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Biosensors for detection of prostate cancer: a review

Sourav Sarkar[1] · Manashjit Gogoi[1] · Mrityunjoy Mahato[2] · Abhijeet Balwantrao Joshi[3] · Arup Jyoti Baruah[4] · Prashant Kodgire[3] · Polina Boruah[5]

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Abstract
Diagnosis of prostate cancer (PC) has posed a challenge worldwide due to the sophisticated and costly diagnostics tools, which include DRE, TRUS, GSU, PET/CT scan, MRI, and biopsy. These diagnostic techniques are very helpful in the detection of PCs; however, all the techniques have their serious limitations. Biosensors are easier to fabricate and do not require any cutting-edge technology as required for other imaging techniques. In this regard, point-of-care (POC) biosensors are important due to their portability, convenience, low cost, and fast procedure. This review explains the various existing diagnostic tools for the detection of PCs and the limitation of these methods. It also focuses on the recent studies on biosensors technologies as an alternative to the conventional diagnostic techniques for the detection of PCs.

Keywords Prostate cancer · Point of Care · Biosensor · Paper based · Microfluidic · Lateral flow assay

1 Introduction

Prostate cancer (PC) is a lethal disease and the second most prevalent type of cancer among men. Siegel et al. reported that 31620 patients died of PC in the USA during the year 2018 (Siegel et al. 2019). In general, the risk of PCs is quite high i.e., 1 out of 8 men is diagnosed with PC in his lifetime (Key Statistics for Prostate Cancer, American Cancer Society). In India, the number of PC cases is lower than that of other western countries. The annual PC rate was reported to be 5-9.1 cases per 100,000 people in a year and it is 110.4 cases for white males and 180.9 for black males per 100,000 US people (Hariharan et al. 2016). The common symptoms for PCs are repeated urination, urination problem, worn-out urinary stream, blood in urine or semen, and acute pain in the lower portion of the back, hips, or thighs. However, prostatitis or benign prostatic hyperplasia also might have similar symptoms. Therefore, it is very difficult to detect PCs from conventional symptoms. It has been reported that PC is diagnosed mostly in the population above 50 years and rarely diagnosed below 50 years of age. Genetic factors are one of the most common risk factors for PC. The risk of transmission of PC to the next generations of a patient is found to increase 2-4 folds.

The most common biomarker used for the identification of PC is the prostate-specific antigen (PSA), a 33 kD proenzyme that belongs to the kallikrein group of proteases namely human kallikrein 3 (hK3). In seminal fluid, its concentration ranges from 0.5-2 g/L (Stenman et. al. 1999). PSA is also found in the saliva (Khan et al. 2018) and urine of men (Kearns and Lin 2018). The concentration of PSA is 0.03-0.34 ng/mL (Ayatollahi et al. 2007) in saliva and men having PSA 1.7 ng/mL in their saliva are evident of having PC (Farahani et al. 2020). The amount of total PSA in healthy individuals is 0-4 ng/mL, however it surges in case of PC patients (Luderer et al. 1995). Human glandular kallikrein2 (hK2) and prostate cancer gene 3 (PCA3) are different biomarkers used for the detection of PC and are found in human serum (Mao et al. 2018). hK2 is a serine protease, and its

✉ Manashjit Gogoi
manash.aec@gmail.com

1 Department of Biomedical Engineering, North-Eastern Hill University, Shillong 793022, Meghalaya, India

2 Physics Division, Department of Basic Sciences and Social Sciences, North-Eastern Hill University, Shillong 793022, Meghalaya, India

3 Biosciences and Biomedical Engineering, Indian Institute of Technology, Indore-453552, Madhya Pradesh, India

4 Department of General Surgery, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong, Meghalaya, India

5 Department of Biochemistry, North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences, Shillong-793018, Meghalaya, India

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amino acid sequence is 79% homologous to that of PSA (Klee et al. 1999). The normal concentration of hk2 should be <0.05 ng/mL and >0.05 ng/mL for patients with PC (Becker et al. 2000). The PCA3 and sarcosine are two other biomarkers of PC present in urine with a normal concentration range of 2-10 ng/mL (Ferro et al. 2016). PCA3 is a non-coding RNA and found only in human prostate tissue (Gutschner and Diederichs 2012). Semen exosomes contain miRNA which also acts as a biomarker for the detection of PC (Barcelo et al. 2019).

Digital rectal examination (DRE), transrectal ultrasound (TRUS), gray-scale ultrasonography (GSU), positron emission tomography/computer tomography (PET/CT) scan, power doppler ultrasonography (PDU), three-dimensional contrast-enhanced power Doppler ultrasonography (3D-CE-PDU), transrectal magnetic resonance imaging (TMRI), PSA level test, and biopsy are the most widely used conventional diagnostic techniques for the examination of PC. All of these diagnostic techniques have their advantages as well as disadvantages. For example, simple and cost-effective techniques have poor sensitivity whereas highly sensitive techniques are very expensive and not easily available to the masses. Biosensors can be used as low-cost alternative tools to the costly conventional instruments for the detection of PCs. In this review, we have discussed the conventional detection techniques and various kinds of biosensors for the identification of PCs along with their challenges and future prospects.

2 Conventional diagnostic techniques for PC detection

DRE is a simple diagnostic procedure used to examine the lower rectum and other internal organs. It is one of the easiest and quickest ways to check the health of a prostate gland (Schroder et al. 1998). DRE has poor performance in lower concentrations of PSA and hence, DRE alone is insufficient for detecting PC.

