

MINI-REVIEW

An update on Nanomaterial-based biosensing systems for discriminative diagnosis of breast cancer

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Abstract

Breast cancer is one of the primary causes of death among women worldwide. Precise diagnosis of breast cancer provides opportunities for early treatment, thereby reducing mortality rate and increasing patient lifespan. Biosensors are diagnostic platforms integrated with different materials for biomarker detection, representing an important tool to detect recurrence and monitor drug effectiveness for breast cancer. Improving the sensitivity and selectivity of biosensor is thus mandatory for the development of point-of-care detection system. Both nanostructured metals and semiconductors are attractive materials in the development of biosensors due to higher surface area, solubility, good electrical conductivity, and appealing optical properties. Nanomaterials are generally used for amplifying the signal, and immobilizing biomolecules and electroactive species. Nanomaterial-based biosensors have enhanced capacity in target identification, which enables disease diagnosis at an earlier stage. This review discusses the diagnosis of breast cancer biomarkers and the recent development of diagnostic systems integrated with nanomaterial-assisted biosensor.

Keywords: Breast cancer; Nanomaterial; Biosensor; Nanotechnology

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1. Introduction

Breast cancer is one of the most common leading causes of cancer-related death globally, with approximately 626,700 deaths and 2 million new cases recorded in 2018.¹ The severity of breast cancer is mainly divided into four Stages (I, II, III, and IV). The starting Stage (I) corresponds to the phase of tumor formation, while the end stage (IV) refers to metastasis (Figure 1). Identification of early-stage breast cancer, together with the ensuing treatments, could reduce the mortality rate to 50%. For achieving maximal effectiveness in treatment, reliable and accurate detection of breast cancer is thus mandatory. The existing armada of diagnostic methods for breast cancer, such as X-ray mammography, magnetic resonance imaging, biopsy, mammography, and ultrasound, have an effective cancer identification rate of 80% to 90%.²⁻⁴ However, these imaging techniques are costly, demanding high technical knowledge, and only available in developed regions, in

