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Nanosensors and their applications in early diagnosis of cancer

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ABSTRACT

According to WHO and other key statistics, cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. By identifying cancer early, it is more likely to respond to treatment, resulting in a better chance of survival as well as a lower cost of treatment. Early detection of cancer and avoiding delays in treatment can significantly improve the lives of cancer patients. Nanomaterial-based sensors with the ability to extract and identify tumor-specific biomarkers, circulating tumor cells, or extracellular vesicles secreted by the tumor have the potential to diagnose cancer considerably earlier and enhance patient long-term survival. In this review, we provide the application of nanosensors for the early detection of cancer and the recent techniques for clinically diagnosing cancer patients' biomarker levels. Furthermore, the presented works are compared based on their sensitivity and selectivity in the detection of different kinds of cancer biomarkers.

1. Introduction

1.1. Invention and general development procedure of nanosensors

Nanosensors are devices that utilize nanotechnology to detect and respond to specific physical, chemical, or biological stimuli at the nanoscale level. The invention and development of nanosensors involve a multi-step procedure, which can be summarized as follows:

- Conceptualization and Design: The first step is to conceptualize the idea for a nanosensor and define its intended purpose and target application. This involves identifying the specific analyte or stimulus to be detected and determining the desired sensitivity, selectivity, and operational parameters. The sensor design also considers the appropriate nanomaterials, transduction mechanisms, and fabrication techniques to achieve the desired functionality.
- Nanomaterial Selection: Nanosensors often incorporate nanomaterials that exhibit unique properties at the nanoscale. These materials can include nanoparticles (e.g., metal, semiconductor, or carbon-based), nanowires, nanotubes, or two-dimensional materials (e.g., graphene). The choice of nanomaterial depends on factors such as their sensing capabilities, compatibility with the target analyte, stability, and ease of fabrication.
- Sensing Mechanism: Nanosensors employ various sensing mechanisms to detect and transduce the target stimulus into measurable signals. These mechanisms can include optical, electrical, magnetic, thermal, or mechanical principles. For example, optical nanosensors may rely on changes in light absorption, fluorescence, or surface plasmon resonance, while electrical nanosensors may measure changes in electrical conductivity or capacitance.
- Fabrication Techniques: Nanosensors are typically fabricated using nanofabrication techniques, which allow precise control over the size, shape, and composition of the nanostructures. Common fabrication techniques include top-down approaches (e.g., electron beam lithography, focused ion beam milling) and bottom-up approaches (e.g., chemical vapor deposition, self-assembly). These techniques enable the production of nanosensors with high precision and reproducibility.
- Surface Functionalization: Nanosensors often require surface functionalization to enhance their selectivity and sensitivity towards the target analyte. Functionalization involves modifying the nanosensor's surface with specific receptors or recognition elements that can interact selectively with the analyte of interest. These receptors can be antibodies, enzymes, DNA sequences, or molecularly imprinted polymers.
- Signal Transduction and Readout: Once the target stimulus interacts with the nanosensor, the resulting changes in the sensor's properties

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or signals need to be transduced and measured. This can involve converting physical or chemical changes into electrical signals, optical signals, or other measurable outputs. Signal transduction methods may include electrical measurements, spectroscopy, imaging techniques, or mass-sensitive detection methods.

- Testing and Optimization: After fabrication, the nanosensors undergo rigorous testing to evaluate their performance, sensitivity, selectivity, and response time. The sensors are exposed to known analytes or stimuli under controlled conditions to validate their functionality. Based on the test results, iterative optimization processes are carried out to improve the sensor's performance and reliability.
- Integration and Packaging: Once the nanosensors have been developed and optimized, they can be integrated into larger systems or devices for practical applications. This may involve incorporating the sensors into microfluidic platforms, wearable devices, or electronic circuits. The packaging of nanosensors ensures their protection, stability, and ease of use in real-world environments.
- Commercialization and Scaling: Successful nanosensor technologies can undergo commercialization and scaling to enable mass production and widespread adoption. This involves manufacturing processes, quality control measures, and establishing supply chains to meet market demands.

It's important to note that the development of nanosensors is a highly interdisciplinary field, involving expertise from various disciplines such as nanotechnology, materials science, chemistry, physics, biology, and engineering.

1.2. Working principle of nanosensors

A nanosensor can measure down to the level of single molecules. A nanosensor consists of a sensor, analyte, transducer, and detector. Typically, nanosensors work by tracking the electrical changes in the sensor materials. By diffusing from the solution to the sensor surface, the analyte reacts specifically and efficiently, resulting in a change in the physicochemical properties of the transducer surface, which in turn alters the optical or electronic properties of the transducer surface, causing an electrical signal which can be detected[1].

1.3. Recognition elements/sensing elements

Nanosensors can detect several analytes and be selective, some of them can detect only one type of analyte and are known as single sensors, while others can detect many types of analytes and are known as multiplex sensors. A nanosensor's recognition element reveals its selectivity and specificity. Many recognition elements have been used in the design of nanosensors, including antibodies, aptamers, enzymes, and some functional proteins. The most common recognition elements in nanosensors are aptamers and antibodies[2].

1.4. Nanosensor types

Nanosensors can be defined and categorized by their constituent materials, their detection targets, and the signals they use to transmit information. Materials that are used to fabricate nanosensors are including silicon nitride cantilevers, metallic/ magnetic nanoparticles, nanotubes, nanochannels, and others. The detection target of nanosensors can be antibodies, peptides, biological molecules, dangerous inorganic analytes, aptamers, enzymes, and others[3].

1.4.1. Nanosensors based on nanoparticles and nanoclusters

Noble metal nanoparticles have excellent size-dependent optical properties that have been used to make optical nanosensors. Several factors affect the spectrum of a phenomenon called localized surface plasmon resonance (LSPR), including the size, shape, and material of the particles and their environments. Single-molecule limit of detection for large biomolecules can be obtained by LSPR nanosensors due to their high sensitivity. In addition to metal nanoparticles, semiconductor quantum dots have been used to build optical nanosensors based on fluorescence measurements and nanoscale probes containing dyes are being developed as optical sensors to detect analytes whose fluorescence is quenched in contact with analyte; nanoparticle films have been used for gas sensors; magnetic nanoparticles bound to biorecognition molecules (i.e. DNA, enzymes, etc.) have been used to enrich the analyte to be detected[4].

