokinase-type plasminogen activator (uPA) and its inhibitor plasminogen activator inhibitor-1 (PAI-1) are proteins involved in tumor invasion and metastasis. Their levels in breast cancer tissue have been associated with tumor aggressiveness and poorer prognosis in some cases. They are sometimes used as prognostic markers in breast cancer, particularly in patients with hormone receptor-positive disease [53].
- **MammaPrint and Oncotype DX**: MammaPrint and Oncotype DX are gene expression profiling tests that are used to predict the risk of breast cancer recurrence and guide treatment decisions in certain patients. These tests are not technically tumor markers in the traditional sense, but they are important molecular markers that have been extensively studied in breast cancer [54].
- **MUC1:** MUC1 is a glycoprotein that is overexpressed in breast cancer and is associated with tumor progression and poor prognosis. A meta-analysis of 18 studies reported a pooled sensitivity of 59.3% and specificity of 85.3% for MUC1 in breast cancer [55].
- **PIK3CA:** PIK3CA is a gene that is frequently mutated in breast cancer and is associated with more aggressive tumor behavior and poorer prognosis [56]. Testing for PIK3CA mutations can be used to guide treatment decisions, as some PIK3CA inhibitors are available for clinical use. The sensitivity and specificity of PIK3CA testing can vary depending on the specific test used and the population being tested [57].
- It is important to note that the sensitivity and specificity of tumor markers can vary depending on a variety of factors, including the specific assay used, the stage and type of cancer, and other patient and disease characteristics. In addition, some tumor markers may be more useful for certain purposes (e.g., screening, diagnosis, prognosis, or monitoring treatment response) than others.
- **Prosigna and EndoPredict** ; are both commercial gene expression tests that are used to help guide treatment decisions for women with early-stage breast cancer.
- Prosigna is a gene expression test that measures the activity of 50 genes related to breast cancer. It uses a proprietary algorithm to calculate a score called the Prosigna Risk of Recurrence (ROR) score, which estimates the likelihood of a cancer recurrence within 10 years. The ROR score is used to help guide treatment decisions, such as whether to use chemotherapy or not. Prosigna is often used in conjunction with other clinical factors, such as tumor size and grade, to make treatment decisions [58].
- EndoPredict is another gene expression test that measures the activity of 12 genes related to breast cancer. Like Prosigna, it uses a proprietary algorithm to calculate a score called the EndoPredict score, which estimates the likelihood of a cancer recurrence within 10 years. EndoPredict is also used to guide treatment decisions, such as whether to use chemotherapy or not. In addition, EndoPredict can be used to help determine the appropriate duration of hormonal therapy [59].
- Both Prosigna and EndoPredict have been shown to provide valuable information to help guide treatment decisions for women with early-stage breast cancer. However, the specific use of each test may depend on a variety of factors, including the characteristics of the tumor and the preferences of the patient and healthcare provider
- BCI stands for Breast Cancer Index, which is a commercial gene expression test used to help determine prognosis and guide treatment decisions for women with estrogen receptor-positive (ER-positive), HER2-negative breast cancer that has not spread to the lymph nodes (lymph node-negative).Several studies have shown that the Breast Cancer Index test can provide valuable

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

information to help guide treatment decisions for women with ER-positive, HER2-negative, lymph node-negative breast cancer. The specific use of the test may depend on various factors, including the patient's age, menopausal status, and other clinical characteristics [60]

Summary for tumor markers table 1

HER2: Sensitivity = 75-85%, Specificity = 80-95% [31].
ER: sensitivity of 96.6% and specificity of 98.5% [31].
CA 27.29: Sensitivity = 60-70%, Specificity = 70-90% [49].
HE4: sensitivity of 73.3%, specificity 65.3% [43].
CEA: sensitivity 67.9%, specificity 73.8% [38].
CA 15-3: sensitivity of 70.5 and specificity of 80.5% for CA 15-3 in patients with metastatic breast cancer [49].
PR: sensitivity 94.8 % and specificity of 92.6%, respectively [35].

MUC1: sensitivity of 59.3% and specificity of 85.3% for MUC1 in breast cancer [55].

BRCA1 and BRCA2: Sensitivity and specificity can vary depending on the specific test used and the population being tested.
PIK3CA: Sensitivity and specificity can vary depending on the specific test used and the population being tested.

There isn't a single cutoff value for all breast tumor markers, as different markers may have different reference ranges, and cutoff values can also vary by laboratory and assay methods. Common breast tumor markers cutoff values

CA 15-3 (Cancer Antigen 15-3): Elevated levels of CA 15-3 can indicate the presence of breast cancer. However, there is no single specific cutoff value for CA 15-3, and the reference range can vary by the laboratory. Typically, levels above 30 U/mL may raise suspicion[61], but this can vary.