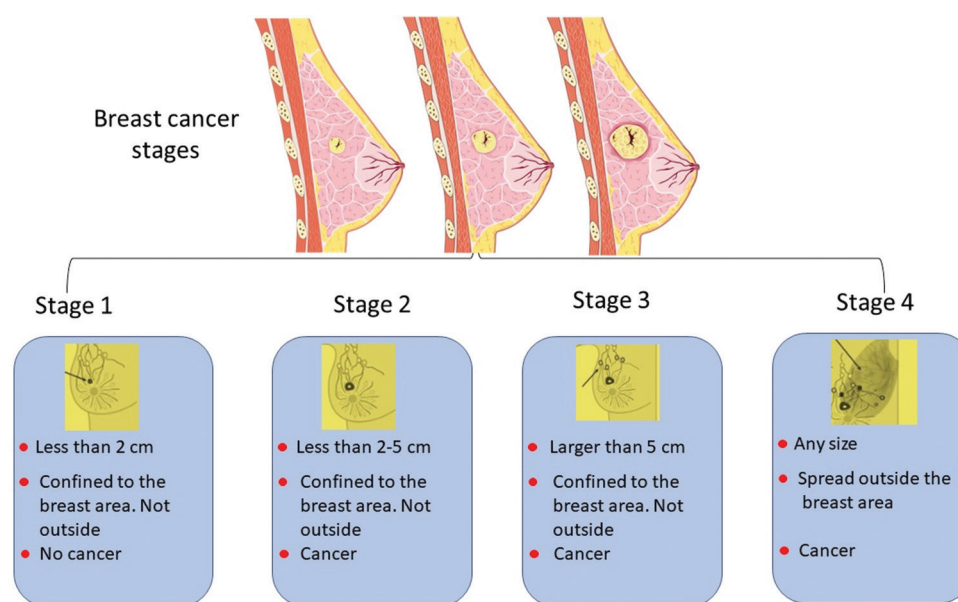


Figure 1. Stages of breast cancer

addition to their reduced cost-effectiveness and sensitivity for detecting cancer at earlier stages.⁵ In particular, common imaging techniques face difficulty in accurately imaging denser breast tissue.⁴ Therefore, it is essential to create an effective biomarker and sensitive, user-friendly biomolecular diagnostic tool for breast cancer.⁶⁻⁸ As an alternative to imaging techniques, biosensors with high-affinity blood-based biomarkers are developed for early identification of breast cancer. Radioimmunoassay, enzyme-linked immunoassay, and immunohistochemistry are commonly employed for aiding breast cancer diagnosis, but these methods could cause negative or false positive results, warranting new and effective detection approaches for breast cancer.

The current landscape in breast cancer diagnosis underscores the need to develop early-detection techniques since better treatment outcomes and survival rates depend on early identification. It is crucial to create screening systems that are more economical and accurate, particularly for people who have more risk factors. Investigating imaging techniques and biosensors with nanotechnology helps to enhance the sensitivity and specificity of breast cancer diagnosis. These needs are often reflected in the dynamic character of breast cancer diagnostic techniques, which are enhanced to improve patient outcomes through personalized approaches, accessibility, and accuracy. To overcome these hurdles, improving material-assisted biosensors that quantify blood-based biomarker is mandatory for diagnosing breast cancer. Nanostructured materials can be effectively applied in a biosensor to identify target molecule and enhance analytical performance. This

present review highlights the current development of various biosensing techniques featuring nanomaterial-based biosensors that identify clinical/biological markers for breast cancer.

2. Nanotechnology in biosensors

Biosensors are largely made up of biocomponents, which include aptamers, enzymes, antibodies, glycans, and nucleic acids.^{9,10} The interaction between a bioreceptor and an analyte typically trigger several chemical and physical changes, such as heat release, creation of new chemicals, charge movement, or changes in mass and pH. To detect these changes, the biosensing system should be equipped with a signal processing function, which includes appropriate format amplification and presentation. The output signal is then amplified and sent to a data processor after passing through microelectronics or other modalities^{11,12} (Figure 2). This strategy has the potential to significantly influence medical diagnosis and therapy, especially in the development of diagnosing diseases.¹³⁻¹⁵

Functional and technical improvements of biosensors are viewed as a future clinical feat due to the need to detect biomolecules at minute levels to identify diseases. Nanomaterials have drawn a lot of attention in the field of biosensors for improving analytical performances and disease identification. Nanomaterials have zero-to-three-dimension structures in tubular, single, fusion, and irregular forms. A wide range of materials, including copper, silver, gold, silica, and non-metallic carbon nanotubes such as graphene, graphite, and carbon nanowire, are effectively utilized for developing highly sensitive biosensors and

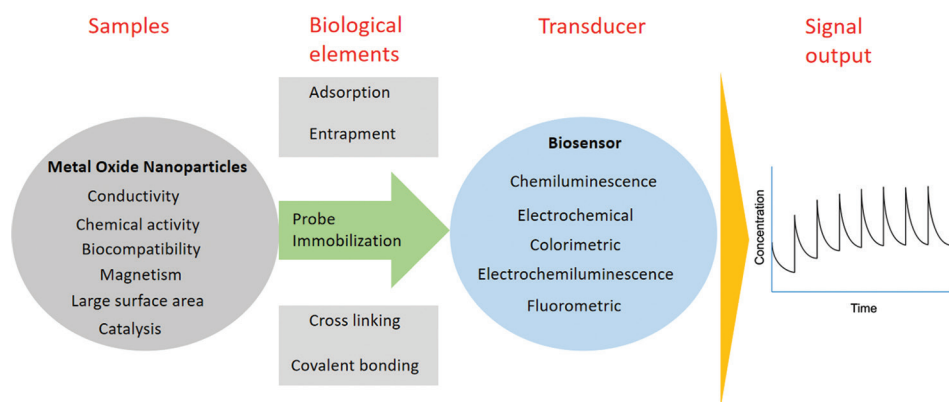


Figure 2. Schematic representation of biosensor. The interaction between the bioreceptor and analyte leads to chemical and physical changes, which will be interpreted by the signal processing system involving amplification. The output signal is amplified and displayed.