Nanosensors based on nanoparticles and nanoclusters offer several benefits and drawbacks. Here are some of the key points to consider:

- Benefits:

1. Sensitivity: Nanoparticles and nanoclusters possess high surface-to-volume ratios, which enhance their sensitivity to changes in the surrounding environment. This makes them excellent candidates for detecting and measuring small quantities of analytes or signals.
2. Selectivity: Functionalizing nanoparticles and nanoclusters with specific molecules or coatings allows for high selectivity in sensing particular substances or target analytes. This enables precise detection and discrimination of various chemicals, biomarkers, or pollutants.
3. Miniaturization: Nanosensors can be miniaturized to extremely small sizes, enabling their integration into various devices and systems. This feature is particularly advantageous for applications where space is limited, such as wearable devices, medical implants, or environmental monitoring in confined spaces.
4. Versatility: Nanoparticles and nanoclusters can be engineered with different materials and structures, providing versatility in sensor design and functionality. They can be tailored to respond to specific stimuli, including light, temperature, pressure, or chemical interactions, expanding their applicability to diverse sensing scenarios.
5. Real-time monitoring: The small size and rapid response of nanosensors make them suitable for real-time monitoring applications. They can provide continuous, instantaneous data collection, allowing for immediate detection of changes or events.

- Drawbacks:

1. Signal-to-noise ratio: Nanosensors, particularly those based on individual nanoparticles, can be susceptible to noise and interference. Background signals, fluctuations, or impurities in the environment can affect the accuracy and reliability of measurements, requiring careful signal processing and calibration.
2. Stability and reproducibility: Nanoparticles and nanoclusters may exhibit variations in their physicochemical properties, leading to challenges in reproducibility and long-term stability of sensor performance. Manufacturing processes need to be optimized to ensure consistent sensor behavior across different batches.
3. Cost: The production and functionalization of nanoparticles and nanoclusters for sensing applications can be expensive, especially when large quantities or specific materials are required. The cost factor may limit their widespread adoption, particularly in resource-constrained settings.
4. Integration challenges: Integrating nanosensors into existing systems or devices can be technically complex. Ensuring compatibility, power supply, and data transmission with other components or electronics may present challenges that need to be addressed during the design and implementation stages.
5. Biocompatibility and toxicity: When considering nanosensors for biomedical applications, the biocompatibility and potential toxicity of nanoparticles or nanoclusters must be thoroughly evaluated. The interaction between the nanosensors and living systems should be carefully assessed to ensure their safe and effective use.

It's important to note that the benefits and drawbacks can vary depending on the specific application and the type of nanoparticles or nanoclusters used. Ongoing research and technological advancements aim to address these challenges and further enhance the capabilities of nanosensors for various fields.

1.4.2. Nanosensors based on carbon nanotubes, nanofibers, and nanowires

Carbone nanotubes (CNTs) are robust and have inert structures, but their electrical properties are highly sensitive to the effect of charge transfer and chemical doping by various molecules. Accordingly, most carbon nanotube-based sensors are field effect transistors (FET). To make CNTs selective to the target analyte, functionalization of them is an effective method. The molecular recognition interactions between functionalized CNT and target analytes are used to develop various types of sensors. For example, researchers decorated single-walled carbon nanotubes (SWCNTs) with gold nanoparticles (AuNPs) to obtain nanosensors[5]. They have been used to maximize gas sensor responses in exhaled breath analysis for the detection of volatile organic compounds (VOCs) which are biomarkers for various diseases; for example, acetone, hydrogen sulfide, ammonia, and toluene can be used as biomarkers for evaluating diabetes, halitosis, kidney malfunction, and lung cancer, respectively[6,7].

Nanosensors based on carbon nanotubes, nanofibers, and nanowires offer numerous benefits in various applications. However, they also have certain drawbacks that need to be considered. Let's explore the benefits and drawbacks of each type:

- Carbon Nanotube-based Nanosensors
- Benefits

1. High sensitivity: Carbon nanotubes possess exceptional electrical, mechanical, and thermal properties, enabling high sensitivity in detecting and measuring various substances, such as gases, chemicals, and biomolecules.
2. Fast response time: Carbon nanotubes can rapidly detect changes in their electrical properties when exposed to analytes, leading to quick response times for nanosensors.
3. Small size: Carbon nanotubes are inherently nano-sized structures, allowing for the fabrication of extremely small and compact sensors suitable for integration into miniaturized devices.
4. Versatility: Carbon nanotubes can be functionalized and tailored to detect specific analytes, making them versatile for a wide range of sensing applications.
5. Durability: Carbon nanotubes are mechanically robust and can withstand harsh conditions, making them suitable for sensing in challenging environments.

- Drawbacks:

1. Manufacturing complexity: The fabrication of carbon nanotube-based nanosensors can be complex and expensive, involving precise manipulation and alignment of individual nanotubes.
2. Sensor-to-sensor variability: Carbon nanotubes can have variations in their electrical properties, leading to variability in sensor performance, which may require additional calibration steps.
3. Sensitivity to environmental factors: Carbon nanotube-based sensors can be sensitive to environmental factors such as temperature, humidity, and contaminants, which may affect their performance and reliability.

- Nanofiber-based Nanosensors:
- Benefits:

1. Large surface area: Nanofibers typically have a high surface-to-volume ratio, which enhances the interaction between the analyte and the sensor surface, resulting in increased sensitivity.
2. Flexibility: Nanofibers can be fabricated into flexible and wearable sensors, allowing for conformal integration onto various substrates and the monitoring of physiological parameters.
3. Biocompatibility: Many nanofibers, such as those made from biopolymers, exhibit excellent biocompatibility, making them suitable for biomedical sensing applications and implantable devices.
4. Tunable properties: Nanofibers can be engineered with specific properties, such as porosity, surface chemistry, and functionalization, enabling tailoring for different sensing applications.

- Drawbacks:

1. Limited electrical conductivity: Some nanofibers may have poor electrical conductivity, which can restrict their use in certain applications requiring high electrical sensitivity.
2. Fragility: Nanofibers can be fragile and prone to damage or breakage, which may reduce the durability and robustness of the sensors.
3. Fabrication challenges: Producing nanofiber-based sensors with uniformity and controlled alignment can be challenging, limiting their large-scale production.