In TRUS, ultrasound waves are allowed to interact with the walls of the rectum and the neighboring areas of the prostate. The waves rebound from the organs and tissues are transformed into anatomical images and then displayed on the computer screen. TRUS biopsies are taken randomly without targeting any cancer lesions, therefore, are prone to diagnostic errors. DRE technique is useful for patients having PSA levels >4 ng/mL (Puech et al. 2013).

GSU is a traditional imaging method for PC and provides greater temporal and spatial resolution compared to PDU. GSU can detect microbubbles which are used as a contrast agent for better imaging and ultrasonography (US). PDU uses doppler imaging technique and allows sensitive detection of fluid flowing blood vessels present in the prostate. 3D-CE-PDU is found to be more efficient and accurate than PDU (Unal et al. 2000). The micro-vessels in malignant tumors are smaller and uniform than benign or normal tissues. If the microvascular density increases in PC, these imaging techniques fail to detect the malignant lesions (Halpern 2006).

PET/CT scan is used generally to detect and locate malignant PC. The malignant prostate tumors located at the transition zone, are often missed by conventional imaging techniques. PET/CT scan is not sufficient for differentiating cancerous prostate lesions from benign hyperplasia, but it can at least detect local recurrence and lymph node metastasis (Schmid et al. 2005).

MRI produces comprehensive 3D images of soft tissues or organs of the human body. MRI is found to be a superior technique for cancer compared to other techniques. The levels of PSA in the human body sometimes are elevated due to other benign factors and result in wrong predictions, which can be confirmed through the biopsy process. In such cases, MRI is predictive enough to dismiss these kinds of negative reports (Kirkham et al. 2006). However, it is expensive and available in sophisticated laboratories.

PSA is a common biomarker used for detecting PC using fluorescence techniques (Harma et al. 2001), and enzyme-linked immunosorbent assay (ELISA) (Chang et al. 2018, Stowell et al. 1991), and bioluminescent enzyme immunoassay (Seto et al. 2001). PSA levels may increase even in a variety of non-cancerous conditions, like infection, trauma, inflammation in the prostate, as well as in benign prostatic hyperplasia. Hence, PSA monitoring might have low accuracy (Yao et al. 2018).

The tissues in the prostate gland are tested for malignancy during a prostate biopsy. In order to perform biopsy, the prostate tissue section is collected using a needle. It is usually recommended for PSA levels ranging from 4 - 10 ng/mL (Matlaga et al. 2003).

3 Biosensors for prostate cancer detection

As per the International Union of Pure and Applied Chemistry (IUPAC), the definition of "biosensor" is “a device that uses specific biochemical reactions mediated by isolated enzymes, immunosystems, tissues, organelles or whole cells to detect chemical compounds usually by electrical, thermal or optical signals” (Jurado-Sanchez 2018). These devices detect signals as per the concentration of the analyte in biological samples and convert them to measurable signals with the help of a transducer. A bioreceptor or biorecognition element is connected with transducers to detect the presence and amount of the analyte. The analytes interact with bioreceptors and the signals are recorded by the transducers, which gives qualitative and quantitative values of the analyte

(Fig. 1). These devices are categorized as per the biorecognition elements or transducers used. For detection of PCs, biosensors are required because of the fact that the conventional diagnostics techniques are either not efficient or very expensive. Biosensors are cost-effective and portable.

The biosensors reviewed in this report, have been classified according to the types of transducers used, and the applications of these biosensors for the identification of PC are discussed in the following sections.

3.1 Electrochemical biosensors

Biochemical reactions such as reactions between enzymes-substrates and antigen-antibody are converted to electrical signals (e.g., current, voltage, impedance, etc.) by electrochemical biosensors. Clark was the first to conceptualize an electrochemical biosensor in 1962, and he explained the functioning of glucose enzyme electrodes for monitoring blood glucose levels (Clark and Lyons 1962). The glucose electrochemical biosensor was fabricated with three screen-printed electrodes (SPE) viz. working electrode (iridium-containing carbon), reference electrode (Ag/AgCl), and counter electrode (Au). (Fig. 2i) (Shen et al. 2007). In another study, a biosensor was fabricated with PLLA (carboxylated poly-L-lactide) nanoparticles along with ssDNA conjugated GO (graphene oxide)-for detecting two biomarkers simultaneously i.e., VEGF and PSA using two-electrode electrochemical technique (Fig. 2ii). It was one of the earliest label-free electrochemical biosensors for rapid and accurate detection of two cancer biomarkers (Pan et al. 2017). Screen-printed electrodes (SPE) were used for developing an immunochromatographic biosensor (electrochemical) for the swift and accurate identification of PSA. The biosensor had a test strip that consisted of four specific zones viz. sample loading zone, conjugation zone, test zone, and absorption zone (Fig. 2iii). The SPE was placed underneath the test zone of the strip. Then the secondary antibodies are bound to the specific analytes. This binding resulted in the propagation of electrical signals which were detected by the SPE corresponding to the analyte concentration (Lin et al. 2008).