diagnosing various diseases.¹⁶⁻²⁵ Nanomaterials are utilized in two ways for improving biosensor. It is conjugated with target and/or analyte molecule and functionalized on the sensing surfaces to improve the biomolecular interactions. In the second case, it is used to fabricate the sensing electrode, which enhances the analytical performances in biosensor. In particular, nanomaterials are used mainly for surface functionalization and to prepare the nanodevices using nanometals as a transducer. Surface modification is important for enabling detection of target analyte at lower levels. This is achieved by the better and proper arrangement of biomolecules on the sensor surfaces, which enhances analytical performances of biosensors. The uniform-sized nanomaterials increase the surface-to-volume ratio and help to achieve higher immobilization of biomolecules on the sensing surfaces.^{26,27} Within the group of nanomaterials, gold is a versatile, mostly used metal in biosensor development due to easier production, functionalization, and biocompatibility.^{28,29} By virtue of their optical property, gold nanoparticles (GNPs) can be used to develop simple colorimetric sensors that allow for target molecule identification through naked-eye detection. Given the color change property of GNPs during aggregation (purple), various salt-induced colorimetric assays have developed with DNA, aptamer, and antibody. In this type of assay, DNA or aptamers are conjugated with GNPs and mixed with the target. If the target is in the solution, DNA or aptamers are released from GNPs and attached to the target, changing its color to purple (in an aggregated state) under high ionic condition. In the absence of a target, DNA or aptamers bind with GNP and form aggregation. This simple colorimetric assay helps to identify various biomarkers and diagnose diseases such as cancer.^{30,31} Apart from that, nanomaterials such as carbon-derived materials have conductivity and the ability to enhance electron transfer, which help to increase

the current flow on the electrochemical sensor on the interaction of biomolecules on the sensor surface.

3. Surface functionalization on nanomaterials for cancer diagnosis

Early detection of cancer allows for the formulation of an effective treatment, which potentially extends the patient's lifespan. Nanomaterials are effectively applied for various surface functionalization on carbon-derived materials aimed for cancer diagnosis and implemented in various biosensor developments. Researchers have developed a biosensor with multi-walled carbon nanotube (MWCNT) to identify cancer. The cancer biomarker (antigen) was immobilized on the sensing surface through the MWCNT. Polyethylene glycol (PEG) is used as a blocking agent to reduce biofouling. PEG can bind on the excess amine surfaces, block the binding of other biological molecules on the electrode, and reduce biofouling. It has been proved that MWCNT can increase immobilization of antibody on the interdigitated electrode and enhance the interaction of target antigen with its antibody and help with diagnosis²⁴ (Figure 3). Similar strategy can be followed to diagnose breast cancer and detect other clinical biomarkers. In another research, the captured DNA for the specific gene type b3a2 sequence was immobilized on the sensor through the chemical linker with graphene oxide and identified by the target DNA. The graphene-modified electrode lowered the DNA detection to 10 aM.³² In a different researches, biosensor integrated with iron oxide nanoparticles was developed for cancer detection. Iron oxide nanoparticle has the desirable features, such as large surface area, high bioactivity, and stability are easily amenable to surface functionalization and preparation.³³ In that research, iron oxide was synthesized with a greener method, and used for surface functionalization to attach antibodies on the sensor surface. More antibodies were attached to the surface of