- Nanowire-based Nanosensors:
- Benefits:

1. Ultra-high sensitivity: Nanowires exhibit exceptional electrical properties, allowing for ultrasensitive detection of analytes even at low concentrations.
2. Direct transduction: Nanowires can directly convert analyte binding events into electrical signals, simplifying the sensing process and enabling label-free detection.
3. Compatibility with integrated circuits: Nanowires can be seamlessly integrated with existing electronic circuitry, facilitating the development of integrated sensor systems and enabling multiplexed sensing.
4. Small footprint: Nanowire-based sensors can be fabricated in arrays, enabling parallel sensing and high-throughput screening of multiple analytes simultaneously.

- Drawbacks:

1. Surface contamination: Nanowires can be susceptible to surface contamination, which can interfere with the sensing performance and require careful handling and cleaning procedures.
2. Fragility: Nanowires are typically very thin and delicate, making them prone to mechanical damage during fabrication or operation, which may affect sensor functionality.
3. Cost: The production of nanowire-based sensors can be costly due to the specialized fabrication techniques and the use of expensive materials.

It's important to note that the field of nanosensors is rapidly advancing, and ongoing research and development efforts aim to address many of the current limitations associated with these nanomaterial-based sensors.

1.4.3. Nanosensors based on graphene

Functionalized graphene, which is a type of carbon-based nanomaterial, has great potential to be used in chemical and biological sensors. Researchers have developed sensing devices with exceptionally high speed, using the distinctive 2D structure of graphene oxide (GO) combined with its superpermeability to water molecules ("Ultrafast graphene sensor monitors your breath while you speak"). It has been discovered that chemical vapors change graphene transistor noise spectra, allowing scientists to detect many vapors with a single device made of pristine graphene - no functionalization of the graphene surface necessary ("Selective gas sensing with pristine graphene")[8].

Nanosensors based on graphene offer several benefits due to the unique properties of graphene. However, they also have certain drawbacks that need to be addressed. Let's explore both the benefits and drawbacks of nanosensors based on graphene:

- Benefits:

1. High Sensitivity: Graphene is an exceptional material known for its high sensitivity to various stimuli. Graphene-based nanosensors can detect even small changes in temperature, pressure, strain, or chemical composition, making them highly sensitive sensors for a wide range of applications.
2. Fast Response Time: Graphene's thin and two-dimensional structure enables rapid response to changes in the environment. Nanosensors based on graphene can detect and transmit signals quickly, making them suitable for real-time monitoring applications.
3. Wide Detection Range: Graphene-based nanosensors can detect a broad spectrum of signals, including electromagnetic waves, gases, chemicals, and biomolecules. This versatility makes them valuable in diverse fields, such as environmental monitoring, healthcare, and industrial applications.
4. Miniaturization: Graphene is a two-dimensional material, which allows for the development of nanoscale sensors. These nanosensors can be integrated into tiny devices and systems, enabling miniaturization and integration into various platforms, including wearable devices and Internet of Things (IoT) applications.
5. Low Power Consumption: Graphene-based nanosensors typically have low power requirements due to their small size and efficient signal transduction mechanisms. This low power consumption is advantageous for applications that require prolonged battery life or energy-efficient operation.

- Drawbacks:

1. Scalability: While graphene-based nanosensors show great promise, scaling up their production and integration into practical devices can be challenging. Achieving large-scale, cost-effective fabrication methods while maintaining high-quality graphene is an ongoing research area.
2. Signal-to-Noise Ratio: Graphene-based nanosensors can be susceptible to noise interference, affecting the signal-to-noise ratio and potentially limiting their sensitivity. Shielding techniques and careful design considerations are necessary to mitigate this issue.
3. Stability and Durability: Graphene is prone to degradation under certain environmental conditions, such as humidity and exposure to reactive substances. Ensuring the stability and long-term durability of graphene-based nanosensors remains a technical challenge.
4. Specificity: Graphene-based nanosensors may face challenges in achieving high selectivity and specificity for target analytes. Overcoming cross-reactivity and interference from background signals is crucial for reliable and accurate sensing.
5. Cost: Currently, the production of high-quality graphene at large scale can be expensive, limiting the widespread adoption of graphene-based nanosensors. However, ongoing research and technological advancements are expected to address this drawback in the future.

It's important to note that research in graphene-based nanosensors is rapidly evolving, and ongoing advancements may help address some of the current drawbacks. As the field progresses, the benefits of nanosensors based on graphene are expected to outweigh their limitations, leading to innovative applications in various domains.

1.4.4. Nanosensors based on bulk nanostructured materials

While nanoparticles have several properties that make them useful for nanosensor applications, their catalytic behavior is the most important in electrochemical sensors. The design of gas diffusion electrodes can be improved through the use of platinum nanoparticles supported on materials such as porous carbon or noble metals. Furthermore, nanoparticles have a high surface area, making them ideal for immobilizing molecules, polymers, or biomaterials to produce composite materials with tailored surface properties. For instance, the modification of metal nanoparticles with pre-designed receptor units and assembly on surfaces could lead to improved electrochemical sensors. Proper functionalization of nanoparticles can also allows the making of highly-selective and sensitive electroanalytical procedures. Eventually, amplifying labels of limited stability, such as liposomes or enzymes can be replaced with an equivalent or improved sensitivities with stable nanoparticles[4].

Nanosensors based on bulk nanostructured materials offer several benefits and drawbacks. Let's explore them:

- Benefits:

1. Enhanced Sensitivity: Bulk nanostructured materials possess a high surface-to-volume ratio, which results in an increased number of active sites for sensing. This higher surface area enables the detection of lower concentrations of analytes, leading to improved sensitivity compared to conventional sensors.
2. Improved Selectivity: Nanosensors based on bulk nanostructured materials can exhibit enhanced selectivity by modifying the surface chemistry or functionalizing the materials. This allows for specific interactions with target analytes, reducing interference from other substances and improving the accuracy of sensing.
3. Faster Response Time: The reduced size and enhanced surface area of bulk nanostructured materials enable faster diffusion and interaction with analytes. As a result, nanosensors based on these materials can provide real-time or near real-time measurements, making them suitable for rapid detection applications.
4. Miniaturization and Integration: Bulk nanostructured materials can be fabricated into miniature sensor devices. Their small size and compatibility with microfabrication techniques enable the integration of multiple sensors onto a single chip. This miniaturization and integration facilitate portability, cost-effectiveness, and the development of sensor arrays for multi-analyte detection.
5. Versatility: Bulk nanostructured materials can be engineered with a wide range of properties and functionalities. By tailoring the composition, structure, and surface properties, nanosensors can be designed to detect various analytes, including gases, chemicals, biomolecules, and even specific types of nanoparticles.

