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Evolution in Biosensors for Cancers Biomarkers Detection: A Review

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Abstract
Advancement in the field of biosensor/bioelectronics technology has been exploited in the biomedical field for diagnostics and therapy. The potential of this technology in identifying molecular targets has become projected as new generation diagnostics particularly in cancer diagnostics. Cancer being the second cause of death among all diseases in the US and worldwide, the early diagnosis becomes the growing research area in this field. The conventional techniques to detect cancer are expensive, painful, time-consuming, and low sensitivity and specificity. Recently, investigators have developed several types of biosensors to detect specific molecular markers of cancer. Biosensors are classified as point of care/diagnostic tools that can be conducted at home by the patient. This review describes a detailed investigation of different cancer biomarkers and various biosensors developed to detect the biomarkers, the principles, and detection limits, which could assist to detect cancer in early stages.

Keywords Biosensor · Biomarker · Cancer · Optical · Piezoelectric · Electrochemical

1 Introduction

Cancer is the main health issue in the United States and the world. It is the second cause of morbidity and mortality worldwide, about 8.8 million people died in 2015. According to the World Health Organization Lung (1.76 million deaths), Colorectal (862,000 deaths), Stomach (783,000 deaths), Liver (782,000 deaths), and Breast (627,000 deaths) are the most widespread cancers that lead to death [1].

Cancer is caused by the uncontrolled division of cells continuously. Cancer can spread around tissues through blood and it can start in any part of the human body. Unlike normal cells, cancer cells follow an unregulated cell division leads to a tumor mass [2]. There are two types of tumors, one is malignant tumors that can spread around tissues and the human body, and the other is benign tumors that do not spread around tissues and the human body. Cancer is genetic and inherited disease [3]. It is caused by altering the genes that monitor the function of the cells. Moreover, cancer is related to environmental exposure such as radiation, UV rays, and chemicals in smoke. These factors lead to damage to the DNA.

Early diagnosis of cancer is very important that can increase the chance of cure and decrease the cancer death rate [4, 5]. For this aim, current techniques to detect cancer include CT scan, ultrasound, MRI, PET scan, X-ray, and biopsy [2]. However, some of these methods are expensive, painful, time-consuming, and low sensitivity [6, 7]. In addition, genomic detection methods such as polymerase chain reaction (PCR) [8] and DNA sequencing [9] are used to detect cancer biomarkers. Recently, investigators use immunoassays techniques such as ELISA to detect cancer biomarkers that indicate the presence of the cancers [10]. These techniques are very selective and sensitive, but they are high cost, prolonged and sometimes they can not detect a low concentration of the biomarkers that are present in the early stages of the cancers [11]. Table 1 demonstrates the limitation of the current methods for the early detection of cancers.

Hence, developing a new low-cost, highly sensitive, and rapid method for the early diagnosis of cancers is required. In the current era, investigators have developed biosensors to detect cancers by using different biomarkers found in blood,

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Table 1 The limitation of current detection methods for cancers

Detection method	Limitation
Computerized tomography (CT)	Expensive, using radiation [12, 13]
Pozitron emission tomography (PET)	Expensive [14]
Magnetic resonance imaging (MRI)	Expensive, using a magnetic field, not suitable for all patients, low specificity [14, 15]
Mammography	Low specificity, less sensitivity [16]
Biopsy	Expensive, painful, requires trained people [17]
ELISA	Expensive, time-consuming [18]

sputum, urine, and other biofluids. Biosensors have great advantages that raise medical care and develop the quality of health and life. In this review, we will discuss the advancements in the field of biosensors that are used to detect various types of cancer biomarkers in the early stages, including breast cancer, lung cancer, and prostate cancer.

1.1 Cancer Biomarkers

Biomarkers are significant tools that assist in detecting cancer in the early stages. Biomarkers are biological molecules that indicate the condition and the state of the diseases, and they are found in cancer cells, blood, urine, and other biofluids. These molecules could be DNA, RNA, proteins, and enzymes [19, 20]. Biomarkers also play a crucial role in monitoring the effect of the treatment in the cancers such as chemotherapy or radiation [21], because the alternation in the expression of the specific protein can be indicated by biomarkers that are measured in the biofluids. There are many cancer biomarkers that can detect different kinds of cancers. Figure 1 shows some common cancer biomarkers [22–27].

Biomarkers can be classified into two main categories: Protein biomarkers and DNA biomarkers. Protein biomarkers are widely used to detect cancers because they are prognostic markers. DNA markers are also used to detect cancers; they give information about the development of tumor growth, but they can't be detected in the early stage of the cancers [28, 29]. For instance, the most common proteomic biomarker for breast cancer is the human epidermal growth factor receptor 2 (Her-2) which is a member of the EGFR family, because it is a prognostic marker that can be detected in breast cancer at the early stages [30, 31]. Her-2 promotes breast cancer growth. The normal levels of Her-2 in the blood are 2–15 ng/mL, but in breast cancer, the levels might be increased to 15–75 ng/mL [32]. The Her-2 levels are considered to diagnose cancer stage and tumor size [33]. There is the additional proteomic biomarker for advanced breast cancer which is cancer antigen 15–3 (CA 15–3). It is a member of the mucins family [34]. It is mostly used to monitor the therapy of breast cancer [35–39]. The normal

