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Biosensor applicability in breast cancer diagnosis

Abstract

Breast cancer is the most commonly diagnosed cause of cancer among women worldwide, early detection and treatment monitoring is of great importance, so advances in diagnostic device technologies are needed to develop highly sensitive detection methods. Noninvasive, such as biosensors. This study aimed to conduct a systematic literature review to describe the applicability of available biosensors for the diagnosis of breast cancer. A literature review was performed with the specific keywords in the Scientific Information Database (SID), PubMed and Science Direct electronic databases, from 2014 to 2019. Relevant literature findings showed the development and applications of related biosensors. to the diagnosis of breast cancer, combining response efficiency as well as a less costly and non-invasive procedure, where some devices perform tests on body fluid samples such as blood serum, saliva and urine samples, biosensors are responsible for characterizing and even quantify physiological or pathological changes present in the applied biological environment. It is concluded that advances in research and development of biosensors applied to the diagnosis of breast cancer is of great importance, as these devices provide an innovative, efficient and cost-effective screening in order to identify the biological changes related to breast cancer. Reduce costs involved in the process of diagnosis and monitoring of the disease.

Keywords: biosensors, breast cancer, diagnosis

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Abbreviations: RIA, radioimmunoassay; IHC, immunohistochemistry; TPS, tissue polypeptide specific antigen; TPA, tissue polypeptide antigen; CEA, carcinoembryonic antigen; SPR, surface plasma resonance; ThT, Tioflavin T

Introduction

Breast cancer is the leading cause of cancer death among women worldwide, approximately two million new cases and 626,700 deaths in 2018, representing 25% of all cancer cases and 15% of all women. cancer deaths among women.[1,2] Early detection of breast cancer reduces long-term mortality rates, however, has limitations regarding early-stage cancer cell identification.[3] Currently, diagnostic techniques include mammography, biopsy, magnetic resonance imaging, ultrasound, among other methods capable of detecting 80 to 90% of cancers. In addition, biomarker-based expression techniques such as immuno absorbent assay (ELISA), radioimmunoassay (RIA) e immunohistochemistry (IHC) are also used in the diagnosis.[4–6] However, these methods have limitations with false positive or negative results, which erroneously imply unnecessary interpretations and biopsies. Thus, studies emphasize the development of highly sensitive and noninvasive detection methods such as biosensors, which are sensitive, specific, economical and responsive devices through the direct evaluation of physiological fluids such as blood, serum, urine, saliva, among others.[5] Biosensors are analytical devices that quantify the biological characteristics of tissues and body fluids, which have physical parameters through local O_2 concentration and pH, or specific biomarkers, for example, diabetes monitoring biosensors.[7] The biosensor consists of three main parts, a biomarker (target molecule), a bioreceptor (recognition element) and biotransducer components (translates the chemical signal into the measurable physical signal, such as electrical, optical, etc.), which play an interactive role and define the technical specifications of the biosensor.[5,8] Biosensors are responsible for quantifying the morphological characteristics of cells by means of a relevant and quantitative physiological or pathological reading of the cellular response to the signaling pathway. Studies show that biosensors quantitatively monitor dynamic cell changes such as cell adhesion and morphology through signal transduction pathways.[9]

The biomarker "is a biological molecule found in blood, body fluids or tissues as a signal of a normal or abnormal process or condition or disease".[10] Based on the literature, these biomarkers should be accessible and sensitive enough to detect specific tumors without causing false positive results .[11] Breast cancer biomarkers can be classified for screening, prognosis, diagnosis and monitoring of the disease.[12] The main prognostic biomarkers of early-stage breast cancer used to identify patients most likely to benefit from hormone therapy and adjuvant chemotherapy are: tumor size, grade, lymph node status, number of positive lymph nodes, estrogen receptor status and progesterone, and epidermal growth factor 2 receptor status (HER2).[13] Scientific evidence reports the discovery of new biomarkers, considered promising in the early and reliable diagnosis of minimally active breast cancer, such as DNAs, mRNAs, cell surface receptors, transcription factors and proteins.[14] Ikegwuonu et al.,[7] stated that the cellular environment in which the tumor develops is rich in blood vessels, immune and inflammatory cells, in which biosensors are employed for real-time monitoring of tumor cells, providing the possibility to analyze and relate the biology of each tumor to cancer-specific treatment.[7] The need to determine tumor biomarkers of different natures in minimally invasive samples has contributed to the development of electrochemical biosensors associated with nanotechnology in order to generate a low cost, robust, easy to apply and ultrasensitive grade in breast cancer diagnosis.[15]