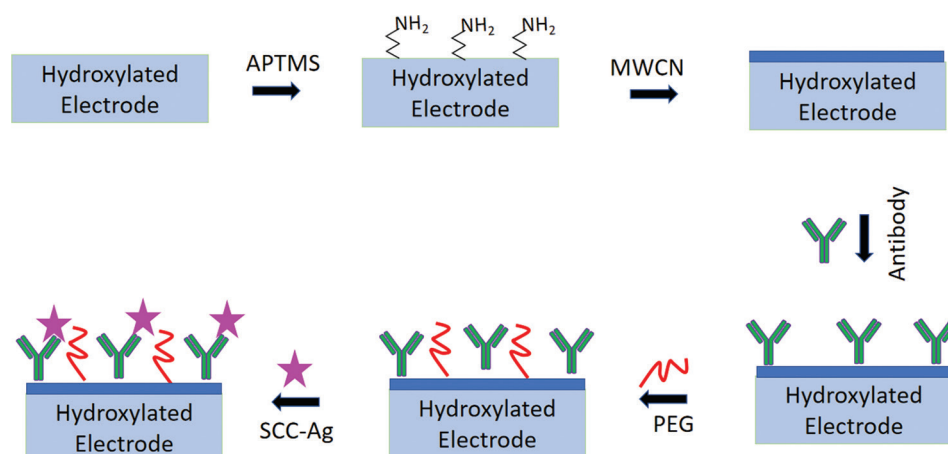


Figure 3. Cancer identification on multi-walled carbon nanotube (MWCN)-modified electrode. Antibodies targeting squamous cell carcinoma antigen (SCC-Ag) were immobilized on the sensing surface of MWCN and recognized by SCC-Ag.

Abbreviations: APTM: 3-Aminopropyl)-trimethoxysilane; PEG: Polyethylene glycol.

the iron oxide, leading to increased detection of antigens.³⁴ In another research, single-walled carbon nanotube (SWCNT) with gold urchin (GU) nanocomposites were used for surface functionalization to construct a cancer biosensor. Attached on SWCNT-GU microelectrodes junction through a chemical linker, SRY-box containing gene-17 (SOX-17)-specific DNA was used to identify target DNA by an electrochemical impedance sensor. SWCNT-GU composites increase the rate of capture DNA immobilization on the sensor surface, thereby improving the interaction of capture DNA with target DNA, which serves as an important clue for cancer diagnosis.³⁵

4. Biomarkers for breast cancer

Biomolecules such as RNA, proteins, antibodies, and DNA may exist in free form and circulate in the bloodstream and are used as biological markers for diagnosing breast cancer³⁶⁻³⁸ (Figure 4). Methylation of DNA is the predominant form of molecular change in various cancers. Studies found that testing of DNA methylation helps to predict breast cancer. In particular, RASGRF1 (Ras-specific guanine nucleotide releasing factor 1), DACH1 (Dachshund homolog 1), CPXM1 (carboxypeptidase X), and HOXA10 (Hox-A10) were found as the suitable methylation markers for breast cancer screening.³⁹ Apart from that, circulating proteins are attractive molecules for the analysis and recognition of breast cancer. For instance, trefoil factors TFF3, TFF2, and TFF are biomarkers not only suitable for diagnosing breast cancer but also helpful for discriminating cancer cells from healthy cells.⁴⁰ Besides proteins, proteinaceous biomarkers, including vascular endothelial growth factor, serum apolipoprotein C-1 (apoC-I), human epididymis secretory protein 2 (HE2),

pleiotrophin (PTN), and matrix metalloproteinase-9 (MMP-9) are promising biomarkers for the detection of triple-negative breast cancer (TNBC).⁴¹⁻⁴⁴ Apart from that, circulating antibodies, RNAs and miRNAs are also used for screening and monitoring breast cancer.

5. Detection of breast cancer biomarkers by nanomaterial-based biosensor

Detection of biomarkers using biosensing technique is helpful to monitor the progression of breast cancer stages as well as treatment progress. Various nanomaterial-based biosensing techniques have been introduced by researchers to monitor breast cancer progression. This kind of biosensing technique, coupled with the detection of blood-based biomarkers, is easier to operate and more convenient than standard biopsies.