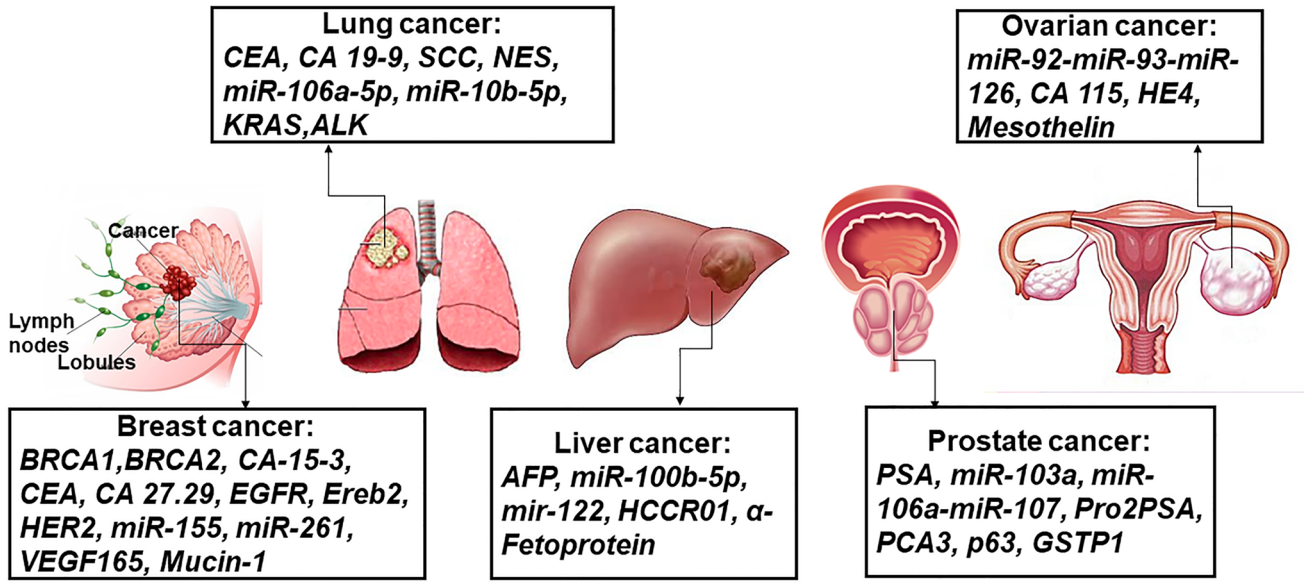

Fig. 1 The most common biomarkers for the detection of various cancers

concentration levels of CA 15–3 in the serum are less than 30 U/mL, in breast cancer, the levels will increase in the serum from stage 1 to stage 4 of cancer [39]. Furthermore, BRCA1 is a DNA biomarker. BRCA1 can be destroyed by mutation so that leads to raising the risk of having breast cancer [40]. There are other markers that are related to breast cancer such as BRCA2, CAE, and CA 27.29 [11].

In addition, prostate-specific antigen (PSA) is the current superior serum marker for prostate cancer detection and monitoring the patient after the therapy of prostate cancer. PSA is created inside the duct and acinar cells of the prostate. The normal levels of PSA in the body between the range 0.5–2 ng/mL, so 4–10 ng/mL levels of prostate cancer occurs [19]. GSTP-1 is a new biomarker for prostate cancer which was recently found in prostate cancer patients [41].

Moreover, lung cancer is detected by multiple biomarkers because it is difficult to indicate lung cancer by one specific marker [42]. The most popular proteomic biomarker for detecting lung cancer is a carcinoembryonic antigen (CEA). It is used to distinguish between malignant and benign tumors. In healthy people, the range levels of CEA in serum are 2–2.5 ng/mL, but above these levels, lung cancer occurs [43]. The high expression of CEA biomarkers can also cause breast or ovarian cancer [21]. The higher amount of the CEA in the patient's body, the lower chance of survival [44]. Neuron-specific enolase (NSE) is another biomarker for lung cancer. NSE is a glycolytic enzyme which is located in the cytoplasm and cell membrane. The levels of the NSE normally are 9 ng/ml and the levels can be higher in cancer patients [45].

The biomarker levels are very low in the early stages of the cancers. Thus, the techniques are used for cancer detection must be sensitive, selective, and specific. Biosensors are promising methods for cancer detection in the early stages with high sensitivity and specificity.

2 Biosensor

The biosensor is a bioanalytical device that is utilized to detect analytes by converting them into an electrical signal to be analyzed in an electronic form [46]. In 1962, the first biosensor is introduced by Clark and Lyons, it was the first glucose biosensor to detect the level of glucose in the human body [47]. Since then, the biosensor has been improved to be an efficient detectable device for multiple applications in the medical, industrial, and environmental fields.

In the medical field, the biosensor is a novel technique because it is classified as a point of care/diagnostic tool that can be conducted at home by the patient, so they can monitor their health. For instance, blood-glucose biosensors are very common to use by diabetic patients at home to diagnose and monitor the level of blood glucose [48]. Recently, biosensors are being used widely for cancer detection in the early stages because biosensors provide better sensitivity and stability than other methods [4]. Furthermore, biosensors play a significant role in autoimmune diseases' detection. An impedance biosensor is used to detect systemic lupus erythematosus (SLE), which is an autoimmune disease; vascular cell adhesion molecule-1 (VCAM 1-) is utilized as a marker to indicated SLE [49]. The biosensor is being used pervasively in the medical field to detect and diagnose pathogens and infectious diseases [50]

In the food industry, biosensors are applied to provide healthy food for the customers and detect the pathogens or chemical agents in the food that cause diseases [51, 52]. Enzyme-based biosensors and immunosensors are very popular to use in the food industry [53]. Foodborne and waterborne pathogens are a crucial aspect of public healthcare. Approximately 420,000 people died annually due to foodborne and waterborne diseases [54]. For this reason, many studies have been done to detect Foodborne and waterborne pathogens by applying biosensors. The electrochemical immune sensor was developed to detect Salmonella, the biosensor was able to detect salmonella with high sensitivity, stability, and selectivity [55]. E-coli bacteria are a major issue in food contamination and health hazard. Enzyme-based biosensors can detect E-coli successfully [56].

In the environmental field, the detection of the contamination caused by air, water, and the soil is important to protect human health. Different kinds of biosensors can detect a toxic levels of heavy metals [57]. In addition, the application of biosensor in pesticide detection is currently established [58]. Organophosphates are common to utilize as pesticides; it damages the biodiversity by killing the beneficial microbes and insects which exist in the soil. Enzyme-based biosensors help to indicate and monitor the level of organophosphates [59]. The main reason for all these applications of biosensors is to protect humans by detecting any hazards that can affect human health and life. The biosensors are used in broad applications because it is a new, economical, highly sensitive, and rapid technique that will improve the quality of humans' life. This review will focus on the different types of biosensors and their application in cancer biomarker detection.

2.1 The Structure of the Biosensor

The biosensor consists of two main parts which are receptor recognition elements and transducer. Receptor recognition elements such as nucleic acid, protein, enzyme, antibody, or antigen which attract the analytes and convert them into electrical energy [60]. The transducer is the device used to transform the electrical energy to a signal such as electrochemical, optical piezoelectric, and thermal (calorimetric) transduction. Figure 2 illustrates