Nanomaterials with specific characteristics, such as metal oxide and metal nanoparticles, nanospheres and integrated nanostructures, such as graphene or reduced graphene oxide, composed of metal oxide or metal oxides and multi-walled carbon nanotubes, provided biosensors for the determination of biomarkers in breast cancer with high sensitivity and diagnostic accuracy.[15] Currently, the development of minimally invasive and effective methods for the monitoring of specific biomarkers of body fluids through biosensors, which contribute to the early detection of breast cancer, treatment and monitoring of

metastases, is of paramount importance in clinical oncology practice. to ensure a good prognosis for the patient.[11] Contextually, biosensor variability requires a systematic analysis and a correct understanding of the materials used and their corresponding biomarkers. In addition, the literature still lacks information on the clinical feasibility of these materials, since we have observed that many authors emphasize how successful the chosen biomarkers and biosensors have been shown to be. In order to follow the advances in the literature, this review focuses on the main components and mechanisms involved in the development of biosensors and biomarkers for the early diagnosis of breast cancer. To simplify understanding, the current review has been divided into two main parts (1) biomarkers and (2) biosensors, and subdivided into their counterparts to discuss all aspects associated with development and their applicability. For this, the aim of this study was to describe the applicability of available biosensors for the diagnosis of breast cancer through a systematic literature review to identify human research available in the electronic databases Scientific Information Database (SID), PubMed and Science Direct. The analysis of the articles found in the databases was performed in three steps. First, the titles of the articles were read, in which those titles that did not meet the above criteria were excluded. In the second stage, the abstracts of the selected studies were read, and those that did not agree with the theme were excluded. In the last phase, a thorough reading of the study was performed (Table 1).

Table 1 Summary of selected contemporary breast cancer biomarkers and biosensors

Author(s)	Biomarker	Biosensor
Chen et al.28	c-erbB-2	c-erbB-2
Eletxigerra et al.[30]	c-erbB-2	magnetoimmunosensor
Meisam et al.[49]	CD44	nanobiosensor based on graphene / gold nanoparticle
Monteiro et al.[33]	HER2 antigen	nanohole arrays on gold thin film
de Oliveira et al.[31]	anti-ErbB2	stainless steel capillary electrodes
Dong et al.[47]	H2O2 released form MDA-MB-231 and T47D cell lines	trimetallic AuPtPd nanocomposites
Gupta et al.[34]	MUC1	gold nanoparticles and graphene oxide nanocomposite film
Hasanzadeh et al.[35]	CA 15-3 antibodies	immunoassay based on gold nanospear
Ivanova et al.[32]	DNA-oligonucleotide	Nanowire silicon biosensor
Zheng et al.[29]	CA153, CA125 and CEA	microfluidic immunoassay
Han et al.[48]	nti-CD44 monoclonal	magnetic-fluorescent iron oxide-carbon hybrid nanomaterials
Li et al.[36]	HER2+	gold nanoclusters entrapped in mesoporous silica nanoparticles