A PC biosensor was fabricated using oligonucleotide with MWCNT composite by detecting miRNA-141 using electrochemical technique. Peptide nucleic acids or locked nucleic acids could be used to increase sensitivity and LOD due to their higher attraction toward miRNA-141 (Tran et al. 2013). A PSA sensor was fabricated by electrochemical immunoassay using magnetic beads with LOD < 0.1 ng/mL (Sarkar et al. 2008). Another total PSA sensor was developed using horseradish peroxidase-labeled antibody on the SPE electrode (Sarkar et al. 2002). A dual mode (impedimetric and amperometric) PSA biosensor

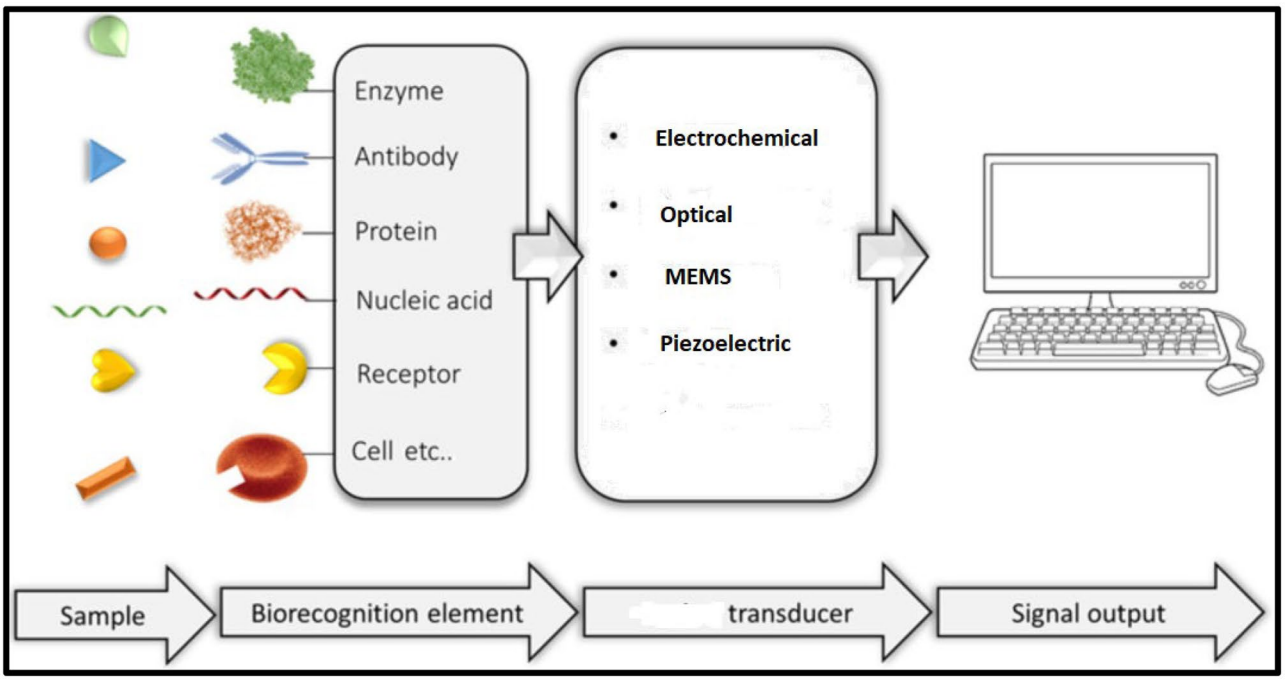

Fig. 1 Schematic representation of a biosensor (Damborsky et al. 2016), which uses various biological elements such as enzymes, antibodies, proteins, etc. The analyte (sample) reacts with the biorecognition element which helps the biosensor to measure the amount of analyte present in the substrate. It is converted to measurable signals by the transducer. Reproduced with permission from Damborsky et al. (2016)

was developed using gold nanoparticle assembly with LOD upto 10 ng/mL (Jolly et al. 2017). In another study, a microfluidic PSA sensor was fabricated by coating GO-Fe_3O_4 composite on SPE electrode with anti-PSA antibodies and the LOD was found to be 15 fg/mL in serum sample (Sharafeldin et al. 2017). PSA detection was reported using rolling circle amplification (RCA) reaction using poly(thymine)-coated CuNP with LOD of 0.02 ± 0.001 fg/mL (Zhu et al. 2016).

3.2 Optical biosensors

An optical biosensor uses an optical transducing system, which include surface plasmon resonance (SPR), localized SPR, interferometers, optical resonators, gratings, and refractometers. These biosensors send optical signals that are correlated with the concentration of the analyte (Chen and Wang 2020; Ramsden 1997). The surface of the transducer consists of biorecognition elements such as antibody molecules or molecules with special affinity properties (Homola et al. 1999).

Fluorescent immunoassay, radioimmunoassay, and ELISA have been used as conventional techniques which are reported to be specific and sensitive. But these methods need skilled manpower, are expensive, and time-consuming. Optical biosensors use quantum dots and luminescent nanoparticles, which have better photostability and tunable emission properties (Sapsford et al. 2006). Surface plasmon resonance (SPR) is a resonant vibration of the conduction electrons of metal using a polarized light at a specific angle i.e., angle of resonance (Amendola et al. 2017). Some optical biosensors need an SPR chip that contains a functional layer of interacting molecules. The working principle of SPR biosensors and functionality have been reviewed (Hoa et al. 2007, Homola 2008). The resonance in SPR is measured in terms of wavelength, incidence angle and intensity of reflected light (Fig. 3).