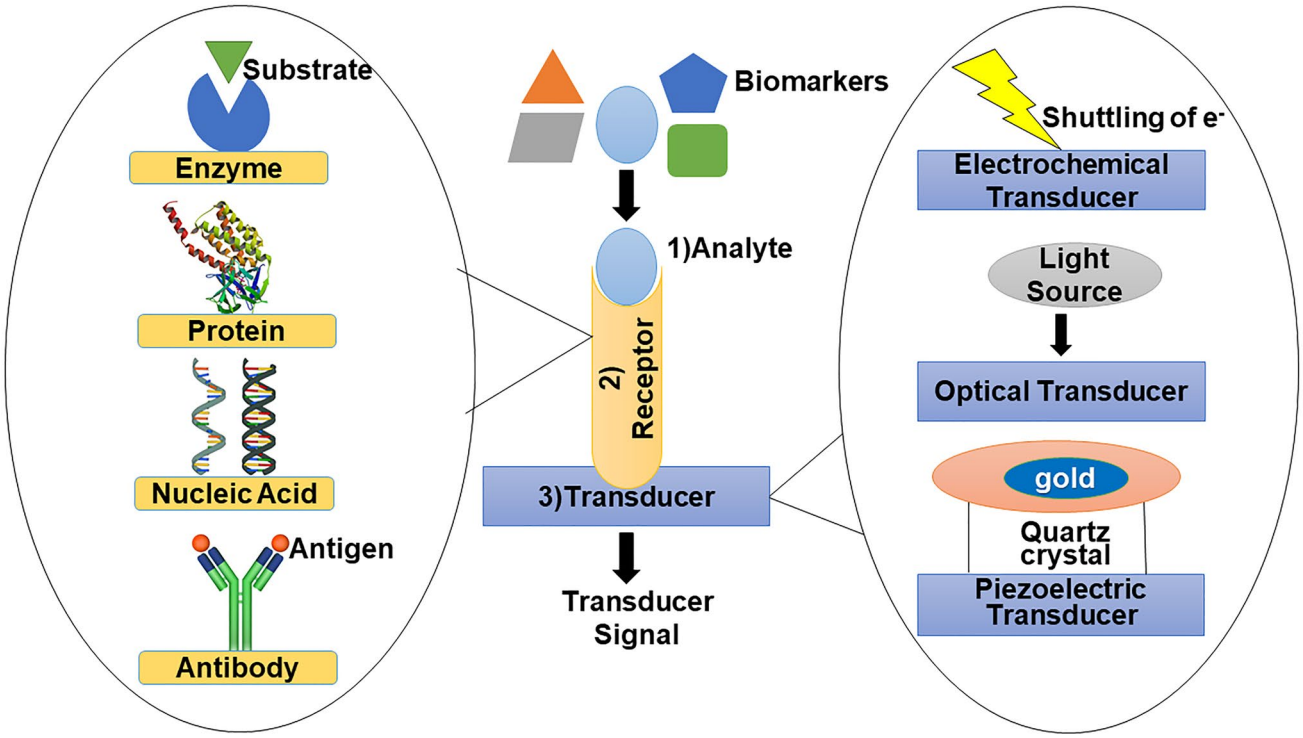

Fig. 2 Schematic representation of the transduction system of the biosensor (1) The analyte attracts to the receptor (2) The receptor could be an enzyme, protein, nucleic acid, or antibody. Electrical energy is generated by the chemical interaction between the analyte and the receptor. (3) The signal is being transduced by the transducer (electrochemical, optical, or piezoelectric) to the processor

the principle of the biosensor. Each type of transducers has features. For instance, the electrochemical transducer makes use of potentiometric, amperometric, or conductimetry/impedimetric principles. The electrochemical biosensor measures the change in impedance. This transducer is the most common to use because it is easy, rapid, and cost-effective [61]. However, currently, optical and acoustic (QCM) transducers have become popular to use in multiple applications because most of the electrochemical transductions still need labels like enzymes, but optical and QCM can provide label-free test easily [11]. The optical transducer is based on light, and it has many types of biosensors such as fluorescence, surface plasmon resonance (SPR), and spectroscopy of optical waveguides [62]. Piezoelectric is a different type of biosensor, it uses a quartz crystal microbalance (QCM) which is a device that measures the change in the mass by measuring the frequency change of quartz crystal resonator [63]. QCM devices are very common, especially in the medical field [52]. Thermal transduction is a rare mechanism, and it is based on calorimetry that measures the change of temperature [64].

2.2 Types of Biosensors

2.2.1 Electrochemical Biosensor

The electrochemical biosensor is widely used in the medical field especially for cancer detection and bioengineering filed because it is inexpensive, rapid, easy to use, and simple. It is also classified as a point-of-care device [11]. The electrochemical biosensor transforms biorecognition molecules and the biomarker interaction to electrochemical signals that can be measured (conductance, potential, impedance, current) [65]. The electrochemical transducer consists of three electrodes systems such as the working electrode (WE), reference electrode (RE), and counter electrode (CE) (Fig. 3a). The interaction between a target molecule and a bioreceptor occurs at the working electrode surface (gold area) [18] (Fig. 3). Electrochemical biosensor uses different techniques to obtain the readout such as electrochemical impedance spectroscopy (EIS), stripping voltammetry (SWSV), cyclic voltammetry (CV), the field-effect transistor (FET), or square wave voltammograms (SWV) [66]. Currently, EIS is the best technique because it gives awareness