Biomarkers in breast cancer diagnosis

In the diagnosis of breast cancer we can mention several serum biomarkers used in clinical practice, such as carcinoembryonic antigen (CEA), carbohydrate antigen 15-3 (CA 15-3), circulating cyto keratins, such as tissue polypeptide antigen (TPA), tissue polypeptide specific antigen (TPS) and cytokeratin 19 fragment (CIFRA-21-1), and the proteolytically cleaved ectodomain of the human epidermal growth factor receptor 2 (s-HER2). He most commonly used serum biomarker is CA15-3, however it has decreased sensitivity in early cancer detection.[16] With technological advances, it was possible to identify new biomarkers, which provided new strategies for screening and early diagnosis. DNA methylation, histone modifications and miRNAs are important regulators of gene expression of normal and pathological development. These are currently considered prognostic biomarkers in cancer, which are being investigated as therapeutic targets.[17] Currently the Food and Drug Administration (FDA) approved blood biomarkers for breast cancer are recommended for monitoring disease recurrence and treatment efficacy but are not used for diagnosis. Specific gene mutation tests, such as the BRCA1 and BRCA2 mutation, are used to screen for breast cancer heredity. In women at normal risk of developing breast cancer, mammography screening is recommended; however, it is a method of low sensitivity.[18]

Biomarkers, including DNA methylation, have potential for early screening and diagnosis of breast cancer[19] DNA methylation encompasses the addition of a methyl group to the cytosine pyrimidine ring in CpG (cytosine phosphate-guanine) dinucleotides by DNA methyltransferases (DNMTs). Promoter methylation is believed to decrease gene expression by recruiting proteins from the methyl binding domain, thereby altering chromatin conformation and preventing binding of transcription factors. In the case of women with breast cancer, studies have shown that promoter hypermethylation silences tumor suppressor genes, including BRCA1, E-cadherin and TMS1.[17,20] Studies on DNA methylation in breast cancer from blood samples (whole blood or white blood cells) or cell-free DNA (cfDNA) isolated in serum or plasma are employed to identify methylation biomarkers between healthy and breast cancer patients.[18] The rationale for such an association is that blood levels of DNA methylation may be a substitute for breast tissue methylation as they represent immunity and inflammation of the target tissue, altered molecular pathways involved in carcinogenesis, or reflect endogenous or exogenous exposures such as hormone levels, alcohol, body mass index, smoking or ionizing radiation.[21]

According to the study by Shan et al.,[19] Twelve markers have been studied for breast cancer tissue detection and combined serum samples ((SFN (14-3-3σ), HOXA11, ARID1a, CBX7, DLC1, P16, RARβ, PCDHGB7, hMLH1, WNT5a, HOXD13, and RASSF1a). These markers represent a variety of cell pathways, including DNA binding, cell cycle, developmental regulation, chromatin binding, cell adhesion, and cytokine activity. Other authors have stated that this evidence of blood DNA methylation and the risk of breast cancer are inconsistent, because to better understand this possible relationship, large prospective studies, real information on systemic exposures and blood samples collected before diagnosis are needed.[21,22] In recent years, studies have stated that microRNAs (miRNAs), small single-stranded RNA molecules that do not encode proteins, may be circulating in body fluid, and peripheral blood miRNA expression may be used as a biological biomarker in the diagnosis and breast cancer prognosis.[23,24] Free circulating miRNAs are usually bound to high density ribonucleoprotein or lipoprotein complexes, or are released into lipid vesicles, micro vestibules, exosomes, or apoptotic bodies, which can be detected in the bloodstream or in body fluids (plasma / serum). These reflect the body's homeostatic response through signs of disease progression, which are proposed as biomarkers in the prognosis and diagnosis of cancer, neurological diseases and diabetes mellitus.[25]

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Stevic et al.,[26] performed a study on the identification of microRNA in plasma-derived exosomes of 435 human epidermal growth factor (HER2) positive and triple negative breast cancer subtypes by means of characterization tests by confocal microscopy, Western blot and ELISA. The study results showed a network of dysregulated exosome miRNAs with specific expression patterns in exosomes of women with positive and triple negative HER2 associated with clinicopathological and risk aspects. Tang et al.,[27] stated that miR-193a-3p promoter hypermethylation was observed in HER2 positive breast cancer and the percentage of methylation was positively associated with tumor stage and grade. Future research in oncology depends on the technological development of new biomarkers and biosensors aimed at detecting, characterizing and tracking the tumor environment during carcinogenesis. This factor is important in early detection and staging of cancer in order to provide better quality of life to patients.