- Drawbacks:

1. Fabrication Challenges: The synthesis and fabrication of bulk nanostructured materials can be complex and require specialized techniques. Achieving a high degree of control over the material structure and properties can be challenging, which may limit the scalability and commercial viability of these sensors.
2. Stability and Durability: Some bulk nanostructured materials may exhibit reduced stability or durability under certain conditions, such as exposure to high temperatures, corrosive environments, or long-term use. Ensuring the long-term stability and reliability of nanosensors based on these materials can be a significant challenge.
3. Cost: The fabrication processes for bulk nanostructured materials can be expensive and time-consuming. Additionally, the use of certain rare or exotic materials in their synthesis may further increase the cost of production. These factors can limit the widespread adoption of nanosensors based on bulk nanostructured materials, particularly in cost-sensitive applications.
4. Standardization and Quality Control: Due to the evolving nature of bulk nanostructured materials and their fabrication techniques, standardization and quality control measures can be lacking.

Consistent performance, reliability, and reproducibility across different batches or manufacturers can be a concern, hindering widespread adoption in certain industries.
5. Potential Toxicity: While many bulk nanostructured materials have been extensively studied for their safety, it is essential to consider the potential toxicity of certain nanoparticles. Some nanosensors based on bulk nanostructured materials may contain elements or compounds that can be harmful to humans or the environment. Proper risk assessment and mitigation strategies should be implemented to ensure safe usage.

Overall, nanosensors based on bulk nanostructured materials hold significant promise for a wide range of applications, but challenges related to fabrication, stability, cost, standardization, and safety need to be addressed for their successful integration into various industries and everyday life.

1.4.5. Nanosensors based on metal-organic frameworks (MOFs)

MOFs are organic-inorganic hybrid crystalline porous materials that are composed of a regular array of positively charged metal ions surrounded by organic 'linker' molecules. The metal ions form nodes that connect the linkers' arms to create a repeating, cage-like structure. Since MOFs have hollow structures, they have an extraordinary amount of internal surface area, making them ideal for gas sensing. Researchers can produce materials that selectively absorb particular gases into custom-made pockets within the structure by constructing the MOF from various metal atoms and organic linkers[9].

Nanosensors based on metal-organic frameworks (MOFs) offer several benefits and drawbacks. Here are some of them:

- Benefits:

1. High surface area: MOFs have an exceptionally high surface area due to their porous structure, providing a large number of active sites for sensing. This high surface area allows for enhanced sensitivity and detection of analytes.
2. Tailorable properties: MOFs can be easily synthesized with tunable properties such as pore size, composition, and functionality. This flexibility enables the design of nanosensors specific to a wide range of target analytes, enhancing their selectivity and sensitivity.
3. Versatile analyte detection: MOF-based nanosensors can detect various analytes including gases, ions, small molecules, and biomolecules. This versatility makes them suitable for applications in environmental monitoring, healthcare diagnostics, and chemical sensing.
4. Signal amplification: MOFs can act as amplifiers by selectively capturing target analytes and concentrating them in their pores. This property can enhance the sensor's signal response, improving the detection limits and overall sensitivity.
5. Stability and recyclability: MOFs exhibit high stability, making them suitable for repeated use and recycling. This characteristic is beneficial for the development of reusable nanosensors, reducing costs and environmental impact.

- Drawbacks:

1. MOF degradation: Some MOFs may exhibit instability under certain environmental conditions, such as exposure to high humidity or extreme pH levels. This can limit their long-term functionality and reliability as nanosensors.
2. Slow response time: The diffusion of analytes into the porous structure of MOFs can lead to slower response times compared to other sensing platforms. This characteristic may hinder their application in scenarios requiring real-time or rapid detection.
3. Fabrication challenges: The synthesis and fabrication of MOF-based nanosensors can be complex and time-consuming. Achieving uniform and controlled growth of MOF films or integrating MOFs onto sensor platforms can present technical challenges, potentially limiting their scalability.
4. Interference and selectivity: While MOFs can offer high selectivity, they may also exhibit interference from other molecules present in the sample matrix. The design and optimization of MOFs for specific analytes can be challenging, requiring careful consideration of potential interferences.
5. Cost considerations: Some MOF materials, particularly those based on rare or expensive metals, can be costly to produce. This factor may impact the scalability and commercial viability of MOF-based nanosensors for certain applications.

It's worth noting that research and development in the field of MOF-based nanosensors are ongoing, and efforts are being made to address some of the drawbacks mentioned above. Continued advancements in MOF design, fabrication techniques, and integration strategies are expected to further enhance their performance and broaden their potential applications.

2. Applications of nanosensors in the early diagnosis of cancer

Nanosensor technology is being researched for its potential medical applications in various areas including diagnosis, for example, antibiotics, hormones, DNA, antibodies, disease markers, and others; investigating biomolecular interactions and biochemical assays including nucleic acids, enzyme assays, proteins, antigen–antibodies, and drug carriers; gas monitoring; and others. This review aims to provide information on the different applications of nanosensors in the early diagnosis of cancer.

2.1. Cancer detection

According to the World Cancer Report from the World Health Organization (WHO) and other key statistics, cancer is a leading cause of death worldwide, accounting for nearly 10 million deaths in 2020. In 2020, the following new cases of cancer were most prevalent:

- Breast (2.26 million cases);
- Lung (2.21 million cases);
- Colon and rectum (1.93 million cases);
- Prostate (1.41 million cases);
- Skin (non-melanoma) (1.20 million cases); and
- Stomach (1.09 million cases).

The leading causes of cancer deaths in 2020 were:

- Lung (1.80 million deaths);
- Colon and rectum (916,000 deaths);
- Liver (830,000 deaths);
- Stomach (769,000 deaths); and
- Breast (685,000 deaths)[10].