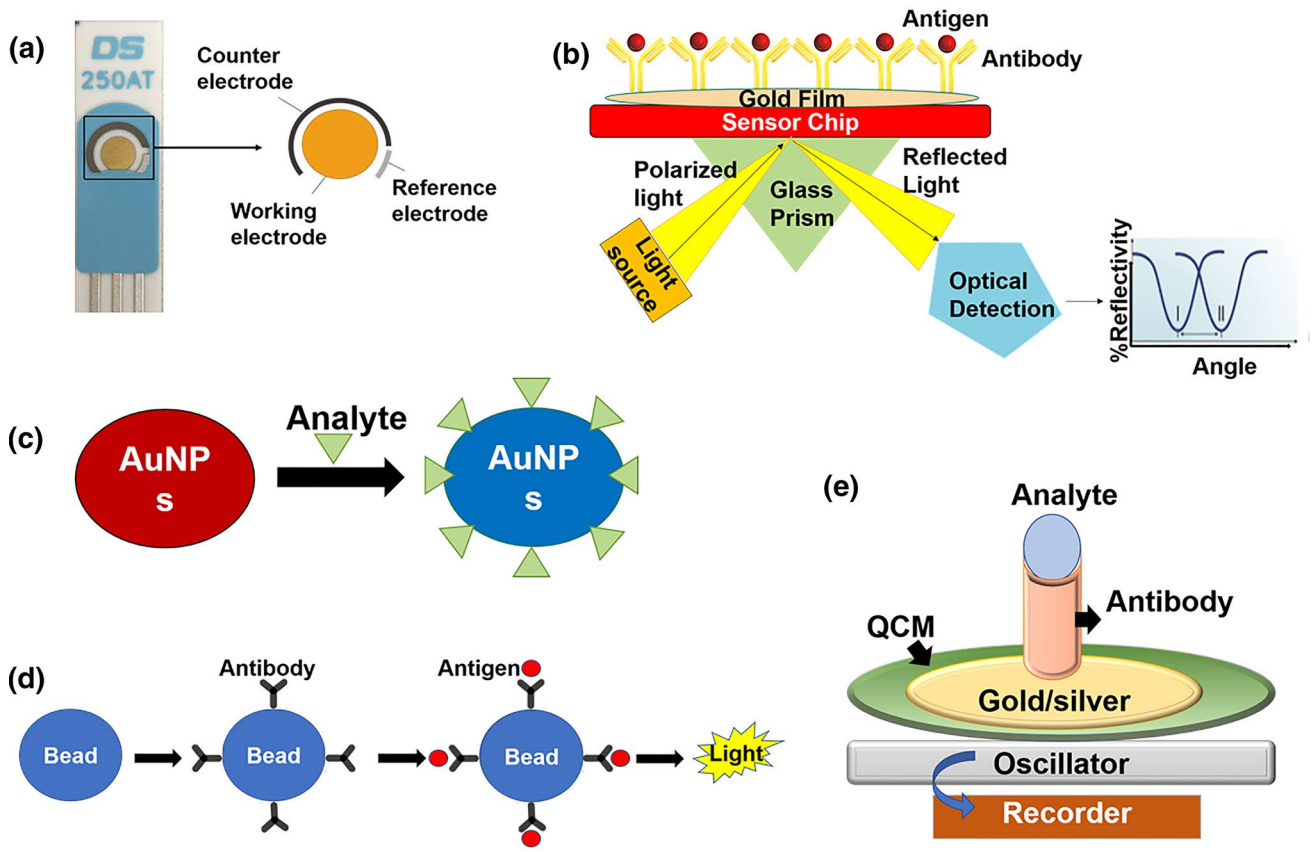

Fig. 3 Showing schematic representation of **a** electrochemical biosensor, **b** surface plasmon resonance-based biosensor. The gold film is coated with Biorecognition molecules, which are Antibodies. The Biorecognition molecules interact with the biomarkers. The interaction between the antibodies and antigens results in changes in the refractive index that leads to a shift in the angle of SPR **c** showing the principle of colorimetric biosensor based on gold nanoparticles, **d** chemiluminescence-based biosensor. The interaction between Recognition elements such as antibody and the biomarkers results in Light emission and **e** the structure and the principle of the piezoelectric biosensor

to biomolecular interaction out of their impact on electron transfer resistance (Ret) [18]. In addition, there are different nanomaterials recently used in electrochemical biosensor including graphene oxide (GO) [67], gold nanoparticle (AuNP), multi-walled carbon nanotubes (MWCNTs) [68], GO with MWCNTs [69] and GO with gold nanoparticle [70] to enhance the efficiency of the method. GO is the most common nanomaterial to use because it is high sensitivity and affinity for biochemical material [71, 72]. Even though there is advancement in electrochemical biosensors due to different nanomaterial strategies, the fabrication of biosensors is still challenging in terms of size, shape, and number of nanoparticles. Also, signal amplification methods are still under investigation to improve the detection sensitivity.

2.2.2 Optical Biosensor

The optical biosensor is a light emission/ absorption-based sensor which measures the alteration in the wavelength of light [73–76]. The change in wavelength is measured by the optical biosensor. Many different optical biosensors have been developed for cancer detection in the early stages. There are many different types of optical biosensors.

2.2.3 Surface Plasmon Resonance (SPR)/Utilize Localized Surface Plasmon Resonance (LSPR) Biosensors

Surface plasmon resonance-based biosensor is an optical method based on the detection of the biomarkers at the surface of the metal (typically gold). Biorecognition molecules, such as the antibody, are immobilized on the surface of the metal, then they interact with the biomarker. This interaction results in the change in the refractive index and the mass of the sensing medium on the metal and it causes a shift in the angle of SPR [77, 78] (Fig. 3b). In addition, some optical biosensors utilize localized surface plasmon resonance (LSPR). LSPR happens when the surface plasmon gets excited by the light on the surface of the gold that causes the creation of scattering peak and spectral absorption [79].

2.2.4 Fluorescence-Based Biosensor

Fluorescence is a kind of luminescence light that is emitted from molecules following the absorption of light. The fluorophore is a molecule that can absorb light at a shorter wavelength to emit it at a longer wavelength [41]. One of the most significant fluorescence-based biosensors is the fluorescence resonance energy transfer (FRET). It is a non-radiative energy transfer between an excitation fluorophore (donor) and an absorption fluorophore (acceptor). The distance between them is very short, 10–100 Å only [80, 81]. FRET-based biosensor usually utilizes nanoparticle like quantum dots (QD) because it is most common for cancer detection. Moreover, it has high fluorescent for semiconducting nanoparticle, and the surface of QD forms bio conjugate with antibodies easily. Also, QD has unique properties that can resist photo blinking and photo bleaching [82–86].

2.2.5 Colorimetric Based Biosensor

The colorimetric biosensor is based on color change on gold (AuNPs) when the analyte presence or absent [87]. It is a simple and rapid operation for cancer detection [66] (Fig. 3c). AuNPs are most common to use in the colorimetric biosensor as a color development because of their property of rapid color changing that can give visual signal quickly [88–91].

2.2.6 Chemiluminescence Based Biosensor

Luminescence is light emission when an excited electron of molecules coming back to the ground state. While an electron in the excited state, chemiluminescence happens during the chemical reactions [92]. Chemical luminescence-based biosensors measure the light emitted by a bio-chemiluminescence, and it is based on the absorption of light. Light emission occurs when biomarker binds to the recognition element such as antibodies (Fig. 3d). The advantages of the chemiluminescence-based biosensor are high detectability and simple measurement tool. The photons are generated by a chemical reaction, then they are measured effectively and easily without nonspecific signals [93].

2.2.7 Piezoelectric Biosensor

The piezoelectric biosensor is used as a quartz crystal microbalance (QCM) device that measures the mass change and the frequency change of quartz crystal resonators [94] (Fig. 3e). Quartz is the most common and most suitable crystal for analytical applications such as electrical, mechanical, and chemical applications. QCM can detect small objects such as protein, nucleic acid, viruses, bacteria, and cells [95]. The fabrication of a piezoelectric biosensor is done by the vapor deposition of silver or gold that serves as an electrode [66]. The piezoelectric biosensor is popular in the medical field because it is easy to make, rapid analysis, economic, and highly sensitive [96].

For the development of biosensors, involving functional biomolecules includes complex processing methods which can cause the destruction of the biomolecules and which dramatically reduce the sensitivity of the biosensor. More detailed investigations are still underway to optimize the desirable biomolecule immobilization approaches to achieve the efficicacy of the optical biosensor.

3 Application Biosensor for Cancers Detections

3.1 Breast Cancer

Breast cancer is a major health issue for women. It is the most widespread cancer among females in the US and worldwide, accounting for 627,000 deaths annually [1]. There are 15–20 glands in each breast called lobes, which are the milk-producing glands. These lobes are linked to the nipple by ducts. The lobes are the place where breast cancer usually starts. The breast also contains lymph nodes and vessels, so sometimes cancer can spread to other organs of the body through the lymph nodes and vessels [97]. As mentioned before, there are various biomarkers for breast cancer detection. There are many studies have done to detect different kinds of breast cancer biomarkers by multiple types of biosensors.