CdSe/ZnS QD based biochips were fabricated using surface plasmon coupled emission (SPCE) technique. PSA was immobilized on SPR glass substrate to fabricate the protein chips. Initially, a gold coated glass was dipped in piranha solution for a short time to eliminate impurities and activate the substrate for PSA immobilization. The substrate was then treated for 3 hours in 3-(aminopropyl) trimethoxysilane solution (APTMS) to activate amine functional groups and the PSA protein was immobilized on it. Sensitivity of the biochips improved due to the presence of QDs and the LOD achieved was equal to 10 fg/mL (Jin et al. 2012). A carbon substrate with QD streptavidin conjugate-based biosensor for PSA was reported with LOD value of 0.25 ng/mL (Kerman et al. 2007). A SPR biosensor was constructed using PSA-α_1ACT monoclonal

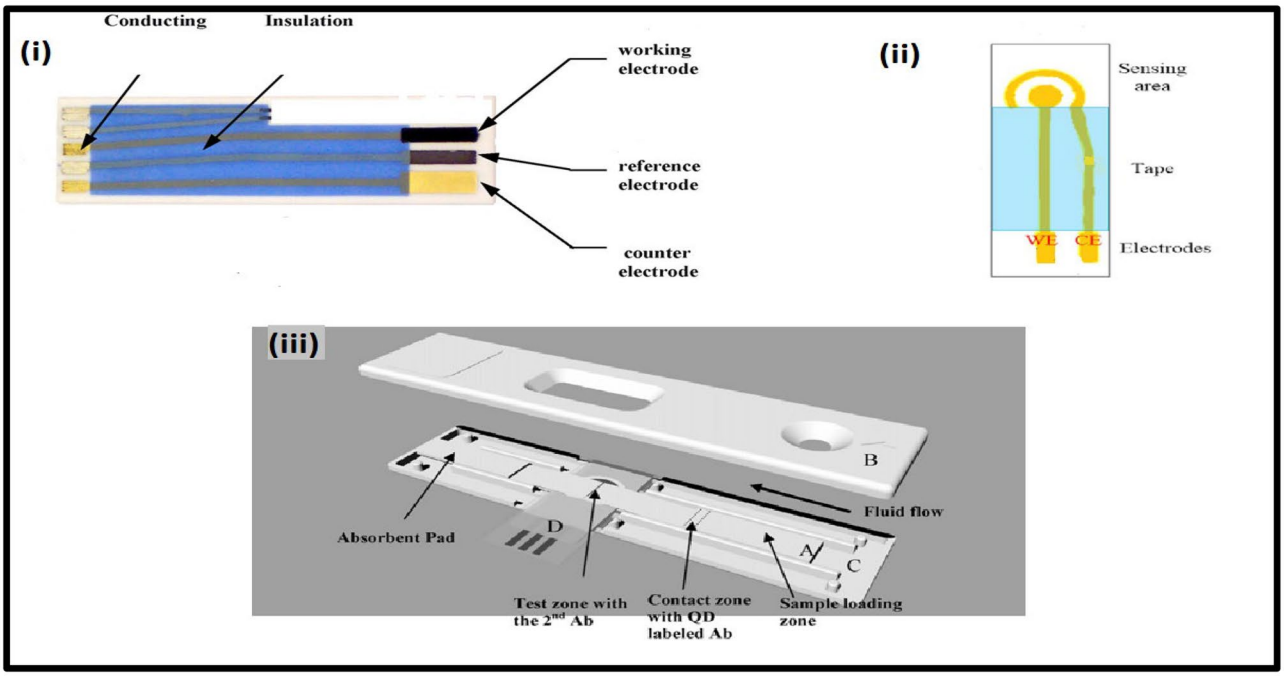

Fig. 2 (**i**) Front view of a screen-printed electrode (Shen et al. 2007) (**ii**) Schematic diagram of modified biosensor where the working and counter electrodes are induced together and the reference electrode remains separated (Pan et al. 2017) (**iii**) Schematic representation of the electrochemical biosensor. (**A**) test strip, (**B**) cover, (**C**) bottom cover, and (**D**) screen-printed electrodes (Lin et al. 2008) Reproduced with permission from Shen et al. (2007); Pan et. al. (2017), and Lin et al. (2008)

antibody for detection of PC (Jang et al. 2009). A microcontact imprinting-based SPR biosensor was fabricated for detecting PSA in clinical samples. It has several advantages, like less activity loss in biorecognition molecules and a very small sample requirement (Erturk et al. 2016).

Localized surface plasmon resonance (LSPR) is an optical phenomenon that occurs while incident light interacts with surface electrons in a conduction band (Willets and Duyne 2007). The resonance frequency of LSPR is dependent on the nanoparticles' characteristics such as structural arrangement, size, charge, interplanar distance, etc. (Petryayeva and Krull 2011). A ultrasensitive LSPR fiber optic biosensor was designed using gold nanodisk arrays for PSA detection with LOD of 0.1 pg/mL (Kim et al. 2019). A LSPR biosensor was developed by modifying the surface of silica nanoparticles with LOD of 10 ng/mL (Endo et al. 2005). Magnetic nanobeads coupled with a peptide were used to create a biosensor based on the SPR phenomenon with very low turnaround time and LOD was 100 pg/mL (Esseghaier et al. 2014). Another LSPR-based biosensor claimed to detect PSA even at 500 pg/mL in mixed human blood in a short time. It contained 32 sensor sites distributed across eight microfluidic channels (Acimovic et al. 2014). A QD-paper-based optical biosensor was reported for simultaneous detection of CEA (carcinoembryogenic antigen) and PSA with LOD of 0.3 ng/mL and 0.4 ng/mL, respectively (Chen et al. 2019). A biosensor based on nanodisk-array was fabricated which could detect PSA with a LOD of 100 fg/mL (Sanders et al. 2014).