By identifying cancer early, it is more likely to respond to treatment, resulting in a better chance of survival as well as a lower cost of treatment. Early detection of cancer and avoiding delays in treatment can significantly improve the lives of cancer patients[10].

Implementing evidence-based strategies for early diagnosis, cancer prevention, and management of patients with the disease can help to reduce and control cancer. However, there is extensive knowledge about the reasons for cancer, preventing, and managing the disease, and only a few significant improvements have been made in curing the disease. It has been proven that early detection is the only way to improve quality of life and life expectancy. For this purpose, nanosensors and highly sensitive nanomaterial-based devices have been developed to detect circulating tumor cells (CTCs), biomarkers, or tumor-derived vesicles

which are released comparatively early from the tumor into the blood which will make a significant change in the morbidity and morality of the disease[11].

2.1.1. Lung cancer

Lung cancer is by far the leading cause of cancer-related mortality in the world, making up almost 25% of all cancer deaths. A greater number of people die from lung cancer each year than from prostate, breast, or colon cancer combined. This situation is mainly because of the late stage of diagnosis. Unfortunately, traditional screening methods such as low-dose computed tomography (LDCT) and chest radiography (CXR) have been indicated to be ineffective in directly detecting lung tumors before spreading and become incurable. For example, the obtained images from CT often display many small lung nodules and at a very early stage, it's not easy to realize which of these nodules are lung cancer and which are benign. Consequently, it's still necessary to take a biopsy from the abnormal tissue to finally detect cancer which is complicated, inconvenient, expensive, and can lead to morbidity and even mortality because of bleeding[12].

2.1.1.1. The biomarkers and detection targets for Lung cancer. Lung cancer is a complex disease, and several biomarkers and detection targets have been identified to aid in its diagnosis and monitoring. Here are some commonly studied biomarkers and detection targets for lung cancer:

1. Carcinoembryonic Antigen (CEA): CEA is a glycoprotein that can be elevated in the blood of individuals with lung cancer. It is used as a tumor marker for various cancers, including lung cancer.
2. Cytokeratin Fragment 21–1 (CYFRA 21-1): CYFRA 21-1 is a soluble fragment of cytokeratin 19, and its levels can be measured in blood samples. Elevated levels of CYFRA 21-1 are associated with lung cancer, particularly non-small cell lung cancer (NSCLC).
3. Neuron-Specific Enolase (NSE): NSE is an enzyme found predominantly in neurons and neuroendocrine cells. Increased levels of NSE in blood can indicate the presence of small cell lung cancer (SCLC).
4. Progastrin-Releasing Peptide (ProGRP): ProGRP is a precursor of gastrin-releasing peptide and is found at elevated levels in the blood of individuals with SCLC. It is used as a biomarker for the diagnosis and monitoring of SCLC.
5. Epidermal Growth Factor Receptor (EGFR) Mutations: EGFR mutations are genetic alterations commonly found in lung adenocarcinoma. Testing for these mutations is essential for targeted therapy selection, as certain EGFR inhibitors are effective against tumors with specific mutations.
6. Anaplastic Lymphoma Kinase (ALK) Rearrangements: ALK gene rearrangements occur in a subset of lung adenocarcinomas. Identifying ALK rearrangements helps in selecting patients who may benefit from targeted therapies that inhibit the ALK fusion protein.
7. Programmed Death-Ligand 1 (PD-L1) Expression: PD-L1 is a protein expressed on the surface of cancer cells. Testing for PD-L1 expression helps in determining the eligibility of patients for immunotherapy with immune checkpoint inhibitors like pembrolizumab or nivolumab.
8. Circulating Tumor Cells (CTCs): CTCs are cancer cells that detach from the primary tumor and enter the bloodstream. Detection and characterization of CTCs can provide valuable information about the presence and progression of lung cancer.
9. Circulating Tumor DNA (ctDNA): ctDNA refers to small fragments of tumor DNA released into the bloodstream. Analysis of ctDNA allows for non-invasive monitoring of genetic alterations and treatment response in lung cancer patients.

It's important to note that the availability and utility of specific biomarkers and detection targets may vary depending on the type and stage of lung cancer, as well as individual patient characteristics. Healthcare professionals rely on a combination of clinical evaluation, imaging tests, and laboratory analyses to diagnose and manage lung cancer effectively.

In the last decade, researchers have worked on developing different kinds of nanosensors for the early detection of lung cancer. MicroRNAs (miRNAs) are highly conserved and tiny noncoding RNAs that regulate gene expression at the posttranscriptional level by binding to the 3′-UTR of target mRNAs. A growing body of evidence indicates that they play a crucial role in various pathological processes, including human cancer. Anran Gao et al.[13] used silicon nanowire field-effect (SiNW-FET) devices to develop multiplexed electrical detection of lung cancer biomarkers. The SiNW arrays were fabricated by an anisotropic wet etching technology using self-stop limitation and integrated with polydimethylsiloxane (PDMS) chips with mass reproducible ability and low-cost character. The nanosensors could sensitively and rapidly detect as low as 0.1 fM lung cancer biomarker miRNA−126 and 1 fg/ml carcino embryonic antigen (CEA) with good specificity. The ability of the nanosensors was investigated in both ideal and clinically relevant samples and they demonstrated high performance in detecting lung cancer. Jesse D. Kirkpatrick et al.[14] used activity-based nanosensors for the urinary detection of lung cancer in mice via noninvasive pulmonary protease profiling. The multiplexed nanosensors performed with sensitivity up to 95% and specificity of 100% for the diagnosis of localized disease in two autochthonous human lung adenocarcinoma (LUAD) models representing *Kras/Trp53* and *Alk-mutant* disease.

Zhuang Hao et al.[15] designed an electrolyte-gated graphene field effect transistor (GFET) nanosensor using aptamer for the rapid, highly sensitive, and specific detection of a lung cancer biomarker interleukin-6 (IL-6) with enhanced selectivity and stability. First, they examined the capability of the nanosensors in measuring the IL-6 concentration and whether the nanosensors could respond to the change in IL-6 concentration in <10 min. Then, they investigated the stability of the nanosensors by storing the nanosensors in a 1× PBS buffer for 24 h and they were still capable of fast detecting IL-6. Finally, the high specificity of the nanosensors to IL-6 over non-target molecules was verified. Tumor cells that split away from the primary tumor and extravasate into and circulate through the bloodstream are called Circulating tumor cells (CTCs).