The electrochemical biosensor is widely used for breast cancer detection. Selwyn et al. [98] have developed the electrochemical immunosensor for breast cancer detection (cancer antigen CA 15–3) using gold nanoparticle-based on CA 15:3 antibody and antigen interaction. CA 15:3 antibodies were immobilized on the gold nanoparticle, then antigen was added and tagged with the antibody, electrochemical impedance spectroscopy (EIS), and potentiostat was performed to read out the results. Experimental results showed that immunosensor can detect 5–75 U/mL of CA 15–3. There is also a different study for CA 15–3 detection that was done by using an electrochemical immunosensor based on graphene oxide and magnetic silica. The study used a sandwich method in which the anti-CA 15–3 antibody was immobilized on the electrode that contains the graphene oxide. Magnetic silica and graphene oxide were utilized as the signal label. A cyclic voltammogram was performed for the measurement. Electrochemical immunosensor was able to detect CA 15–3 concentration 10^{-3}–200 U/mL with the detection limit of 2.8×10^{-4} U/mL [99]. Another study was done by Zhu et al. [100] to detect human epidermal growth factor receptor 2 (HER2) and SK-BR-3 breast cancer cells by electrochemical

immunosensor combined with the gold electrode (AuNPs) and hydrazine advanced silver enhancement. SWSV was applied to analyze the results. As a result, the immunosensor was able to distinguish between HER-2 negative breast cancer and HER-2 positive breast cancer. Moreover, this sensor can indicate 26 cells/mL of SK-BR-3 breast cancer cells in the human blood serum, and able to detect breast cancer successfully in this study. In addition, the sandwich electrochemical biosensor was developed for the detection of breast cancer cells (MCF-7). This sensor was based on a gold electrode and polyadenine-aptamer. The gold electrode was coated with a mixture of AptMUC1 and DTT. Then, the MCF-7 solution was added. MCF-7 cells were sunken in an AptMUC1 functionalized graphene and gold solution. The result was obtained by cyclic voltammetry measurements and electrochemical impedance spectroscopy (EIS). The results suggested that sandwich electrochemical biosensors can be used as a point-of-care device to diagnose breast cancer. Electrochemical biosensor had a high selectivity in discriminating MCF-7 cells towards normal cells and other cancer cells, the detection limit was 8 cells/mL, and the linear range was 10–105 cells/mL [101] (Fig. 4a). Azimadeh et al. [102] have developed electrochemical nano biosensors based on oligo-hybridization to detect the miRNA-155 biomarker. The miRNA-155 is overexpressed in breast cancer. The sensor consists of gold nanorod and graphene oxide. This sensor can detect a low amount of miRNA-155. The linear range of detection was 2.0 fM–8.0 pM with the detection limit of 0.6 fM. In fact miRNA plays an important role in monitoring and controlling different development of cancer and cellular processes. miRNA is a small non-coding RNA molecule that consists of 19–24 molecules [103].

Furthermore, the optical biosensor is used to detect breast cancer biomarkers. Liang et al. [104] have reported surface plasmon resonance-based biosensor with Au/ZnO thin film to detect carbohydrate antigen CA15-3 in the saliva of the human. They used two different surface plasmon resonance (SPR) systems which are SPR biosensor based on thin-film

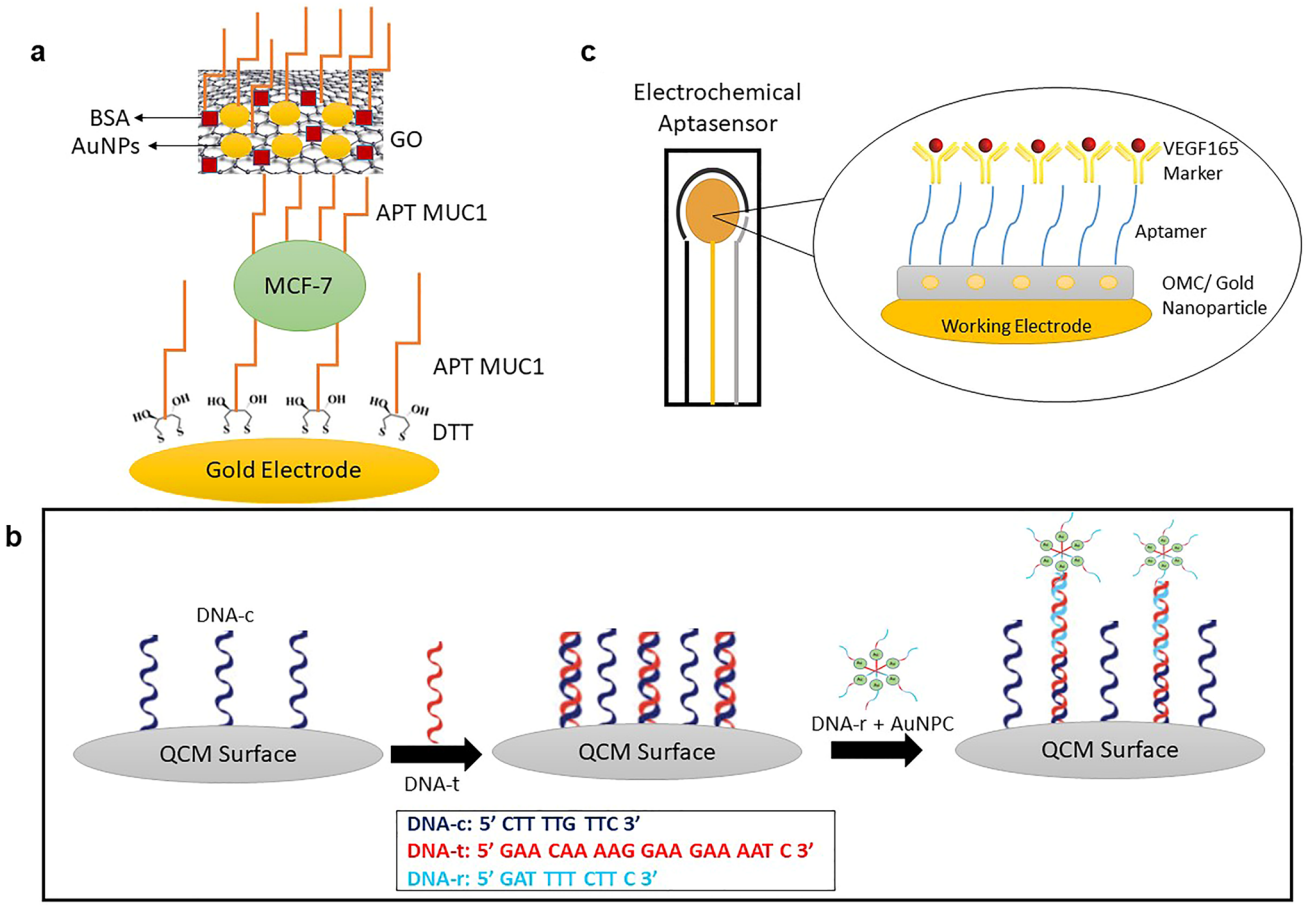

Fig. 4 Breast cancer biosensors: **a** schematic procedure of a sandwich electrochemical biosensor to detect MCF-7 cell and **b** fabrication of piezoelectric biosensor by using DNA sequence and BRACA1 for breast cancer detection. The hybridization happens between unhybridized DNA-r on the AuNPc cluster and DNA-t. Lung cancer biosensor: **c** the schematic shows the procedure of the electrochemical aptasensor used for the detection of VEGF biomarker detection