CA 27.29: Similar to CA 15-3, CA 27.29 is used as a breast cancer marker. Again, the specific cutoff value can vary by laboratory, but levels above 38 U/mL are often considered elevated. CA 15.3 (sensitivity = 57%; accuracy = 87%) was the most effective marker, CA 27.29 (sensitivity = 62%; accuracy = 83%) was the most sensitive and CEA (sensitivity = 45%; accuracy = 81%) was the least sensitive and effective marker[62]

CEA (Carcinoembryonic Antigen): CEA is not specific to breast cancer but can be elevated in various cancers, including breast cancer. The normal reference range for CEA is typically less than 3-5 ng/mL. Elevated levels above this range may indicate a potential issue. In healthy, non-smoking adults, CEA is considered within normal limits at a level of <=3.0 µg/L. Smokers may have elevated CEA, and therefore it is considered within normal limits at a level of <5 µg/L. Pre-treatment serum CEA levels of greater than five µg/L but less than ten µg/L suggests localized disease and a low likelihood of recurrence, hence a favorable prognosis. A serum level of >10 µg/L indicates a higher likelihood of recurrence and poor prognosis[63].

HER2/neu (Human Epidermal Growth Factor Receptor 2): HER2 is a protein marker used to determine the aggressiveness of breast cancer. It's usually measured on a scale from 0 to 3+, with 0 or 1+ considered

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

negative, 2+ equivocal, and 3+ positive. HER2-positive breast cancer may require specific targeted therapies. HER2-low breast cancer suffers from lower concordance among expert pathologists. While most cases can reproducibly be classified, a small proportion (10%) remained challenging[64]

BRCA1 and BRCA2 Mutations: These are genetic markers rather than blood markers. Mutations in the BRCA1 and BRCA2 genes are associated with an increased risk of breast cancer. Genetic testing is used to detect these mutations

EMERGING BIOMARKERS IN BREAST CANCER RESEARCH

Breast cancer research is a dynamic field, and ongoing investigations often reveal new biomarkers that can aid in early detection, prognosis, and treatment response assessment

- **Liquid Biopsies**: **Circulating Tumor DNA (ctDNA) and Circulating Tumor Cells (CTCs):** Liquid biopsies involve analyzing blood samples for the presence of ctDNA is part of cell-free nucleic acids (cfNAs) or Circulating Tumor Cells CTCs shed by tumors. A potential non-invasive technique for identifying and tracking cancer These biomarkers can provide information about the genetic makeup of the tumor, allowing for real-time monitoring of treatment response and potential early detection of minimal residual disease[65]. The release of ctDNA into the blood occurs from a variety of sources, including the primary tumor, circulating tumor cells in the peripheral blood, and distant metastatic foci through a variety of mechanisms including apoptosis, necrosis, ferroptosis, pyroptosis, oncosis, and phagocytosis. the half-life of ctDNA is short which is convenient for a “real-time” approach for analyses of ctDNA for various therapeutic applications[66].
- **Circulating Tumor Cells (CTCs):** CTCs are cancer cells that have detached from the primary tumor and entered the bloodstream. Detection and analysis of CTCs can provide insights into tumor characteristics and help monitor metastasis. Elevated concentrations of these biomarkers during cancer treatment may be used as markers for cancer progression as well as to understand the mechanisms underlying metastasis and treatment resistance. Thus, these circulating markers serve as tools for cancer assessing and monitoring[67]
  CTCs have been detected in patients with early stage cancers and, owing to their association with metastasis, might indicate the presence of aggressive disease, thus providing a possible means to expedite diagnosis and treatment initiation for such patients while avoiding over diagnosis and overtreatment of those with slow-growing, indolent tumours[68]
- **MicroRNA (miRNA):** miRNA Signatures: Certain miRNA profiles are associated with breast cancer subtypes and can serve as potential biomarkers[69] for diagnosis and prognosis. Changes in miRNA expression levels can reflect alterations in cancer-related pathways. The majority of cancers examined so far have demonstrated changes in miRNA levels, highlighting their potential significance in the oncogenic process. This evidence has led to the identification of numerous miRNAs proposed as potential cancer biomarkers for both diagnostic and prognostic purposes. Additionally, miRNA-based therapies have undergone testing in various cancers, yielding measurable clinical benefits for patients[70]
- **Exosome Biomarkers: Exosomal miRNA and Proteins**: Exosomes, small membrane vesicles released by cells, carry specific miRNAs and proteins. Analysis of exosomal content may provide information about the tumor microenvironment and contribute to early detection[71]. The analysis of exosomal content holds significant promise in offering insights into the tumor microenvironment and contributing to the early detection of cancer. Exosomes are small extracellular vesicles released by various cells, including cancer cells, into the bloodstream. They contain a cargo of proteins, nucleic acids, and lipids, reflecting the molecular composition of their cell of origin. Key points about the potential of exosomal content analysis for early cancer detection and understanding the tumor microenvironment include: Exosomes are secreted by tumor cells and carry molecular information

