INTERNATIONAL JOURNAL OF HEALTH & MEDICAL RESEARCH

ISSN(print): 2833-213X, ISSN(online): 2833-2148

Volume 03 Issue 06 June 2024

DOI : 10.58806/ijhmr.2024.v3i06n06

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Laboratory Tests for The Diagnosis of Breast Cancer

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ABSTRACT: Breast cancer (BC) has posed a significant threat to the general health of women globally, with its incidence and mortality rates showing a noticeable increase in China over time. Research indicates that the survival rate for early-stage breast cancer patients is significantly higher compared to those diagnosed at middle or late stages. Therefore, it is crucial to focus on research for the rapid diagnosis of breast cancer. Numerous diagnostic methods have been developed to date, primarily utilizing imaging and molecular biotechnology. These methods have greatly contributed to the diagnosis and follow up of BC. In this review article, a brief explanation has been introduced about the main laboratory methods that are recently used in the diagnosis of BC. It has been concluded that many diagnostic methods have been developed to detect breast cancer at different stages of the tumor. Some of these tests have been used to determine the appropriate chemotherapy method (e.g. molecular tests for gene changes), other are more generic in the determination of many tumor (e.g. complete blood count), while salivary methods are still controversial in the diagnosis of BC.

1. INTRODUCTION

Breast cancer is among the most prevalent malignant tumors affecting women. Its development is influenced by various internal and external factors (Obeagu & Obeagu, 2024). Contributing factors include unhealthy lifestyle choices, environmental influences, and social and psychological aspects. Research indicates that 5% to 10% of breast cancer cases are linked to genetic mutations and family history, while 20% to 30% are associated with potentially modifiable factors (Sun et al., 2017; Mohammad and Al-Fahham, 2021).

Breast cancer originates in breast cells, forming a mass of cancer cells known as a malignant tumor, which can invade and destroy nearby tissue and potentially spread throughout the body. Sometimes, breast cells undergo changes that disrupt their normal growth and function, leading to non-cancerous conditions such as uncommon cysts and hyperplasia. These changes can also result in benign tumors such as intraductal papillomas. (Sinha, 2018)

2. SPECIFIC PROTEINS

Laboratory tests may be performed to investigate specific proteins settled on the tumor cells. These tests include the following:

HORMONE RECEPTOR PROTEINS:

All breast carcinomas are screened for hormone receptors (proteins). Particularly, the most common hormone receptors are: estrogen receptor (ER) and progesterone receptor (PR). Most cases of breast tumors exhibit excessive expression of estrogen receptors and progesterone receptors (Yip & Rhodes, 2014). It was found that the progesterone receptor (PR) regulates the expression and action of estrogen receptors α (ERα) in breast tumors. It is a gene whose activity is increased by the estrogen receptor (ER), and its expression relies on estrogen. Progesterone receptor (PR) is also an important prognostic biomarker in breast tumor, particularly in hormone-positive cases. High levels of PR expression are more commonly found in tumors with a better initial prognosis (such as luminal A) compared to those with luminal B which is a worse initial prognosis (Li et al., 2022).

HER2 (HUMAN EPIDERMAL GROWTH FACTOR RECEPTOR 2) PROTEIN

The HER2 receptor (human epidermal growth factor receptor 2) is a transmembrane tyrosine kinase that, when activated, influences cell proliferation and survival. The HER2 oncogene is located on chromosome 17q12. Overexpression of the HER2

receptor primarily occurs through HER2 gene amplification, which is a key factor in tumor development and progression in certain breast cancers. Approximately 20% to 30% of all breast cancer cases exhibit HER2 protein overexpression or HER2 gene amplification (Krishnamurti et al., 2014). All invasive breast cancers are tested for HER2 protein levels to determine if there is an overabundance. If the HER2 protein levels are unclear, a molecular test may be conducted to assess the number of HER2 gene copies in the cancer cells. (Obeagu & Obeagu, 2024).