Au/ZnO and the Biacore SPR system to measure the presence of the tumor biomarker CA15-3 in human saliva. The detection range of CA15-3 was 2.5–20 U/mL with the SPR system based on thin-film Au/ZnO, and the detection range of CA15-3 was 40–300 U/mL with the biacore SPR system. As a result, the SPR system based on thin-film Au/ZnO can be used to detect CA15-3 in saliva because it has more sensitivity. FRET biosensor based on graphene quantum dots (GQDs) and molybdenum disulfide (MoS2) nanosheet was developed by Shi et al. [105] to detect epithelial cell adhesion molecule (EpCAM), which is a glycosylated protein that can be expressed on the circulating tumor cells surface (CTCs). Breast cancer overexpresses EpCAM, and also is overexpressed by some other cancers. In this work, the donor molecules were PEGylated GQDs, they can raise the emission intensity and block non-specific adsorption of PEGylated GQDs on the surface of the MoS2. Then, MoS2 quenched GQD fluorescence signal. The linear detection range was 3-54 nM, and the detection limit was about 450 pM. This FRET biosensor can detect EpCAM successfully. It was used to detect the expression of EpCAM in MCF-7 cells.

Another type of biosensor was used for breast cancer biomarkers detection which is the Piezoelectric biosensor. Rasheed and Sandhyarani [106] developed a Piezoelectric biosensor which is a quartz crystal microbalance-based genosensor to detect breast cancer 1 gene (BRCA1). They applied a sandwich assay by combining probe DNA with AuNPs, and that results in increasing the mass at the surface and enhancing the sensitivity of magnitude. The result was obtained by using cyclic voltammetric (CV) and chronoamperometry measurement. The biosensor can detect BRCA1 successfully, the detection limit was 10 aM of BRCA1; therefore, the piezoelectric biosensor has good sensitivity, and it will be a potential tool for BRCA 1 detection (Fig. 4b).

A different type of piezoelectric biosensor was developed that is piezoelectric microcantilever sensors (PEMS) to detect HER2 of the breast cancer in the serum of the patients. piezoelectric microcantilever sensors (PEMS) were functionalized with HER2 antibodies against HER2 biomarker, which made the biosensor high sensitivity. This biosensor was able to detect > 2 ng/mL of the HER2 biomarker in the serum [107].

3.2 Lung Cancer

Lung cancer is a serious health concern and the most common cancer in the US and around the world. It is the first cause of death among all cancers, accounting for 1.69 million deaths annually. The treatment of lung cancer is difficult, and it takes a long time with a little improvement in the patient's health. Early diagnosis of lung cancer increases the survival rate and leads to successful treatment [108]. For this aim, different kinds of biosensors have developed for lung cancer detection in the early stages. Lung cancer has various biomarkers.

The electrochemical biosensor has been developed for the detection of lung cancer biomarkers. Recent researches showed successful results of lung cancer detection by multiple types of electrochemical biosensors. Recent work has developed an electrochemical biosensor based on graphene for Carcinoembryonic antigen (CEA) detection. The graphene was grown on copper (Cu) and employing the chemical vapor deposition (CVD) method. Anti-CEA was immobilized in the biosensor (graphene/copper electrode) to make it specific for the CEA biomarker. To measure and analyze the result, electrochemical impedance spectroscopy (EIS) was performed. The biosensor shows the linear range 1.0–25.0 ng/mL with a limit of detection of 0.23 ng/mL. The result indicated that the electrochemical biosensor based on graphene is selective and sensitive to detect CEA biomarkers [109]. Altintas et al. [110] reported magnetic particle-modified capacitive sensor to detect the lung cancer biomarkers which are carcinoembryonic antigen (CEA), cancer antigen CA15-3 and epidermal growth factor receptor (hEGFR). The levels of concentrations of the biomarkers to indicate lung cancer are higher than 5 ng/mL for CEA, 64 ng/mL for hEGFR, and 50 U/mL for CA15-3. The biosensor can detect CEA and hEGFR successfully in the concentration range of 5 pg/mL to 1 ng/mL, whereas it can detect CA15-3 in the concentration range of 1–200 U/mL. From this study, biosensors are a potential method to detect lung cancer in the early stages. Moreover, a high sensitive electrochemical aptasensor based on the carbon-gold nanocomposite modified screen-printed electrode was developed by Tabrizi et al. [111] to detect vascular endothelial growth factor (VEGF165) in serum. AntiVEGF165 was immobilized on the electrode surface to capture VEGF165 marker in the serum, the interaction between the antibody and the marker leads to a change in the charge of transfer resistance. Cyclic voltammetry (CV) and electrochemical impedance spectroscopy (EIS) were used to analyze the result. VEGF165 can be detected by the biosensor in the linear range of 10–300 pg/mL with the detection limit of 1.0 pg/mL. The aptasensor can detect VEGF165 in serum successfully with high sensitivity and selectivity (Fig. 4c).

In addition, various studies were done to detect lung cancer biomarkers by optical biosensors. Surface plasmon resonance-based immunosensor was developed for CEA detection. The immunoassay was used in this study. A self-assembled monolayer was immobilized on the gold surface by using 11-mercaptoundecanoic acid. Then, the antibody was immobilized to capture the antigen. The SPR based biosensor can detect CEA biomarker with a linear range 3–400 ng/mL. The detection limit was 3 ng/mL [112]. Li

et al. [113] reported the FRET-based biosensor between upconverting nanoparticles (UCPs) and palladium nanoparticles (PdNPs) for CEA detection. CEA aptamers were used as biorecognition molecules, and it was bind to hexanedioic acid (HDA) and modified UCPs (HDA-UCPs). The interaction between CEA aptamer and PdNPs made UCPs and PdNPs very close to each other, thus the fluorescence quenching of UCPs reached up to 85%. Biosensor showed that the linear detection range of CEA was 2–100 pg/mL with the detection limit of 0.8 pg/mL in the aqueous buffer. The linear detection range was 4–100 pg/mL in diluted human serum. Furthermore, the colorimetric biosensor was developed to detect the CEA biomarker. This biosensor-based gold Nanoparticle-Decorated Bi2Se3 Nanosheets. The biosensor can detect CEA biomarkers with low concentration as 160 pg/mL [87].