Photonic crystal biosensors are widely used for PC detection, which can controls the propagation of electromagnetic waves that interact with it. Biosensors with photonic crystal structures are used to detect different types of analytes with great efficiency and precision. A photonic crystal-based biosensor was reported for detecting PSA concentrations as lesser as 0.5 ng/mL. The device was fabricated using electron beam lithography technique (Sana et al. 2017). Another very sensitive photonic crystal nanolaser biosensor was investigated for detection of PSA by measuring the movement of laser wavelength. The gadget was very thermostable and reported to be extremely sensitive to other proteins (Hachuda et al. 2015).

3.3 Piezoelectric biosensors

The piezoelectric effect is the capacity of certain materials to generate an electrical signal as a result of applied mechanical stress. QCM (quartz crystal microbalance) is a piezoelectric biosensors, which can detect PSA by the change in resonance frequency as per the change of mass on the sensor surface (Kwak and Lee 2019). Figure 4 shows a schematic quartz crystal microbalance. The compression can be in the form of external pressure.

Metallic electrodes were partially deposited on both sides of a circular quartz crystal to make the QCM. Gold electrodes are commonly used in biosensing applications. The quartz crystal detector used in QCM resonates at the fundamental frequency when an electric field is applied to it (Skladal 2016; Su et al. 2013).

These biosensors work on different resonator modes such as (i) thickness extensional (TE) mode, (ii) thickness-shear (TS) mode, (iii) lateral extensional (LE) mode, and (iv) flexural mode (flex). TE mode resonator provides highest sensitivity as it can generate higher wave velocity and resonant frequency than other existing resonators, and it is found to be better in liquid medium (Pang et al. 2012).

PSA and alpha-fetoprotein (AFP) were detected using a label-free, inexpensive and rapid piezoelectric biosensor with sensitivity of 0.25 ng/mL and faster detection (within 30 minutes) (Su et al. 2017). A piezoelectric microcantilever based PSA biosensor was fabricated by Gupta et al. using COMSOL multiphysics modeling and using lead zirconate titanate (PZT) and SiO2 with detection range of 2 ng to 8 ng (Gupta and Swaminathan 2015). A PZT

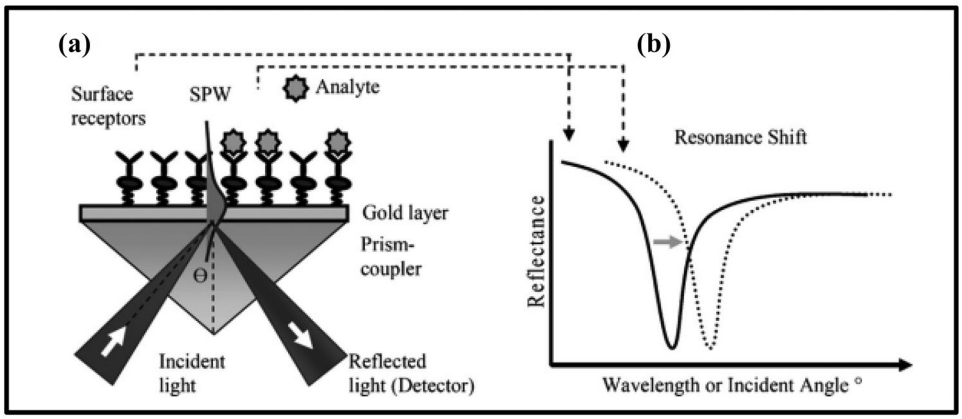

Fig. 3 Representation of SPR phenomenon (**a**) prism-coupled arrangement, (**b**) resonance deviation in the reflected light prism. Reproduced with permission from Hoa et al. (2007)

microcantilever with immobilized PSA antibodies was employed for PSA detection through antibody and antigen binding (Lee et al. 2005). Gopinath et al. (2015) fabricated a biosensor based on microcantilever for detection of various diseases. Whenever the antigen/microorganisms come in contact with the chemically sensitive material on its surface, it results in bending of the microcantilever. These cantilevers have tremendous potential due to ease of combining a PZT nanomechanical cantilever and immobilization of proteins on them which help in making portable label-free diagnostic devices.

4 Emerging biosensors

4.1 Microelectromechanical system (MEMS)-based biosensor

A MEMS-based biosensor is fabricated by depositing an analyte sensitive layer on the top of a microcantilever which ensures biological recognition. The detection of the analyte by the bioreceptors of the sensitive layer creates a difference of stress between the sensitive layer and the microcantilever which results in deflection of the microcantilever. A MEMS sensor using paper as a structural material was fabricated to be useful as paper-based piezoresistive force sensor (Fig. 5). The conductive materials patterned on the paper produced a piezoresistive effect (Liu et al. 2011). MEMS microcantilever sensors are also helpful in quick detection of various antigens present in the body through binding with antibodies immobilized on the cantilever surface and subsequent deflection of the cantilevers (Vashist 2007). The detection of various diseases like tuberculosis, HIV, etc., which can be made faster using MEMS sensors. Feng et al. fabricated a giant magneto-impedance (GMI) sensor using photolithography and wet etching methods with LOD to be 0.1 ng/mL (Feng et al. 2019). MEMS sensors require lesser materials to fabricate which makes them cheaper, easy to use and very much favorable for POC diagnostics.