Biosensors

Despite the growing advantages of identifying breast cancer biomarkers, commonly used diagnostic tests are poorly sensitive, complicated, time consuming, costly, as well as high risk of false positive and false negative. Therefore, there is still an imperative need for simple and fast sensitive and specific methods. To date, the identification of oncogenetic biomarkers has been based on the analysis of biological material acquired through tumor tissue biopsy. Chemically modified electrodes were prominent in studies with biosensors and electroanalysis. It is a relatively modern technique for electrode systems that has a broad spectrum of research and clinical applications. For breast cancer detection, different types of nanoparticles have been anchored to electrochemical biosensors using different specific biomarkers such as c-erbB-2 oncogene, and different antigens and antibodies. The study by Chen et al.,[28] refers to the concentration of the oncogene c-erbB-2 in the saliva of women with breast cancer. However, due to the low concentration of this biomarker, numerous experiments were needed to improve a biosensor based on a fluorogenic solution, as well as to design a signal amplification scheme using a signal transducer probe capable of identifying the specific oncogene in the sample. of DNA present in saliva. Initially, the fluorescent signal is low due to the weak interaction between the probe and the DNA sample, but after the addition of the enhanced solution the signal was amplified, making spectroscopic analysis possible. The authors concluded that using this detection protocol, a relatively simple and fast selective sensor for the detection of amplified DNA was developed, since the sample incubation period was 2hours, which may represent a promising way for the early diagnosis of the DNA breast cancer. However, we found no further studies that have continued this technique for the next five years. In 2018, another research group also relied on spectroscopy as a diagnostic technique for identifying breast cancer.[29] The authors used to create an immunohistochemical fluid aggregated to silver nanoparticles capable of detecting breast cancer biomarkers used in the ELISA assay (CA153, CA125 and CEA antibodies) and the results showed the specificity and reliability of the ELISA-like fluid. Eletxigerra et al.,[30] were also based on the ErbB2 marker, but this time, the study was based on the detection of its antigen by means of a solution from the modified ELISA immunohistochemical test. The authors investigated the possible Biofunctionalization of the solution with magnetic spheres, aiming to shorten the analysis time and simplify the ELISA. Under optimized conditions, the response of the magnetic immunosensor enriched solution was evaluated at different concentrations. The results show that even though ELISA is one of the best commercial agents for immunohistochemical assays, enrichment of the solution with the magnetic immunosensor improved the analysis kinetics, significantly reducing time; improving detection of anti-ErbB2, making It is a technique for diagnosing breast cancer, monitoring and monitoring the patient's metastatic.

In the study by de Oliveira et al.,[31] it was also based on a magnetic sensor anchored to the anti-ErbB2. However, as ELISA-based assays have some disadvantages, such as the exclusion of thermodynamic-kinetic studies in relation to antigen-antibody interaction and the use of labeled molecules that can promote false positive responses, the authors developed stainless steel capillary electrodes to which magnetic beads containing the anchored antibodies were deposited. The sensors were immersed in ErbB2 protein samples, and even at low sample concentrations were effective in identifying by antigen activation. However, this is an initial trial and needs to be replicated in human plasma samples from breast cancer patients to check its efficacy and accuracy. Ivanove et al,[32] started from this same principle and developed a silicon-based nanowire modified with oligonucleotides complementary to the oncogene mRNA, for detection of complementary DNA present in a buffer solution. The biosensor was sensitive to differentiate the marker for breast cancer compared to ovarian cancer. Antigen evaluation in human serum is traditionally obtained by enzyme-linked immunosorbent assay (ELISA), and many studies have been based on antigen-antibody interaction and the use of labeled molecules in immunoassays. Thus, a new biosensor to evaluate HER2 antigen was proposed by Monteiro & Cols[33] the authors developed a thin film with gold nanoparticles deposited in a micro fluid containing the anti-HER2 biomarker for analysis by surface plasmon resonance. The proposed device achieved a medium sensitivity for refractive index variation and is considered effective for bioassays, particularly for breast cancer diagnosis and prognosis. Gold nanoparticles have been widely used in graphene-based hybrid electrochemical biosensors anchored to specific biomarkers[34,35] or silica.[36] The authors report that the hybrid interface provides a large surface area for the effective immobilization of antigens present in immuno enzyme solutions. Gold nanoparticles are believed to favor antigen-antibody binding events in unprocessed human plasma samples, even when antigen concentrations are low. It is concluded that under optimized experimental conditions, biosensors have good sensitivity and specificity.