Another type of biosensor was developed for lung cancer detection is the chemiluminescent biosensor. Qu et al. [114] reported chemiluminescent immunosensor along with immunomagnetic separation for lung cancer biomarker (CEA) detection in human serum. HRP labeled-CEA antibody and immunomagnetic beads (IMBs) with target protein CEA formed a sandwich assay structure which is a IMBs-CEA-HRP labeled antibody. IMBs were used to immobilize CEA on the magnetic field. HRP produced optical signals. These signals can be detected by a luminometer which measures the concentration of CEA in the human serum. The results showed that the linear range of detection was 0–50 ng/mL, and the limit of detection was lower than 5.0 pg/mL. As a result, this biosensor is highly sensitive for lung cancer detection.

3.3 Prostate Cancer

Prostate cancer is the most widespread cancer among men in the US. Prostate cancer starts in prostate gland tissues that are located in front of the rectum and under the bladder. The prostate is responsible for semen production and transports sperm [2, 115]. An electrochemical biosensor is used to detect prostate cancer. Pal and Khan [116] reported electrochemical immunosensor based on gold nanoparticles tagged on graphene oxide surface to immobilize monoclonal anti-PSA antibody for the prostate-specific antigen (PSA) detection in prostate cancer. Immunofluorescence staining was performed to confirm the antibody functionalization by using prostate adenocarcinoma cells (LNCaP). Also, Scanning Electron Microscopy (SEM) and cyclic voltammetry (CV) were performed to read out and analyze the results. The detection limit of PSA is 0.24 fg/mL. The immunosensor gave recovery 97.67% of the precise detection of PSA in the serum of the human. Moreover, Wei et al. [117] have developed electrochemical immunosensor. They used a sandwich assay to detect prostate-specific antigen (PSA). This biosensor based on Au–CoS with graphene and CeO_2 with ionic liquids that doped with CMC/ILs carboxymethyl chitosan complex. The electrode was modified with Au–CoS/graphene to immobilize Anti-PSA on the electrode surface. Differential pulse voltammetry (DPV) and amperometric were performed to analyze the results. The linear range of detection for immunosensor was 0.5–50 ng/mL, and the detection limit was 0.16 pg/mL of PSA. Quenching electrochemiluminescence (ECL) immunosensor based on resonance energy transfer was reported for PSA detection. Nitrogen-graphene quantum dots (NGQDs) were loaded at $Ni(OH)_2$ to produce good emission for electrochemiluminescence (ECL). Also, the $Fe_3O_4@MnO_2$ was combined with microspheres. The sandwich immunoassay was performed based on the mechanism of the quenching between NGQDs/ECL (donor) and $Fe_3O_4@MnO_2$/ECL (acceptor). ECL immunosensor can detect PSA with the concentration linear range of 10−5–10 ng/mL, and the detection limit was 5 fg/mL. This technique was applied in a real sample of serum with the recovery of 94.0–102% [118].

Furthermore, different types of optical biosensors have been developed for prostate cancer detection. An optical fiber SPR based sensor is developed to detect prostate-specific antigen by using a sandwich assay. The sensitivity of the optical fiber SPR sensor was 2.5×10^{-6} refractive index unit (RIU). The optical fiber SPR biosensor is a potential tool to detect PSA biomarker [119]. Yang et al. reported SERS based magnetic aptasensor that uses magnetic nanoparticles (MNPs) core-Au nanoparticles (AuNPs) for detection of prostate-specific antigen (PSA) from the serum. The biosensor shows that the limit of detection was 5.0 pg/mL. Thus, SERS based biosensor is a potential tool that can be used to detect PSA with high sensitive [120].

In addition, a chemiluminescence biosensor was developed, called electrogenerated chemiluminescence biosensor to detect prostate PC-3 cancer cells. The antibody was used as a capture probe and it was immobilized on the graphene electrode. PC-3 cells were captured on the biosensor, and signal probe bound with the captured PC-3 cells result in forming a sandwich. This biosensor can detect this linear range from 7.0×10^2 to 3.0×10^4 cells/mL, with the limit of detection at 2.6×10^2 cells/mL [121].

Another biosensor that is based on the piezoelectric ceramic resonator with a high resonance frequency that serves as transducer was reported by Su et al. for cancer biomarkers detection which is prostate Specific Antigen (PSA) and α-Fetoprotein (AFP). They immobilized the antibodies of the PSA and AFP on the ceramic resonator transducers. The detection of PSA and AFP was obtained from frequency change. This biosensor showed a high sensitivity of detection that can detect 0.25 ng/mL of biomarkers within 30 min [122].

Table 2 Various biosensors for cancers biomarkers detection

Types of biosensor	Types of Cancer	Bio-marker	Detection linear range	Detection limit	Study details	Refs
Electrochemical biosensor	Breast cancer	Her-2	0.2–2 ng/mL	–	This study based on aptasensor platform	[124]
			10^{-5}–10^{2} ng/mL	5 ng/mL	This study based on aptasensor using single stranded DNA aptamer	[125]
			10–110 ng/mL	7.4 ng/mL	This study based on impedimetric immunosensor. Biosensor was applied to detect the HER-2 from serum samples of patients. Result showed that, the sensor is very sensitive and able to detect HER-2 from human serum	[126]
			$10^{-5} \times 10^{6}$ cells/mL	2 cells/mL	This study based on nano-biosensor based on gold nanoparticle. This sensor can detect $HER2^{+}$ SK-BR3 cancer cells	[127]
			0 to 40 µg/L	6.0 µg/L	This study based on impedimetric biosensor based on affibody (affisensor)	[128]
			0–50 ng/mL	2.9 ng/mL	This study based on voltammetric immunosensor, it is multiplexed electrochemical immunosensor. This sensor was developed to detect CA 15–3 and HER2-ECD biomarkers	[129]
		CA15-3	0.1–120 U/mL	0.033 U/mL	This study based on electrochemiluminescenc immunosensor	[130]
			0.1–20 U/mL	0.012 U/mL	This study based on immunosensor modified with graphene (*N*-doped graphene sheet modified electrode)	[131]
			0–70 U/mL	5.0 U/mL	This study based on voltammetric immunosensor, it is multiplexed electrochemical immunosensor. This sensor was developed to detect CA 15–3 and HER2-ECD biomarkers	[129]
			0.1–160 U/mL	0.04 U/mL	This study based on immunosensors that based on the direct electrochemistry of glucose oxidase (GOD)	[132]
		BRACA1	1.0×10^{-18} –1.0×10^{-10} mol/L	1.0×10^{-9} mol/L	This study based on DNA label-free biosensors that based on glassy carbon electrode and 1-pyrenebutyric acid-N-hydroxysuccinimide ester	[133]
			50.0 fM–1.0 nM	1.72 fM	This study based on DNA label-free biosensors that based on polyethylene glycols	[134]
			1.0 fM–10.0 pM	0.3 fM	This study based on DNA label-free biosensors that based on self-assembled peptide monolayer	[135]
		MicroRNA-21	100 aM–1 nM	78 aM	This study based on microRNA biosensor consists of toluidine blue (TB) and gold superlattice	[136]
			0.1–500.0 pM	84.3 fM	This study based on microRNA biosensor that based on methylene blue (MB)	[137]
			10 fM–10 µM	0.2 fM	This study based on nano-genosensor modified with silver nanoparticle and nitrogen-doped graphene	[138]
	Lung cancer	CEA	5 pg/mL to 15 ng/mL	–	This study based on immunosensors using a photovoltaic cell which is electrical reading box	
			1.0–25.0 ng/mL	0.23 ng/mL	This study based on biosensor that based on graphene using chemical vapor deposition	[109]