5.1. Detection of nucleic acid-based breast cancer biomarkers by nanomaterial-based biosensor

Nucleic acid-based cancer biomarkers such as microRNA, circulating DNA, circulating RNA, *BRCA1*, and *BRCA2* genes, and non-coding RNAs are targeted by biosensors aimed for breast cancer diagnosis. A biosensor coupled with miRNA-21, a breast cancer biomarker, was developed on MWCNT-immobilized electrode. A DNA probe was added on the MWCNT, hybridizing the target DNA in a process detectable by impedance spectroscopy and cyclic voltammetry, with a detection limit of 84.3 fM.⁴⁵ Similarly, a simple GNP-based colorimetric assay that could detect miRNA-155 has been developed. In this assay, the DNA probe was bound with a negatively charged GNP through covalent bonding and then the positively charged GNP was attached to the miRNA-155 through

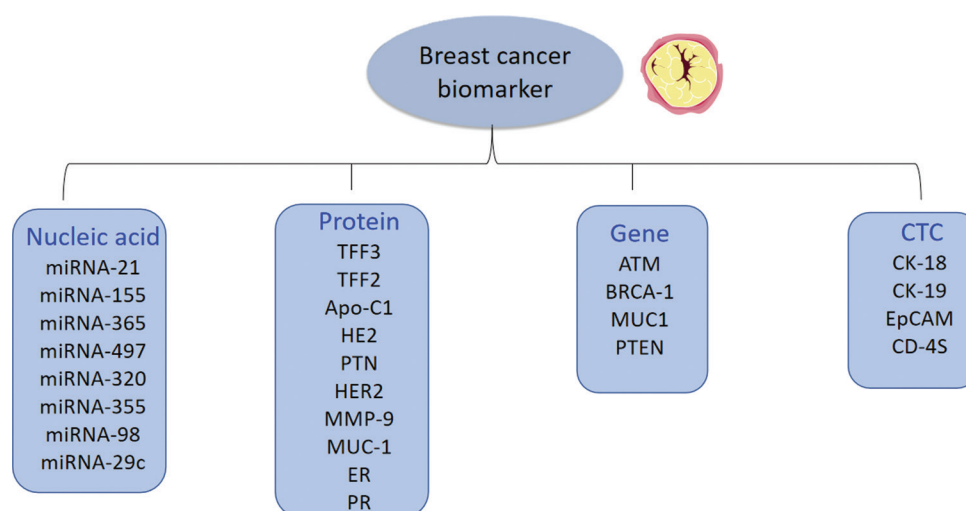


Figure 4. Biomarkers for breast cancer

electrostatic interaction. Following the mixing of these two, hybridization occurred, releasing an optical signal that corresponds to the quantitative levels of miRNA-155. This detection method identifies the miRNA from 100 aM and helps to diagnose breast cancer.⁴⁶ In another research, a sensitive and simple amperometric sensor was created with electrode surface made of GNPs for quantifying miRNA-21. The hybridization happened between the thiolated DNA and the DNA-miRNA-21 conjugated with a specific antibody. The amperometric detection allows the quantification of target miRNA bound to the DNA from 29 fM.⁴⁷ Similar to mRNA, circulating tumor DNA (ctDNA) has been found as a suitable biomarker for diagnosing cancer. For this, researchers prepared a polymeric nanosphere loaded with ferrocene by self-assembling polyacrylic acid on silica nanoparticles and polyethyleneimine-Fc. Using this nanosphere, dual enzyme-mediated amplification method was employed to detect the ctDNA as low as 1.6 fM.⁴⁸