Understanding the metastatic cascade of CTCs has tremendous potential for the identification of targets against cancer metastasis. Christopher M. Earhart et al.[16] developed a magnetic sifter, which is a small microfluidic chip with a dense array of magnetic pores labeled with magnetic nanoparticles that showed a high-efficiency detection of tumor cells.

Hypoxia is mainly known as one of the substantial features in most cancers including NSCLC. Yantao Li et al.[9] suggested O_2 concentration sensors monitor NSCLC excited by near-infrared (NIR) light to eliminate the negative effect of UV or visible light, based on the fact that Infrared light penetrates deeply into tissues, damages minimally and has a high spatial resolution. They used biological metal-organic frameworks (bio-MOFs) as the matrix. Then they fabricated a core/satellite nanostructure, where many upconversion nanoparticles (UCNPs) were attached as antennas onto the surfaces of bio-MOFs including O_2 indicators. These nanosensors could successfully track in vivo NSCLC lesions without long-term biotoxicity.

Ann-Katrine Jakobsen et al. [17] used nanosensors to investigate the TOP1 (Topoisomerase I) and TDP1 (Tyrosyl-DNA phosphodiesterase 1) activities in cryosections from NSCLC tissue samples which were collected at Aarhus University Hospital in 2011 including 24 paired tissue samples (one adjacent non-tumor and one tumor sample from each patient). Their results showed that both TOP1 and TDP1 were upregulated in the tumor tissue compared to the adjacent non-tumor tissue in NSCLC. Eisa Zarepour et al.[18] proposed a method to design a terahertz Wireless NanoSensor Network (WNSN) for monitoring human lung cells and they also showed that there is a temporal sweet

spot in the respiration cycle that can be used to reduce the transmission power of nanosensors. In this study, an online algorithm is proposed to estimate the sweet spots and periodic channel that allows a high power reduction.

The calpain protein is a calcium-dependent, non-lysosomal cysteine protease (proteolytic enzyme) found ubiquitously in mammals and many other organisms. One of the major isoforms of calpain is Calpain 2 (CAPN2). CAPN2 has been proposed as a tumor marker linked to angiogenesis, cell proliferation, and migration in NSCLC. Seung-Hae Kwon et al.[19] designed a human serum albumin-based active calpain 2-triggered nanosensor (HSA − CAPN2) for early detection of CAPN2 in tumor tissues. The results of in vivo and in vitro experiments showed that the HSA − CAPN2 could be effective too for early detection and potential drug carrier to active CAPN2-enriched cancer.

Human exhaled breath contains >3000 VOCs, these VOCs are directly or indirectly related to internal biochemical processes in the body. Using electronic noses (*E*-noses) could be a potential way to screen/analyze systemic diseases and various respiratory by studying the signatures of breath. Silvano Dragonieria et al.[20] used a Cyranose 320 containing a nanocomposite array with 32 polymer sensors as *E*-nose and their study demonstrated that an E-nose can discriminate patients with lung cancer from chronic obstructive pulmonary disease (COPD) patients. S. Chatterjee et al.[21] developed an *E*-nose by the assembly of conductive polymer nanocomposite (CPC) quantum resistive sensors (QRS). The sensors developed in this study appeared to be great candidates for the detection of lung cancer by VOC analysis in breath with a sensitivity of 2.5 ppm, low consumption, a couple of seconds response time, and a large signal-to-noise ratio (SNR $\geq$ 10). Andras Bikov et al.[22] investigated the effects of expiratory flow rate, breath hold, and inclusion of anatomic dead space on the exhaled levels of some volatile compounds and electronic nose data. 27 patients with lung cancer (60 $\pm$ 10 years) and 37 healthy subjects (44 $\pm$ 14 years) participated in the study. Breath-hold, the inclusion of anatomic dead spaces, and expiratory flow rate all significantly altered “breathprints” in healthy individuals ($p < 0.05$), but not in lung cancer patients ($p > 0.05$). These factors also significantly affected the discrimination ability of the electronic nose in the detection of lung cancer. According to G. Peng et al.[23] and Orna Barash[24] et al., gold nanoparticles (GNPs) sensors can distinguish between breath VOCs of healthy individuals and those from lung cancer patients. Nam-Hoon Kim et al.[25] introduced highly selective and sensitive sensors using Pd-functionalized WO_3 nanofibers (NFs). First, they synthesized WO_3 NFs by electrospinning method, and then Pd catalysts were loaded inside and/or outside of the WO_3 NFs. Catalytic Pd-loaded WO_3 NFs showed a good response time in a humid condition which makes them suitable to be used in exhaled breath sensors to detect toluene. Consequently, the Pd-added WO_3 NFs are applicable for use in exhaled breath sensors for the detection of lung cancer.

F.L. Liu et al.[26] presented a highly selective SWNTs biosensor to detect both polar and nonpolar VOCs molecules. To develop this sensor, pentadecane ($C_{15}H_{32}$) and tricosane ($C_{23}H_{48}$) were coated on the surface of SWNTs. The prepared device was exposed to representative VOCs nonpolar molecule decane and polar molecule 1,2,4-trimethylbenzene which are two lung cancer biomarkers. The results showed that the functionalized-SWNTs had a noticeable sensitivity towards VOCs molecules and exhibit a higher selectivity towards polar VOCs biomarkers. Nisreen Shehada et al.[27] used a modified SiNW FET to detect many diseases including lung cancer, asthma, gastric cancer, and chronic obstructive pulmonary disease. The best obtained sensors were examined under real-world clinical conditions using breath samples from 374 patients. The results showed that the SiNW FETs could distinguish and detect between almost all comparisons with >80% accuracy. Alaa Gharra et al.[28] used a nanosensor-array system including layers of GNPs for the detection of lung and gastric cancers. 545 breath samples from 426 adult participants (158 lung cancer patients, 115 gastric cancer patients, and 153 healthy volunteers) were collected at the Jiangyin Hospital.

Applications of nanosensors in the early detection of lung cancer are also summarized in Table 1.

In lung cancer detection, electrochemical methods can detect specific lung cancer biomarkers in breath or blood samples, aiding in early diagnosis and monitoring of treatment response. Fluorescence techniques enable targeted imaging of lung cancer cells or tumor markers, assisting in precise localization and staging. Image-based methods assist in analyzing lung images to detect tumors, assess their size and location, and guide treatment planning.