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

from their parent cells. This includes proteins, nucleic acids (such as DNA, RNA, and microRNAs), and other molecules that can provide valuable insights into the characteristics of the tumor[72]. Exosomes play a role in intercellular communication and are involved in creating a conducive microenvironment for tumor growth[73]

- **Circulating Cell-Free DNA Methylation:** DNA Methylation Patterns: Aberrant DNA methylation patterns in circulating cell-free DNA (cfDNA) can be indicative of breast cancer[74]. DNA methylation is an epigenetic modification that plays a crucial role in regulating gene expression. Aberrations in DNA methylation patterns, particularly in the context of cfDNA, have been associated with various diseases, including cancer. In breast cancer, the normal regulatory mechanisms of DNA methylation can be disrupted, leading to abnormal patterns. These alterations can result in the silencing of tumor suppressor genes or the activation of oncogenes, contributing to the development and progression of breast cancer[75]. Methylation-based markers are being explored for their potential in early detection and risk assessment, also DNA methylation patterns are established or disrupted is a key question in developmental biology and cancer epigenetics[76]. **Advantages;**

  One of the significant advantages of studying cfDNA is that it is easily accessible through a simple blood draw. Analyzing the methylation status of cfDNA provides a non-invasive approach to assess molecular changes associated with breast cancer**.** Aberrant DNA methylation patterns in cfDNA can potentially serveas early indicators of breast cancer. Early detection is crucial for improving treatment outcomes and prognosis**.** Researchers are actively identifying specific DNA methylation markers that are associated with breast cancer. These markers can be tumor-specific, providing a more accurate and targeted approach to diagnosis. Changes in DNA methylation patterns in cfDNA can be monitored over the course of treatment. This allows clinicians to assess the response to therapies and make informed decisions regarding treatment adjustments. Understanding the DNA methylation profile in cfDNA may contribute to the development of personalized treatment strategies. Identifying specific methylation patterns can help tailor therapies to target the unique characteristics of an individual's breast cancer.

- **Immune-Related Biomarkers**: Tumor-Infiltrating Lymphocytes (TILs): The presence of TILs in the tumor microenvironment is associated with better prognosis and response to certain therapies. Prognostic Indicator: High levels of TILs in the tumor microenvironment have been associated with improved prognoses[77] in various cancers[78]. The presence of a robust immune response suggests that the body is actively working to recognize and eliminate cancer cells.

  Predictive Marker for Therapeutic Response: TILs have been identified as predictive markers for responseto certain immunotherapies, particularly immune checkpoint inhibitors. These therapies aim to enhance the immune system's ability to recognize and attack cancer cells.

  Increased Overall Survival: Patients with tumors characterized by a higher infiltration of TILs often experience better overall survival rates. The presence of an active immune response suggests the potentialfor the immune system to control or eliminate the cancer[78].TILs are being investigated as a potential biomarker for treatment response.

- **Metabolomics**: Metabolic Profiles: Metabolomic studies examine the unique metabolic fingerprints associated with breast cancer. Changes in metabolite levels can be indicative of disease presence and progression. Metabolites are the end products of cellular processes, and their levels can be influenced by various factors, including genetic mutations, environmental exposures, and disease states. Metabolomic studies aim to identify specific metabolites that are indicative of breast cancer or provide information about its progression[79]

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Guidelines on the use of biomarkers in patients with invasive breast cancer. European Group on Tumor Markers (EGTM) recommendations. [26] table 2

Table 2

Biomarker	Recommendation
ER	For predicting the response to endocrine therapy in patients with early or advanced breast cancer. Mandatory in all patients.
PR	In combination with ER for predicting response to endocrine therapy in patients with early or advanced breast cancer. Mandatory in all patients.
HER2	For predicting response to anti-HER2 therapy in patients with early or advanced breast cancer. Mandatory in all patients.
Ki67	In combination with established clinical and pathological factors for determining prognosis in patients with newly diagnosed invasive breast cancer, especially if values are low or high.
uPA/PAI-1	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive, HER2-negative, lymph node–negative disease.
Oncotype DX	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive HER2-negative lymph, node–negative and lymph node–positive (1–3 nodes) disease.
MammaPrint	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive, HER2-negative, lymph node–negative and lymph node–positive (1–3 nodes) disease.
Prosigna	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive HER2-negative, lymph node–negative and lymph node–positive (1–3 nodes) disease.
EndoPredict	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy to patients with ER-positive HER2-negative lymph node–negative and lymph node–positive (1–3 nodes) disease.
BCI	For determining prognosis and aiding decision-making for the administration of adjuvant chemotherapy in patients with ER-positive, HER2-negative, lymph node–negative disease.