5.2. Detection of protein-based breast cancer biomarkers

Protein-based tumor biomarkers such as CD44, CD24, VEGF, MUC1, HE2, and MMP are highly correlated with breast cancer. Various biosensors that can quantify these protein biomarkers have been developed for diagnosing breast cancer. MMPs are regarded to be relevant to breast cancer prognosis. Various studies have proved the association between MMPs and tumor growth, metastasis, and invasion in breast cancer. Thus, quantifying MMPs could help with breast cancer diagnosis. GNP-based enzyme-linked immunosorbent assay (ELISA) was developed by researchers to detect MMP-9 in biological samples. GNP was conjugated to polyclonal antibody and attached on

an amine-modified ELISA well. Further, MMP-9 was added and then sandwiched with a monoclonal antibody. The signal was amplified with secondary antibody-conjugated horseradish peroxidase (HRP) and substrate. The GNP-conjugated antibody improved the performance of the detection system, as compared with conventional ELISA, and lowered the detection limit to 1 pM²² (Figure 5). High-sensitive vascular endothelial growth factor (VEGF) electrochemiluminescence biosensor was developed by Cheng *et al.* (2020) by fabricating (VEGF₁₆₅). g-C₃N₄/PDDA/CdSe on the sensor surface. Amine-ended DNA was attached to the surface and then linked with gold-labeled target DNA for hybridization. During the hybridization, nanocomposites were quenched efficiently due to the energy transfer between the cadmium selenide (CdSe) and GNPs. This sensing technique detects the VEGF in a linear range between 2 pg/mL to 2 ng/mL with a limit of detection of 0.68 pg/mL.⁴⁹ Label-free surface plasmon resonance-based biosensor was developed by researchers to quantify the level of human epididymis protein (HE4), which is expressed in ductal carcinoma in the breast tissue. Silver nanoparticles were decorated on the sensing surface using the lithography method and an anti-HE4 antibody was attached to the nanochip. The HE4 detection was based on the shift changes of localized surface plasmon resonance (LSPR) on interaction of HE4 with its antibody. The detection range was between the range of 10 – 10000 pM, and the limit of detection was 4 pM.⁵⁰ In another research, HE4 detection in blood plasma was conducted with a non-fluidic array SPRi technique. The HE4 antibodies were covalently attached on the gold surface using cysteamine linker. The SPR signal was measured before and after the interaction of HE4-containing plasma with its antibody; the limit of detection

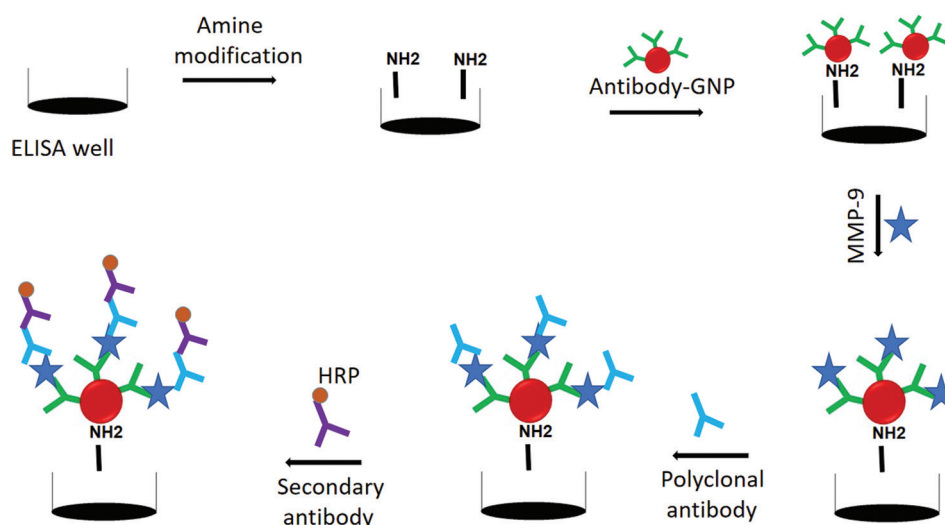


Figure 5. Detection of matrix metalloproteinase 9 (MMP-9), a breast cancer biomarker, on gold nanoparticle (GNP)-based enhanced enzyme-linked immunosorbent assay (ELISA). GNPs are conjugated with polyclonal antibody and attached on an amine-modified ELISA polystyrene plate. MMP-9 is added and then sandwiched with a monoclonal antibody. The signal is amplified by a reaction between a secondary antibody conjugated with horseradish peroxidase (HRP) and a HRP substrate.