4.2 Paper-based biosensor

Paper-based biosensors are emerging biosensors based on optical and electrochemical detection methods. The various physical properties of paper such as density, resilience, and weight can be tuned as per requirement. Paper consists of cellulose fiber which is a hydrophilic fibre matrix that helps in the easy transportation of liquid (Ratajczak and Stobeicka 2020). The properties of hydrophilic fiber can also be adjusted to change its properties such as hydrophilicity, permeability and reactivity. The use of paper-based devices is user friendly, biodegradable, low cost, easily hydrophilic and hydrophobic patterned etc. (Shergujri et al. 2019; Nery and Kubota 2013). Paper-based biosensors are categorized as dipstick assays, lateral flow assays (LFA), microfluidic paper-based analytical devices (μPADs) etc.

Dipstick assays contain previously-stored reagents into a blotting paper, which are submersed into the analyte solutions and subsequently, the color is changes proportional to the analyte concentration (Hu et al. 2014). Dipstick assay is used for optical detection in qualitative manner, which may not be suitable for diagnosis (Posthuma-Trumpie et al. 2009). Lateral flow assays (LFAs) have the reagents immobilized on the strip and the sample is allowed to flow along the longitudinal direction of the strip. ELISA methods are used in LFAs, which comprises four specific sections such as sample pad, conjugation pad, detection pad, and wicking pad (Lee et al. 2013, Lin et al. 2015) which help in efficient detection of analytes. Multiple (Hu et al. 2017) and quantitative assays (Urusov et al. 2019) can be performed using LFAs. Fu et al. (2019) investigated a surface-enhanced Raman scattering (SERS) based LFA for quick detection of PCA3 (prostate cancer antigen 3) mimic DNA with LOD of 3 fM. An ICTS (immunochromatography test strip) platform was fabricated using QD beads for quick detection of PSA with LOD of lower than the accepted level for clinical diagnosis (Li et al. 2014). A fluorescence ICTS was developed to detect PSA quickly by utilizing a novel amphiphilic hydrophobin (HFBI) protein with sensitivity of 0.06 ng/mL (Zhang et al. 2018). A highly sensitive LFA for detection of fPSA (free PSA) was developed using fluorescent

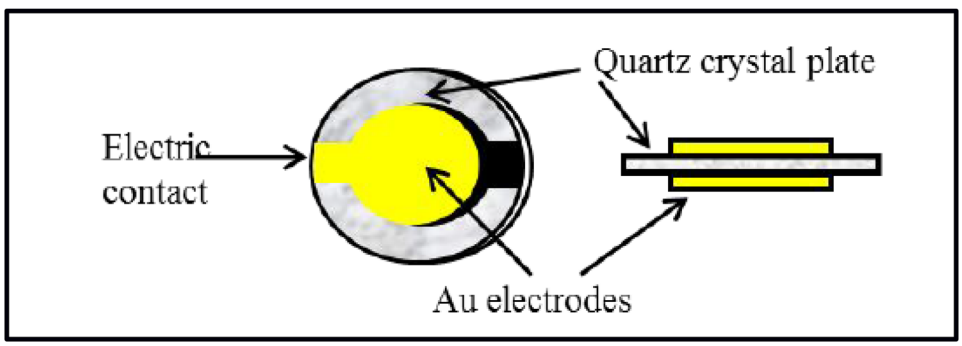

Fig. 4 Schematic representation of Quartz crystal microbalance. Reproduced with permission from Marrazza (2014)

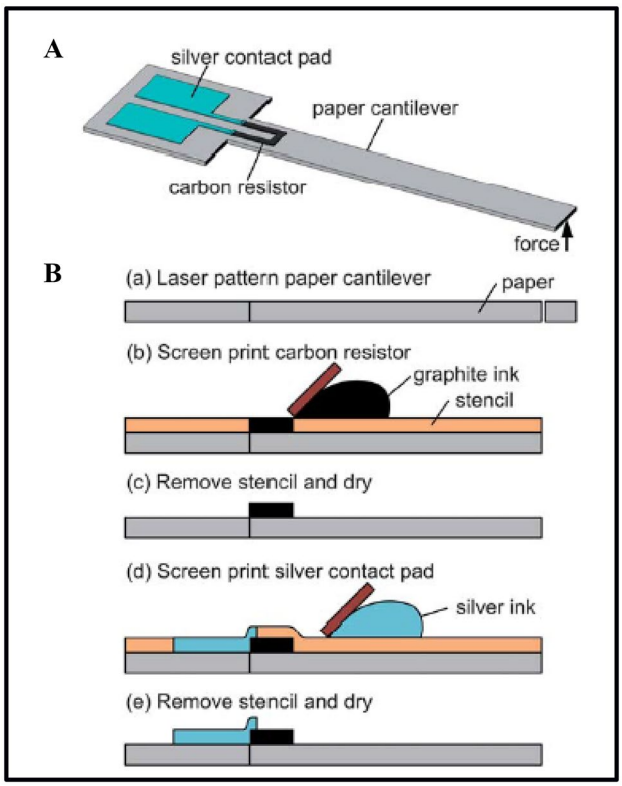

Fig. 5 Paper-based piezoresistive force sensors. (**A**) Diagrammatic representation of the sensor. (**B**) The process of development of the sensor. Reproduced with permission from Liu et al. (2011)

europium(III) chelate doped nanoparticles with a LOD of 0.01 ng/mL (Salminen et al. 2019). Semiconductor polymer dots were used as a fluorescent probe in another ICTS which could detect PSA, AFP (alpha fetoprotein) and CEA (carcinoembryonic antigen) within 10 minutes with LODs well below the accepted level for clinical detection (Fang et al. 2018). In LFA, binding of analytes with their specific biomarker produces results. LFAs are commonly used in POC diagnosis due to its comprehensibility, affordability, and capability to produce quick results.