Table 2 (continued)

Types of biosensor	Types of Cancer	Bio-marker	Detection linear range	Detection limit	Study details	Refs
			0.01–50 ng/mL	3.2 pg/mL	This study based on photoelectrochemical immunosensor	[139]
		mRNA-21	10 nM–50 µM	5 nM	This study based on hybrid DNA hydrogel	[140]
		VEGF165	10.0–300.0 pg/mL	1.0 pg/mL	This study based on aptasensor using carbon–gold nanocomposite	[113]
	Prostrate Cancer	PSA	100 pg/mL–100 ng/mL	1 pg/mL	This study based on receptor sensor (aptamer–MIP sensor)	[139]
			0.005–20 ng/mL and 0.005–100 ng/mL	1.0 pg/mL	This study based on aptasensor using gold nanoparticle	[141]
			0.05–5.00 ng/mL	13 pg/mL	This study based on immunosensors using graphene and methylene blue nanocomposite	[142]
The main advantages of the electrochemical biosensor for cancer detection are sensitive, selective and portable. However, the disadvantages of it are long optimization time and long fabrication						
Optical biosensor	Breast cancer	Her-2	13–100 ng/mL	10 ng/mL	This study based on opto-fluidic ring resonator biosensor using optical ring and microfluidics	[143]
		EGFR	20–100 ng/mL	0.1 ng/mL	This study based on resonance Rayleigh scattering biosensor modeifed with gold	[144]
		CA15-3	1.25–25 U/mL	1.2 -0.4 U/mL	This study based on lectin optical biosensor	[145]
	Lung Cancer	CEA	4 –100 pg/mL	1.7 pg/mL	This study based on fluorescence resonance energy transfer biosensor using palladium nanoparticles	[113]
	Prostrate cancer	PSA	0.1–50 ng/mL	91 pg/mL	This study based on surface plasmon resonance (SPR) biosensor. Clinical samples were used in this study	[146]
Optical biosensors are sensitive, fast and reliable. However one of the major disadvantage is that it is costly and less portability						
Piezoelectric biosensor	Breast cancer	CA15.3	0.5–26 U/mL	–	This study based on quartz crystal microbalance (QCM) biosensor using ZnO nanorods	[147]
		EGFR	0.01–10 µg/mL	–	This study based on immunosensors using quartz crystal microbalance (QCM)	[148]
		BRCA1	–	10 aM	This study based on genosensor based on quartz crystal microbalance (QCM)	[106]
		Her-2	2 ng/mL	-	This study based on piezoelectric microcantilever sensor (PEMS)	[107]
	Prostrate cancer	PSA	150 ng/mL	0.29 ng/mL	This study based on quartz crystal microbalance biosensor using the amplification of nanoparticles system	[149]
The piezoelectric biosensor also provide fast and sensitive output in term of cancer marker detection. However, in addition to the fact that the biosensor is expensive, lack stability is the major disadvantage pertaining to the functioning of piezoelectric biosensor						

Table 2 illustrates the studies done so far using different types of the biosensor to detect different kinds of cancer biomarkers like breast cancer, lung cancer, and prostate cancer. An electrochemical biosensor is widely used in the medical field and it is the best option and method for cancer detection over the other types of the biosensor for many reasons. it is high sensitivity and specificity, low cost, ease of use, portability, fast response, simple preparation [18, 22, 123]. Thus, electrochemical biosensors are most commonly preferred.

4 Limitations of Current Biosensors

Biosensors are effective tools to diagnose different kinds of cancers in the early stages. However, Biosensors for cancer detection have some challenges. The main limitation is that the complication of cancer cells, that one biomarker can evolve differently in many kinds of cancers and many cellular processes [150]. In other words, many biomarkers have low specificity. Thus, it is significant to understand the cancer progression and molecular changes and to develop highly sensitive techniques. Other challenges of the biosensors are the size of the target especially when it is too small, the level of the cancer biomarkers, the non-specific binding, improving sensitivity and selectivity of the biosensor, the cost reduction, and the real-time result and analysis [6].

5 Future Scope

The biosensors for cancer detection are still immature techniques. Future work should more focus on understanding the complexity of the cancer cells and the molecular change for cancer progression, also understanding the mechanism of interaction between the biomarkers and the nanomaterials on the electrode surface to increase the sensitivity and selectivity of the biosensors for cancers detection [46]. In addition, researchers should work on designing multiplex detection for multiple cancer biomarkers. Although biosensors have been developed to detect several biomarkers, the efficiency of these biosensors is still limited; furthermore, in the future, the biosensor could be potential tools for monitoring the effect of the treatment in the cancers such as chemotherapy or radiation, so patients can monitor the level of the biomarkers during or after the treatments. Biosensors tools promise a bright future for detecting and monitoring cancers.

6 Conclusions

It is important to diagnose and detect cancers in the early stages for successful treatment and rapid cure for cancer patients. Recently, there are various techniques for cancer detection in the early stages, but they are low sensitivity, time-consuming, expensive, unable to detect some types of cancers, and painful for patients. These days, Biosensors are new techniques in the medical field that promises early cancer diagnosis, because they play a crucial role in cancer detection in the early stages. They are highly sensitive, cost-effective, easy to use, and rapid methods that can be an efficient alternative for clinical serological diagnosis of cancers and can be conducted at home by patients. In the last decade, Electrochemical, optical and piezoelectric biosensors and other types of biosensors have been developed for cancer detection, including breast cancer, lung cancer, and prostate cancer. The results from studies showed that these biosensors can detect the cancers successfully with a low range concentration of biomarkers. Although biosensors are still immature techniques, they will be an effective and potential point of care devices in the future.

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Compliance with Ethical Standards

Conflict of interest The authors declares that they have no conflict of interest.

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