of HE4 was determined to be 2 pM.⁵¹ Separately, a team of researchers developed an aptamer-based sensor on the gold electrode to detect mucin (MUC1), which has been approved clinically for identifying breast cancer. Aptamer forms stem-loop structures, which create single-stranded narrow and specific binding regions. In addition, aptamer is a short molecule able to generate a properly oriented and aligned attachment on the sensing surface to interact with the desired target. Attached on the gold electrode through self-assembly, thiolated anti-MUC1 aptamer combined with methylene blue can detect MUC1 by interaction with the aptamer, which is detectable by electrochemical aptasensor.⁵²

5.3. Circulating tumor cells (CTCs)

Tumor cells are also part of the wide array of tumor biomarkers, aside from proteins and nucleic acids. CTCs are cells that break off from the tumor and enter the bloodstream where they might grow new tumor tissue. Thus, identifying CTCs could help with the diagnosis of breast cancer, facilitating the planning of required treatment.^{53,54} Breast cancer stages can be identified by CTC biosensors. A team of researchers attached anti-GPR30 antibodies on a biosensor they developed on gold nanofilm on the fiber surface. GPR30 is a membrane receptor that is highly expressed in breast cancers. The anti-GPR30 antibody-attached surfaces allowed for the detection of breast cancer cells with a minimal limit of 5 cells/mL.⁵⁵ In another research, electric impedance spectroscopy with magnetic nanoparticles was introduced to detect breast cancer cell lines. Each cell line represents

different stage of breast cancer, such as early stage, invasive phase, or metastasis. The bioimpedance measures the certain frequency range for various stages with the aid of magnetic nanoparticle-conjugated antibodies. The antibodies were specific for the surface protein for each cell line and identified by flow cytometry and RT-qPCR.⁵⁶ This detection method identifies the cancer type and helps with monitoring the treatment progress.

5.4. TNBC biomarker identification

TNBC is a pathological form of breast cancer, which lacks expression of human epidermal growth factor receptor 2 (HER2), progesterone receptor (PR), and estrogen receptor (ER).^{57,58} Characterized by aggressiveness and shortened survival, TNBC is responsible for approximately 15 – 20% of the total breast cancer cases. VEGF is crucial in the process of tumor spreading and is highly expressed in around 30 – 60% of TNBC patients.⁵⁸ Various biosensors that can quantify the minute level of VEGF have been developed to aid in the diagnosis of early-stage TNBC. Nanocomposites, synthesized with amine-modified SWCNT, methylene blue, and GNPs, were used to functionalize the working electrode of electrochemical sensor. On the electrode, immunoassay was developed to detect the VEGF level as low as 10 pg/mL.⁵⁹ Similarly, enhanced VEGF detection could also be achieved by catalase-mediated chemiluminescence immunoassay using a quantum dot for signal transduction. Under suitable condition, the chemiluminescence ELISA can detect VEGF in a linear range of 2 – 35000 pg/mL, with a limit of detection of 0.5 pg/mL.⁶⁰ HER2 quantification also serves as a strategy

Table 1. Nanomaterial-based biosensors and biomarkers for breast cancer diagnosis