Current perspectives

Breast cancer is a major cause of mortality in women worldwide, however early-stage screening and diagnosis technologies such as mammography, MRI and ultrasound, for example, have limitations related to early diagnosis accuracy.[37] According to Qiu et al.,[37] mammography is less effective for early detection of breast cancer in young women aged 40 to 49 years, early-stage primary lymph node negative breast cancer and in situ ductal carcinoma, which justifies the positive influence on breast enlargement. demand for the development of more effective technologies for early diagnosis. Corroborating the above study, Wang[3] He said mammography is less effective in women with dense breast tissue and under 40years of age because they are less sensitive in 1mm tumors, about 100.00 cells. Contrast-enhanced digital mammography has better accuracy in women with dense breasts; however, it has high cost and high radiation levels. Magnetic resonance imaging (MRI) detects small lesions, which cannot be detected by mammography; however, it has a high cost and low specificity leading to under diagnosis. Positron emission tomography

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(PET) is the most accurate method for visualizing tumor spread and its therapeutic response.

Thus, the search for more effective and faster alternatives for breast cancer diagnosis has been based on the use of biosensors made from different types of biomaterials, the focus of which has been specific biomarkers for gene-protein expression breast cancer. In 1914 Michaelis and Kramsztyk measured the pH of several mammalian tissues after dissection. Decades later, in 1927 Buytendijk pioneered the use of a pH electrode for medical purposes, later in 1962 Professor Leland C. Clark Jr., one of the creators of the biosensor concept, presented his study with the electrochemical system in which Oxidized glucose was trapped in a Clark electrode by means of dialysis membrane, thus resulting in a glucose biosensor. In 1977 Cammann introduced and spread the term biosensor. In 1982 with the development of surface plasma resonance (SPR) techniques with an optical biosensor, there was a major boost in studies involving surface chemistry and a greater interaction between physics, chemistry and biology in order to broaden knowledge and development of new biosensor devices mainly in the medical field.[38–40] There are different biosensors used to detect markers in cancer. The classification of optical biosensors includes optical fiber, fluorescence, optical resonance and surface plasma resonance (SPR), which is widely used for protein and DNA cell analysis. Piezoelectric sensitive biosensors with antibodies that specifically bind to the biomarker such as HER-2, developed for breast cancer detection.[3] To design electrochemical biosensors to detect biomarkers, three characteristics are required: recognition elements to interact with biomarker, a measurable signal, and a data management system, so they can capture changes in dielectric properties, size, and charge distribution while the formation of antigen and antibody complex formed on the electrode surface.[41]

The evolution in the field of electrochemical biosensors has been presented with the applicability of different nanomaterials such as nano composites, ionic liquids, polymers and metallic nanoparticles are used to improve electrocatalytic properties and binding with cells and tissues to be used.[3,42] The study by Chen et al.,[28] It was based on current studies suggesting that soluble fragments of the oncogene c-erbB-2, located on chromosome 17, q21, may be released from the cell surface and become detectable in breast cancer patients. However, due to the low concentration of this oncogene and the complex saliva composition, conventional fluorescent biosensors do not meet the clinical diagnostic requirements for direct detection of c-erbB-2 oncogene in saliva. To increase analytical sensitivity, many DNA amplification techniques were reported until water-soluble Tioflavin T (ThT) was a G-quadruplex-specific fluorescent indicator among other forms of DNA, including single stranded, duplexed, or triplexed. Stimulated by all the above findings, a fluorescent spectroscopy biosensor was developed, and it was possible to detect the oncogene, which may represent a promising path for early sensitive, simple, fast and economical diagnosis of breast cancer. However, the study found limitations due to experimental variables such as saliva temperature and pH and signal-noise due to oncogene concentrations.