SCREENING METHODS FOR BREAST CANCER

Mammography: Mammography is the most widely used screening modality for the detection of breast cancer. In 2015, the American Cancer Society (ACS) recommended that women with an average risk should undergo regular screening mammography starting at age 45 (strong recommendation).Women who are between 45 to 54 years should undergo screening annually, and women 55 years and older can undergo biennial or annual screening[80] .There is evidence that it decreases breast cancer mortality in women aged 50 to 69 years and that it is associated with harms, including the detection of clinically insignificant cancers that pose no threat to life (overdiagnosis). The benefit of mammography for women aged 40 to 49 years is uncertain[81],however some studies prove that mammography screening reduces breast cancer mortality for women aged 39 to 69 years[82]

ISSN No. 2321-2705 | DOI: 10.51244/IJRSI |Volume XI Issue II February 2024

Clinical breast exam: This method involves a healthcare provider manually examining the breasts to detect any lumps or other abnormalities. While there is currently controversy regarding the recommendation for women to perform self-breast exams for breast cancer screening, the medical practitioner nonetheless must evaluate a patient who presents with changes noticed during a self-breast exam[83, 84]. According to the National Comprehensive Cancer Network screening guidelines, women aged 25 to 40 who show no symptoms and have no specific risk factors for breast cancer should have a clinical breast examination every 1 to 3 years. On the other hand, women above the age of 40, those with elevated risk factors for breast cancer, a history of breast cancer, or who are experiencing symptoms are advised to undergo more frequent clinical breast exams[83].

Breast self-exam: This involves a woman examining her own breasts to detect any changes or abnormalities. Breast self-examination (BSE) is regarded as the fundamental technique for screening and detecting breast cancer in its early stages[85]. It can enhance awareness about breast cancer and serve as an alert for both women and healthcare professionals to prioritize more comprehensive screening measures, especially for women with a family history of breast cancer.

Magnetic resonance imaging (MRI): Mammography is the favored approach because of its affordability and a favorable balance between benefits and risks. Nonetheless, mammography does have certain limitations, including exposure to X-rays, challenges in interpreting images in dense breast tissue, and the potential for overdiagnosis. Compared to other imaging techniques, MRI stands out with its notably superior sensitivity and specificity[86]. This method uses powerful magnets and radio waves to create detailed images of the breast tissue, which can be helpful in detecting small tumors or abnormalities. MRI exhibits an impressive sensitivity for precisely evaluating the extent of DCIS (Ductal Carcinoma In Situ), reaching as high as 89%, surpassing the sensitivity levels of mammography, tomosynthesis, or ultrasound[87]. While MRI is not typically used as the primary method for breast cancer screening, it is recommended as a supplementary screening tool for women with extremely dense breast tissue who have normal mammography results. The inclusion of MRI in such cases has been found to significantly reduce the occurrence of interval cancers compared to relying solely on mammography over a two-year screening period[88].

Breast ultrasound: This method uses high-frequency sound waves to create images of the breast tissue, which can help detect cysts or other abnormalities.

Digital breast tomosynthesis (DBT): This is an advanced form of mammography that takes multiple X-ray images of the breast tissue from different angles, producing a 3D image that can help detect small tumors that may be missed by traditional mammography.

Molecular breast imaging (MBI): This method uses a radioactive tracer to produce images of the breast tissue, which can help detect small tumors or abnormalities that may not be visible on other imaging tests.early detection improve breast cancer survival rates, and provides useful information for women and healthcare providers in selecting the most appropriate screening method based on individual risk factors and preferences.It’s important to note that the American Cancer Society and other organizations recommend that women receive regular mammograms starting at age 40 (or earlier if they are at high risk for breast cancer), and that they discuss their individual risk factors and screening options with their healthcare provider to determine the most appropriate screening plan.

AUTHOR DECLARATION

- All authors declare that they have no conflicts of interest.
- No funding was used in this study.

- The datasets generated during and/or analyzed during the current study are available in the [PUBMED] repository, [https://pubmed.ncbi.nlm.nih.gov].

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