Target	Probe	Biosensor	Nanomaterial	Limit of detection	References
miRNA-21	DNA	Impedance spectroscopy	MWCN	84.3 fM	45
miRNA-155	DNA	Optical sensor	Gold nanoparticle	100 aM	46
miRNA-21	DNA	Amperometric sensor	Gold nanoparticle	29 fM	47
ctDNA	DNA	Electrochemical sensor	Silica nanoparticle	1.6 fM	48
MMP-9	Antibody	ELISA	Gold nanoparticle	1 pM	22
VEGF	DNA	Electrochemiluminescence	Gold nanoparticle	0.68 pg/mL	49
HE4	Antibody	Surface plasmon resonance	Silver nanoparticle	4 pM	50
HE4	Antibody	Surface plasmon resonance	Gold	2 pM	51
MUC1	Aptamer	Electrochemical sensor	Gold	0.65 ng/mL	52
VEGF	Antibody	Electrochemical sensor	SWCN-Gold	10 pg/mL	59
VEGF	Antibody	Chemiluminescence ELISA	Quantum dot	0.5 pg/mL	60
HER2	Antibody	Electrochemical sensor	Silver	2 cells/mL	62
HER2	Antibody	LSPR sensor	Gold and silver	3.7×10^{-7} M	61
CTC	Antibody	Plasmonic biosensor	Gold	5 cells/mL	57

Abbreviations: CTC: Circulating tumor cells; ELISA: Enzyme-linked immunosorbent assay; HE4: Human epididymis protein; HER2: Human epidermal growth factor receptor 2; LSPR: Localized surface plasmon resonance; MMP-9: Matrix metalloproteinase-9; MUC1: Mucin; VEGF: Vascular endothelial growth factor.

to diagnose TNBC. Sensors with GNPs-grafted graphene and polyaniline nanostructure were functionalized on the electrode sensor to detect the HER2. Further, the authors replaced the silver electrode, instead of the gold one, in the system, which enabled a minimal HER2 detection limit of 2 cells/mL.³ Similarly, HER2 can be detected by monoclonal antibody trastuzumab with plasmonic nanoparticles. Negatively charged GNPs were mixed with optimized silver nanoparticle in the development of a surface plasmon sensor for detecting HER2 by the corresponding antibody. The gold and silver nanoparticles collectively enhanced the localized surface plasmon activity, coupled with a detection limit of 3.7×10^{-7} M.⁶¹ The aforementioned discussed studies concerning the development of nanomaterial-based sensors can be replicated using ingredients that target other biomarkers of interest, yielding sensors that are complementary to other biosensors (Table 1).

6. Conclusion

Breast cancer is the primary cancer significantly affecting the health and lifespan of women. Early identification of breast cancer could prompt advanced planning of proper therapy so as to increase lifespan of the patients. In a number of biomedical applications, such as the diagnosis and therapy of cancer, nanomaterials have demonstrated considerable potential. Nanomaterials have special qualities that can improve imaging methods, facilitate targeted therapy, and improve early diagnosis in the context of breast cancer detection. This paper reviews the special attributes of nanomaterials used in biosensors that contribute to

enhanced sensitivity, selectivity, and overall performance. Coupled with imaging, biosensors for biological markers facilitate early diagnosis of breast cancer. The merging between nanomaterials and biosensors contribute to further improvement of sensor for identification of various diseases. Apart from the current developments concerning the integration of nanomaterials into biosensors, further research is warranted for diagnosing breast cancer using biomarker-based biosensors. The further research endeavor is empowered the availability of a wide range of identified biomarkers, which aid in the generation of multiplex cancer detections. While the nanomaterials usage holds tremendous promise for the diagnosis and treatment of breast cancer, further study is necessary to resolve safety issues, enhance their qualities, and guarantee their clinical efficacy. Furthermore, it is important to thoroughly assess the ethical issues surrounding the use of nanomaterials in medicinal applications. Advances in a variety of technologies and methods are expected to play a major role in the future of breast cancer diagnosis, with a focus on enhancing precision, early identification, and personalized treatment. To improve outcomes for those who are at risk of or have already been diagnosed with breast cancer, the identification of breast cancer in the future is expected to entail a multidisciplinary strategy that combines technology breakthroughs, data integration, and a personalized medicine framework. The future course of breast cancer detection and treatment will be greatly influenced by ongoing research, teamwork, and technology developments.

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Conflict of interest

There are no conflicts to declare.

Author contributions

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Writing – original draft: All authors

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Ethics approval and consent to participate

Not applicable.

Consent for publication

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Availability of data

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