In parallel, Pandya et al.,[43] manufactured a microchip biosensor with inter digital electrodes to measure the impedance of benign and carcinogenic breast tissues. Human breast tissue was tested from a total of ten cases of high-grade invasive ductal carcinoma. They found that cancerous breast tissue samples had significantly different bioimpedance characteristics compared to benign breast tissue samples. It was also observed that by decreasing the electrode spacing, the effective electrode area is increased, increasing the sensitivity of the device. However, we recognize that there may be slight intra- and inter-experimental differences under experimental conditions, including tissue heterogeneity, microtome settings, room temperature, etc. Arkan et al.,[44] studied the response of the carbon nanotube biosensor containing gold nanoparticles to detect human epidermal growth factor 2 (HER-2) associated with breast cancer, the nanoparticles were inserted in order to extend the antigen immobilization and immunization area extension In the biosensor electrode, this method was efficient, objective and with good reproducibility to determine HER-2 in serum samples. Cardoso et al.,[16] studied the action of an electrochemical biosensor with another carcinogenic marker miRNA-155, the expression of this biomarker is also considered as a risk marker for breast cancer, the studied samples containing traces of breast cancer cells showed a signal corresponding to the expression of miRNA-155.

Salahandish et al.,[45] verified a high efficiency in the detection of cancer cell markers in blood samples by means of a biosensor constituted by functionalized graphene structure with silver nanoparticle coating instead of gold nanoparticle. The authors verified that the biosensor with a nitrogen functionalized graphene nanocomposite structure with silver nanoparticles, presented good conductivity and stability, allowing HER2 antigens to adhere to the electrode without the need of biological enzymes, facilitating and simplifying the process. Therefore, this biosensor can be used not only for early cancer diagnosis, but also for monitoring efficacy of treatment therapy. Guo et al.,[46] studied a new photoelectrochemical biosensor for detection of HER2 by double signal amplification, resonance of surface plasmons with gold nanoparticles, improved photoelectric transfer favoring detection of HER2 even at low concentrations, showing good stability and selectivity, thus proving to be effective in the process of diagnosis and follow-up of breast cancer treatment. Another diagnostic technique using HER2 antibody was tested by Li et al.,[36] the authors investigated a new colorimetric assay with HER2 antibody bound to a hybrid platform of gold nanoparticles trapped in mesoporous silica nanoparticles. Leveraging HER2 antibody specificity and biosensor catalytic capacity, showing that it is sensitive, selective, economical and simple in operation. The immunohistochemical colorimetric assay of HER2 + breast cancer cells from tumor tissue demonstrates the potential application of this biosensor in the clinical diagnosis of breast cancer. These approaches can easily be extended to other cells by simply changing the recognition ligand for a variety of applications involving cancer diagnostics, bioanalysis and bio nanotechnology. In principle, the continuous monitoring capabilities offered by biosensors could be used to detect preclinical disease biomarkers in presumptively healthy individuals. However, until gaps in our knowledge and understanding of disease-specific biomarker patterns are addressed, this remains a more distant perspective for biosensor technology.[47–49]

Conclusion

Based on the articles analyzed, it was possible to understand the applicability of biosensors in the diagnosis of breast cancer by different biomarkers. Breast cancer mortality rate can be prevented at the primary prevention level through innovative screening programs and preventive measures focused on identifying risks in a timely manner with the use of biosensors. However, the difficulty in standardization of specific biomarkers demonstrates that further lines of study relating the application of biosensors in the diagnosis of breast cancer are still needed.

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Conflict of interests

Authors declare that there is no conflict of interest.

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