The microfluidic paper-based analytical devices (μPADs) are mostly used for POC diagnostics. Cellulose is used as a substrate in μPADs, which helps the microfluidic devices in performing flow of fluid without any external source of energy. μPADs can be used for simple qualitative tests as well as more complex and difficult qualitative tests (Arugula and Simonian 2014). Some special fabrication methods are employed to create hydrophilic channels on hydrophobic paper (Rezk et al. 2012). A paper-based colorimetric biosensing device was fabricated for the detection of PSA, hydrogen peroxide and glucose with detection range of 0.1-10 ng/mL (Zhou et al. 2014). A paper-based immunochromatographic biosensor (POC) for PSA detection was fabricated using quantum dots with LOD of 0.02 ng/mL (Liu et al. 2007).

A low-cost μPADS can be fabricated using paper-based microfluidic technique and using wax screen printing to create hydrophilic/hydrophobic channels on the substrate. This technique can be used for both colorimetric as well as electrochemical detection (Dungchai et al. 2011). The visible color changes were interpreted with imaging software for estimating the analyte concentration.

4.3 Field effect transistor (FET) based biosensor

The field-effect transistor-based biosensor (BioFET) uses a biological recognition element attached with a FET (Maddalena et al. 2010; Lee et al. 2014), where the charge or the potential effect, is used to detect the analyte. BioFETs are generally fabricated from an ISFET (ion-sensitive FET) by customizing the gate or coupling it with different bioreceptors (Schoning and Poghossian 2002). A bio-recognition layer is attached chemically or electrostatically on the transducer surface (Fig. 6). Carriers of charge travel from the source (S) to the drain electrode (D) when bias voltage is applied and the flow of charge-carriers is restricted by a third electrode, gate (G). A BioFET is switched on or off by applying an electrical potential at the gate. The biochemical binding on the surface of the transducer is then converted to a measurable electronic signal.

PSA was detected with a LOD of 1 fg/mL using a molybdenum disulfide (MoS_2) FET biosensor. DNA tetrahedron and biotin-streptavidin were conjugated to the FET which enhanced the antigen-antibody binding (Zhang et al. 2021). A graphene FET (POC) was fabricated to detect PSA with LOD of 1 pg/mL (Mandal et al. 2021). A silicon nanowire FET was fabricated for instantaneous detection of PSA. Gold nanoparticles were used for functionalization of the nanowires which added a covalent attachment of antibodies through their thiol groups, which resulted higher efficiency of the transistor and LOD of 23 fg/mL (Presnova et al. 2017). Rodriguez et al. (2019) used gold nanoparticles to fabricate a porous silicon FET biosensor for PSA detection using conductance of the FET with LOD of 0.1 ng/mL. Another single-walled CNT FET based biosensor was fabricated for instantaneous and sensitive protein detection with LOD of 84 pM (Chen et al. 2016). The PSA was detected using indium oxide (In2O3) nanowires and SWCNT as a FET biosensor and using anti-PSA antibody with LOD of 5 ng/mL (Lee et al. 2012).

4.4 Challenges and future prospects

The development of biosensors has progressed a lot since its emergence in the medical field. But technology always leaves behind some alternatives which need further research

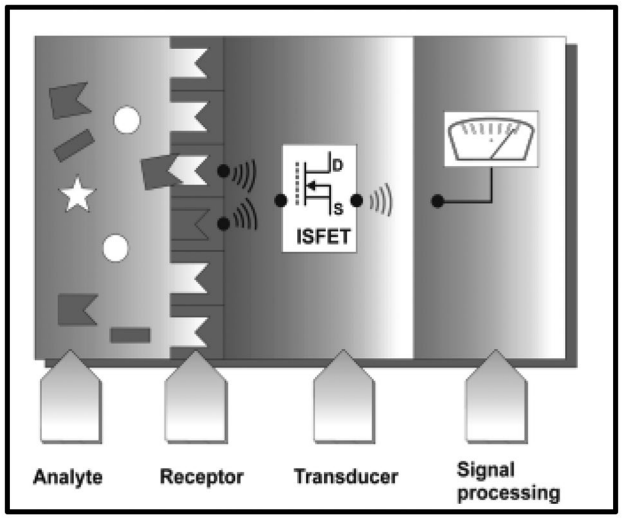

Fig. 6 Schematic diagram of a BioFET. Reproduced with permission from Schoning and Poghossian (2002)

and improvement. The main challenges are recognizing small molecules, achieving better sensitivity and selectivity in detecting different analytes, cross-linking, and immobilization of bioreceptors on the substrate. Diagnosis of PCs requires the detection of multiple biomarkers at the same time using an individual chip. In the near future, biomarkers pattern software and microfluidics can be included to make promising devices for application in this area (Tothill 2009). Amplification of sensitivity of biosensors has been a major issue. Several processes for enhancing the sensitivity have been used. Nanorods with high aspect ratio are preferred over the spherical nanoparticles to improve sensitivity of these devices. The observation of protein and protein interactions poses a greater challenge than that of nucleic acids as new amplification technologies are not available. Complex association of the proteins and their stronger non-specific binding to solid supports also adds to this scenario. Hence, the nanoparticles which contain mixed monolayers are expected to fully promote the potentiality of protein-nanoparticle hybrids (Wang 2005).