PD-L1 PROTEIN

The programmed cell death-1 receptor (PD-1) is a protein that inhibit immune cells, it is found on the outer membrane of immune effector cells. It is primarily triggered by PD-L1, which can be expressed by all healthy cells. The PD-1/PD-L1 pathway plays a nuanced role in maintaining peripheral T-lymphocyte tolerance and regulating inflammation. In cancer, PD-L1 translation appears to be a key mechanism for immune evasion. In cases of advanced or metastatic triple-negative breast cancer, testing the cancer tissue for the PD-L1 protein can indicate if the cancer is more likely to respond to specific immunotherapy drugs combined with chemotherapy. (Schütz et al., 2017).

3. MOLECULAR TESTS FOR GENE CHANGES

In certain cases, physicians may look for certain genetic mutations in breast cancer cells to identify whether particular targeted therapies or immunotherapy drugs might be beneficial. These molecular analyses, also referred to as genomic or biomarker tests, can be conducted on tissue samples obtained from a biopsy or surgery for breast cancer.

Some of these tests might also be conducted on venous if the biopsy sample is very tiny, and all other tests cannot be done. This sample include the DNA from unlived tumor cells (called as circulating tumor DNA, or ctDNA). Those ctDNA enter the blood systemic arteries from original tumor tissues, and the count of those cells containing ctDNA is about 1 ~ 102/mL in systemic blood (Obeagu & Obeagu, 2024).

In a previous study, Jin et al (2020) tested the detection CTCs to assess the diagnostic power of circulating tumor cells in BC. Their findings indicated that circulating tumor cells (CTCs) can distinguish breast cancer (BC) patients from those with benign breast conditions or healthy individuals, aiding in early cancer detection and staging. CTCs could serve as a new biomarker for BC diagnosis. In a study by Ma et al. (2020), 21 patients were monitored over time during treatment, revealing that the molecular tumor burden index (mTBI), which measures the percentage of circulating tumor DNA (ctDNA) in samples, was positively correlated with tumor size as measured by computed tomography ($P < .0001$, Pearson $r = .52$), and detected disease progression 8-16 weeks earlier. Thus, ctDNA could be used to evaluate tumor heterogeneity and predict treatment outcomes in metastatic breast cancers.
Such mutations that may be investigated for include:

- ***BRCA1* and *BRCA2* gene mutations:** For pateints with an high grade levels of BC HER2-negative breast cancer, physician may recommend the patients for testing a hereditary BRCA1 or BRCA2 mutation. If women have any of these gene mutations, chemotherapy with the those drugs : olaparib or talazoparib, might be recommended (Mahdavi et al., 2018).
- ***PIK3CA, AKT1*, and *PTEN* gene mutations:** These three genes encode proteins within the same intracellular signaling pathway that promotes cell growth. Cancer cells may exhibit alterations in one of these genes. Over 50% of breast tumors have changes in one or more genes in the phosphatidylinositol 3-kinase (PI3K) pathway, including PTEN loss (34%), PIK3CA mutations (31%), PTEN mutations (5%), and AKT1 mutations (3%). Although PI3K and mTOR inhibitors are currently approved for the treatment of advanced breast cancer, AKT inhibitors have recently been introduced as a new therapeutic approach (Andrikopoulou et al., 2022).
- ***ESR1* gene mutations:**
- The ESR1 gene encodes the blueprint for the estrogen receptor (ER) protein within cells. In metastatic estrogen receptor (ER)-positive breast cancer, the emergence of ESR1 mutations during treatment with aromatase inhibitors is a prevalent mechanism of resistance to hormonal therapy. Both experimental and clinical investigations have shown that ESR1 mutations may already be present in primary tumors and become more prevalent during metastasis. In additions, these mutations display a distinct transcriptional profile that promotes tumor progression, suggesting that specific ESR1 mutations may impact the spread of cancer. Various research groups have utilized sensitive detection techniques, including liquid biopsies from patients, to monitor ESR1 or truncal somatic mutations to predict treatment response and disease progression. Some of these methodologies may eventually be utilized to tailor sequential treatment strategies for individual patients. (Dustin et al., 2019).
- **Tumor mutational burden (TMB):** TMB quantifies the number of gene mutations that may be deemed irregular and susceptible to attack by the body's immune system. In clinical practice, there's scant data on the precise relevance of this biomarker in breast cancer. Nevertheless, breast cancer demonstrates an intermediate TMB in comparison to other malignancies. About 5% of all breast cancers exhibit a TMB $\geq$ 10 mut/Mb, with metastatic tumors showing a higher occurrence of elevated TMB compared to primary tumors, at 8.4% versus 2.9% respectively. (Barroso-Sousa et al., 2023).