2.2. Breast cancer

Globally, there were 2.3 million women diagnosed with breast cancer in 2020 and 685,000 deaths. The number of women diagnosed with breast cancer in the past five years reached 7.8 million at the end of 2020, making it the most prevalent cancer in the world. At the end of 2020, breast cancer was the most prevalent cancer in the world, with 7.8 million women alive and having been diagnosed in the past 5 years. Globally, breast cancer causes more disability-adjusted life years (DALYs) for women than any other form of cancer. In every country of the world, breast cancer can occur at any age after puberty, but it is more prevalent in older women.

2.2.1. The biomarkers and detection targets for Breast cancer

Breast cancer biomarkers and detection targets are important tools in the diagnosis, prognosis, and treatment of breast cancer. Here are some commonly used biomarkers and detection targets for breast cancer:

1. Estrogen Receptor (ER): ER is a hormone receptor that helps determine whether a breast cancer tumor is hormone receptor-positive or hormone receptor-negative. ER-positive tumors can be treated with hormone therapies that target this receptor.
2. Progesterone Receptor (PR): Similar to ER, PR is a hormone receptor that helps classify breast cancer tumors as hormone receptor-positive or hormone receptor-negative. PR-positive tumors may respond to hormone therapies.
3. Human Epidermal Growth Factor Receptor 2 (HER2): HER2 is a protein that plays a role in cell growth and division. Overexpression or amplification of HER2 is associated with aggressive breast cancer. HER2-positive breast cancers can be treated with targeted therapies like trastuzumab (Herceptin).
4. Ki-67: Ki-67 is a protein that indicates the level of cell proliferation or growth. It is used as a marker to determine the growth rate of breast cancer cells and is often associated with a more aggressive disease.
5. BRCA1 and BRCA2: BRCA1 and BRCA2 are genes that are associated with an increased risk of developing breast cancer. Mutations in these genes are often found in hereditary breast and ovarian cancers and may influence treatment decisions.
6. CA 15–3 and CA 27.29: These are tumor-associated antigens that can be measured in the blood. Elevated levels of these antigens may indicate the presence of breast cancer and can be used for monitoring disease progression or treatment response.
7. Circulating Tumor Cells (CTCs): CTCs are cancer cells that have detached from the primary tumor and entered the bloodstream. Detection and analysis of CTCs can provide valuable information about disease progression, metastasis, and treatment response.
8. Circulating Tumor DNA (ctDNA): ctDNA refers to fragments of tumor DNA that are released into the bloodstream. Analysis of ctDNA can provide information about tumor genetic mutations, treatment response, and minimal residual disease.
9. Mammographic Density: Mammographic density refers to the amount of fibrous and glandular tissue compared to fatty tissue in the breast. High mammographic density is associated with an increased risk of breast cancer and can be used as a risk assessment tool.

Table 1
Applications of nanosensors in the early detection of lung cancer.

No.	Biomarker/Target	Nanomaterials/Methods	Sensitivity/ LOD[a]	Specificity	Reference
1	Decane, undecane, hexanal, heptanal, benzene, and TMB[b]	MTPP-AuNR nanocomposites: The seed-mediated growth approach was utilised to create AuNR, and solution co-blending was employed to create MTPP-AuNR nanocomposites, which were then used to make an optical chemical sensor.	ND[c]	NA[d]	Danqun Huo et al. [29]
2	α-Phellandrene, Styrene, dodecane, and 4-methyl	AuNPs[e] and SWCNT[f] capped with polycyclic aromatic hydrocarbons	100%	95%	Inbar Nardi-Agmon et al.[5]
3	Benzaldehyde, nonanal, decanal, tetradecane, 5-methyl-tridecane, 6-methyl-5-heptane-2-one, acetophenone, 2,4-bis(1,1-dimethylethyl)-phenol, 2-ethyl-1-hexanol, 1,3-bis (1,1-dimethylethyl)-benzene, 1,3-dimethyl-benzene, and styrene	AuNPs: Using AuNPs, the gadget analyses volatile organic compounds (VOCs) in the headspace of (subtypes of) lung cancer cells.	96%	86%	Orna Barash et al. [24]
4	Various VOCs	AuNPs: The sensors were made up of layers of gold nanoparticles (GNPs) with 13 distinct organic ligands in two different forms (manual and printed), resulting in 26 different sensors in each nanosensor system.	76–100%	75–100%	Alaa Gharra et al. [28]
5	Malondialdehyde	Poly(dopamine)-Chitosan -AgNPs: Chitosan was electrodeposited on the surface of a PDA-modified glassy carbon electrode, and Ag nanoparticles were deposited on the Poly(dopamine)-Chitosan.	1.45 μM	ND	Mohammad Hasanzadeh et al. [30]
6	Styrene (ethenylbenzene), 2.2.4.6.6-pentamethyl heptanes, 2-methyl heptanes, decane, propyl benzene, 1-hexene, hepatanal, 1,4-dimethyl benzene, undecane, methyl cyclopentane, 1-ethyl-2-pentylcyclopropane, trichlorofluoro benzene, benzene, 1-ethylethenyl benzene, cyclohexane, 1-heptene, TMB, 2-methyl-(isoprene)-1,3-butadiene, 3-methyl octane, 1-hexene, 3-methyl nonane, hexanal, and 2,4-dimethyl heptanes	SWCNTs-coated with nonpolymeric organic materials: Array of sensors to detect lung cancer and to differentiate between the VOCs found in the breath of patients with lung cancer.	ND	ND	Gang Peng et al.2008[31]
7	Various VOCs	AuNPs: In a humid environment, an array of AuNP-based sensors quickly identified the breath of lung cancer patients from the breath of healthy persons.			Gang Peng et al.2009[23]
8	40 common VOCs that appear in>85% NSCLCs	AuNPs functionalized with tert-dodecanethiol, 2-ethyl-hexanethiol, and decanethiol	100%/ 10 ± 5 ppb	100%	Orna Barash et al. 2009[32]
9	DNA methylation	Single QD[g]-based: Using tricyclic ligation chain reaction (LCR)-mediated QD-based fluorescence resonance energy transfer (FRET), we developed a single QD-based nanosensor for sensitive detection of DNA methylation at both CpG and non-CpG sites.	10^{-11} M/ 1.0 aM	NA	Zi-yue Wang et al. [33]
10	H_2O_2	4MPBE[h]-coated AuNPs: H_2O_2-sensitive 4MPBE was used to coat the nanosensor.	0.49 μM	ND	Shigekuni Hosogi et al.[34]
11	MicroRNA	QD-based: A QD-based microRNA nanosensor for point mutation tests employing rolling circle amplification mediated by primer production.	50.9 aM	ND	Ya-ping Zeng et al.[35]
12	Aldehydes, alcohols, ketones, nitriles, alkanes, dienes, hydrocarbons, and benzene derivations	MCNPs[i]: A appropriate micrometric electrical transducer was coated with a chemiresistive MCNP layer.	ND	ND	Ulrike Tisch and Hossam Haick [36]
13	Mucin-1	Zn-Bp-MOFs[j]: Coordination was used to create zinc-based MOFs with pyridine (Zn-Bp-MOFs) to improve the ECL responses of zinc meso-tetra(4-sulfonatophenyl) porphine (Zn-TP).	0.23 pg mL^{-1}	Good	Li-Yan Huang et al.[37]
14	MicroRNAs	CMOS[k]-compatible SiNW[l]-based: A self-limiting anisotropic wet etching-based SiNW-FET biosensor that is CMOS compatible.	1 zeptomole	High	Na Lu et al.[38]
15	Hypoxia	poly(N-vinylpyrrolidone)-conjugated iridium (III): The poly(N-vinylpyrrolidone)-conjugated iridium(III)	High	High	Xianchuang Zheng et al.[39]