Table 1 Types of biosensors used for detection of PC

Sl. No.	Type of biosensors	Biomarkers	Limit of Detection (LOD)	Reference
1.	Electrochemical	VEGF and PSA	0.05-100 ng/mL (for VEGF) and 1-100 ng/mL (for PSA)	(Pan et al. 2017)
2.	Electrochemical	PSA	0.02 ng/mL	(Lin et al. 2008)
3.	Electrochemical	miRNA-141	N/A	(Tran et al. 2013)
4.	Electrochemical	Free PSA	0.1 ng/mL	(Sarkar et al. 2008)
5.	Electrochemical	Total PSA	N/A	(Sarkar et.al. 2002)
6.	Electrochemical	PSA	10 ng/mL	(Jolly et al. 2017)
7.	Electrochemical	PSA	15 fg/mL	(Sharafeldin et al. 2017)
8.	Electrochemical	PSA	0.02 fg/mL	(Zhu et al. 2016)
10.	Optical	PSA	10 fg/mL	(Jin et al. 2012)
11.	Optical	Total PSA	0.25 ng/mL	(Kerman et al. 2007)
12.	Optical	PSA	N/A	(Jang et al. 2009)
13.	Optical	PSA	0.1 ng/mL	(Kim et al. 2019)
14.	Optical	PSA	100 pg/mL	(Esseghaier et al. 2014)
15.	Optical	PSA	500 pg/mL	(Acimovic et al. 2014)
16.	Optical	CEA and PSA	0.3 ng/mL (for CEA) and 0.4 ng/mL (for PSA)	(Chen et al. 2019)
17.	Piezoelectric	PSA and AFP	0.25 ng/mL	(Su et al. 2017)
18.	Piezoelectric	PSA	N/A	(Lee et al. 2005)
19.	Piezoelectric	PSA	N/A	(Gopinath et al. 2015)
20.	Paper based	PCA3	3 fM	(Fu et.al. 2019)
21.	Paper based	PSA	0.33 ng/mL	(Li et al. 2014)
22.	Paper based	fPSA	0.01 ng/mL	(Salminen et.al. 2019)
23.	Paper based	PSA	0.06 ng/mL	(Zhang et al. 2018)
24.	Paper based	PSA,AFP and CEA	2.05 pg/mL (for PSA), 3.30 pg/mL (for AFP) and 4.92 pg/mL (for CEA)	(Fang et al. 2018)
25.	Paper based	PSA	10 ng/mL	(Zhou et al. 2014)
26.	Paper based	PSA	0.02 ng/mL	(Liu et al. 2007)
27.	FET	PSA	1 pg/mL	(Mandal et al. 2021)
28.	FET	PSA	23 fg/mL	(Presnova et al. 2017)
29.	FET	PSA	0.1 ng/mL	(Rodriguez et al. 2019)

Most of the sensors need calibration before every use and incubation in buffer solutions. Some sensors can detect the analyte only at a certain level of concentration. The stability of the biosensor also adds to this factor. Biosensors depend on the bioreceptors, and the long-term storage and usage of bioreceptors is a big challenge as bioreceptors are susceptible to changes in temperature, pressure, and pH value. Any alterations in the normal environment conditions might result in a decrease of the sensing ability. Biosensor with a higher stability range is much more preferred as the conditions of the environment keep on changing over the period of time. In the present scenario, the stability of the biosensors in a changing environment is quite a big challenges. It has also been reported that sometimes biosensors need to detect multiple analytes for specificity. Some specific cancerous cells might require more than one analyte for its confirmation. Hence, to achieve the greater specificity of the biosensor dual-sensing capacity needs to be developed (Liu et al. 2017).

Biosensors are becoming indispensable in today's world due to their enormous potential in both research and commercial applications. Combination of microfluidic technology and 3D printing helps in reduction in cost and detection of multiple analytes. However, according to the World Health Organization (WHO), we should have ASSURED (affordable, sensitive, specific, user-friendly, rapid and robust, equipment free, and delivered to those in need) devices to cater to the needs of the masses (Srinivasan and Tung 2015).

5 Conclusion

The present review deals with the different issues related to biosensors applied for detection of PC. The conventional screening methods like DRE, PSA tests, US imaging, and MRI are either not efficient in detecting PCs or are very expensive. The expensive diagnosis methods are not affordable to the common masses. Hence, biosensors with capability to detect multiple biomarkers for efficient PC detection are need of the hour. Though there are many hurdles in biosensor development, extensive research work is going on to develop different futuristic POC biosensors and notable progress has been achieved in recent years. Integration of microfluidics, 3D printing, and artificial intelligence techniques will have a significant effect in engineering ASSURED biosensors for early detection of PC (Table 1).

Abbreviations PC: Prostate cancer; DRE: Digital rectal examination; TRUS: Transrectal Ultrasound; GSU: Gray-scale ultrasonography; PET/CT: Positron emission tomography/computer tomography scan; PDU: Power doppler ultrasonography; 3D-CE-PDU: Three-dimensional contrast-enhanced power doppler ultrasonography; TMRI: Transrectal magnetic resonance imaging; PSA: Prostate-specific antigen; ELISA: Enzyme-linked immunosorbent assay; SPE: Screen-printed electrodes; LOD: Limit of detection; VEGF: Vascular endothelial growth factor; MEMS: Microelectromechanical systems; SPR: Surface plasmon resonance; QD: Quantum dot; LSPR: Localized surface plasmon resonance; QCM: Quartz crystal microbalance; PZT: Lead titanate zirconate; LFA: Lateral flow assay; μPAD: Microfluidic paper-based analytical devices; POC: Point- of- care

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Declarations

Conflict of Interest The authors declare that they have no conflict of interest.

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