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- ***NTRK* gene changes:** Tropomyosin receptor kinases (TRKs), that are well-described enzymes of the cell membrane receptor tyrosine kinase (RTK) family, are transcribed from the neurotrophic receptor tyrosine kinases (NTRKs) genes. However, TRKs could modulate cell division, maturation and even cell death. Fusions of gene including NTRK may behave as oncogenic triggers of a wide variations of geriatric and pediatric tumors, and TRKs are now successful antitumor targets. Hence, it's imperative to swiftly pursue a thorough comprehension of TRKs and associated TRK inhibitors to propel the advancement of novel TRK inhibitors for prospective clinical utilization. This review is dedicated to outlining the biological functions of TRKs and NTRK fusion proteins. (Jiang et al., 2021).

4. BLOOD TESTS

At the point of detection and management initiation, the complete blood count (CBC) can provide insight into the inflammatory condition within the tumor. Research indicates that various inflammatory cell counts in peripheral blood and their ratios serve as significant prognostic indicators for numerous cancers. These include monocyte, lymphocyte, neutrophil, and thrombocytes counts, as well as ratios such as neutrophilic cells-to-lymphocytic cells ratio, thrombocytes-to-lymphocytic cells ratio, lymphocytic cells-to-monocytic cells ratio, systemic inflammation response index (SIRI) and systemic immune-inflammation index (SII) (Xie et al., 2023).

Blood chemistry tests can indicate if some of your organs, such as the liver or kidneys, are not functioning properly. For example, cancer spreading to the bones might cause elevated levels of calcium and alkaline phosphatase. If breast cancer spreads to the liver, it can elevate liver function tests like aspartate aminotransferase (AST) or alanine aminotransferase (ALT). Although breast cancer does not spread to the kidneys, poor kidney function shown in bloodwork could affect the use of certain chemotherapy drugs like cisplatin. Leser et al. (2023) found that AST, ALT and alkaline phosphatase (AP) exhibited a significant elevation in comparison to normal reference about six months proceeding to the diagnosis of liver metastases.

Breast cancer cells sometimes produce substances called tumor markers detectable in the blood. For breast cancer that has metastasized, tumor markers like, cancer antigen 27-29 (CA 27-29, cancer antigen 15-3 (CA 15-3), and carcinoembryonic antigen (CEA), may be checked. However, blood tests for these tumor markers are not used alone to diagnose or monitor breast cancer (Seale & Tkaczuk, 2022).

5. SALIVARY BIOMARKERS

Prior to the manifestation of clinical, histological, and radiological indicators, leveraging saliva for cancer diagnosis holds potential for pioneering personalized medicine strategies (Koopaie et al., 2022).

Several investigations have proposed a spectrum of salivary biomarkers, spanning proteomic, metabolomic, transcriptomic, and reagent-free biophotonic analyses. Despite these merits, the presence or concentration of biomarkers in saliva may diverge from those in other bodily fluids, underscoring the necessity of identifying salivary biomarkers with acceptable sensitivity and specificity for breast cancer diagnosis. While studies have explored salivary biomarkers across various malignancies, the pathophysiological impact of these cancers on salivary profiles remains uncertain. Some evidence suggests that cells within salivary glands and mammary glands exhibit comparable pathological and functional characteristics. Additionally, salivary gland cells release exosome-like microvesicles harboring proteins and mRNAs, detectable in saliva. (Wang et al., 2017).

CONCLUSIONS

Many diagnostic methods have been developed to detect breast cancer at different stages of the tumor. Some of these tests have been used to determine the appropriate chemotherapy method (e.g. molecular tests for gene changes), other are more generic in the determination of many tumor (e.g. complete blood count), while salivary methods are still controversial in the diagnosis of BC.

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