(*continued on next page*)

Table 1 (*continued*)

No.	Biomarker/Target	Nanomaterials/Methods	Sensitivity/ LOD[a]	Specificity	Reference
		complex (Ir-PVP) and poly(e-caprolactone)-b-poly (Nvinylpyrrolidone) (PCL-PVP) were combined to produce comicelles, which were then used to create the nanosensor.			

[a] LOD: limit of detection.
[b] TMB: 1,2,4-trimethylbenzene.
[c] ND: not determined.
[d] NA: not applicable.
[e] AuNPs: gold nanoparticles.
[f] SWCNT: Single-walled carbon nanotubes.
[g] QD: quantum dots, MTPP:metalloporphyrin.
[h] 4MPBE: 4-mercaptophenylboronic acid pinacol ester.
[i] MCNPs: Monolayer-capped metallic nanoparticles.
[j] Zn-Bp-MOFs: Zn-based metal organic frameworks with pyridine.
[k] CMOS: complementary metal oxide semiconductor.
[l] SiNW: Silicon nanowire.

Yu Chen et al.[6] used a nanoscale-gated biological field effect transistor for the detection of the breast cancer serum biomarker protein CA15.3 down to levels of concentration <20 units/ml. They used a "top-up" method to fabricate the nanoscale biosensor with complete control of the geometry by lithography and standard semiconductor processing techniques in a complementary metal-oxide-semiconductor (CMOS)-compatible process. The nanowires were functionalized with CA15.3 and 3-aminopropyl- triethoxysilane (APTES) was used to silanize the device.

The chemical energy needed to power the cell's biochemical reactions is mainly produced by a type of membrane-bound cell organelles known as mitochondria. This energy is stored in adenosine triphosphate (ATP) which is a small molecule.

Wrong functioning of mitochondria can result in many diseases, such as mitochondrial encephalomyopathy, Leigh syndrome, lactic acidosis, hepatopathy, stroke-like episodes, tubulopathy, and cancer. Therefore, understanding the relationship between mitochondrial pH (pH_m), tumoral metabolism, and cancer is very important. Consuelo Ripoll et al.[40] designed a nanosensor with a double modification of the quantum dot (QD) surface. On the one hand, the surface of the QD surface was modified with mercaptopropionic acid (MPA) which affects the photoluminescence (PL) lifetime of the QDs. On the other hand, for specific mitochondrial delivery, Szeto-Schiller (SS) peptides were added to the surface. This nanosensor was used to correctly measure the intra-mitochondrial pH using fluorescence lifetime imaging microscopy (FLIM) that can serve as a potential biomarker for the early detection of different metabo phenotypes in breast cancer cell lines.

Yu-Husan Kuo et al.[41] developed a CMOS-based capacitive nano-biosensor for the first time for early detection of miRNA-195, as the breast cancer-specific biomarker in blood. They combined CMOS integrated circuits and an interdigitated electrode (IDE) as a nano-sensor. The advantages of this nanosensor are compactness, miniaturization, high specificity, and high sensitivity. Their results showed that the limit of detection (LOD) could be as low as 0.617 fM proving that the nanosensor had high specificityand high sensivity and could be a good option for early detection of breast cancer.

Due to its superior temporal and spatial resolution, optical fluorescence imaging is one of the most widely used methods for imaging in vivo. Because it is non-invasive and real-time, this approach is a desirable imaging modality for medical applications like biosensing, cancer diagnostics, and medical testing. The vast majority of fluorescence probes, which are necessary for optical fluorescence imaging, are visible (400–700 nm). When imaging inside the body, visible light has several limitations, though. The opacity of biological components including hemoglobin and water increases as they absorb light within the visible range. Additionally, due to the scattering of visible light caused by these elements within biological tissue, the penetration depth of visible fluorophores is decreased. Additionally, biological tissues exhibit self-fluorescence (also known as autofluorescence) in the visible range due to the presence of several luminous macromolecules that affect any images that are captured. Light scattering and autofluorescence are diminished by NIR light because biological components in tissue absorb it less. As a result, research into developing fluorescent probes that emit in the NIR has increased. NIR—I, or the first NIR optical window, includes wavelengths between 700 and 950 nm. The second NIR optical window, or NIR-II, covers the wavelength range of 1000 nm to 1700 nm. The attenuation coefficient of biological elements falls even lower within this range, lowering the opacity of tissue and the quantity of light scattering within it. Biological tissue's autofluorescence is likewise decreased by the NIR-II wavelength range, which has better picture quality and a deeper penetration depth than visible light and NIR—I. Research on NIR-II fluorescence probes is currently being hampered by the lack of readily available probe material and the high cost of imaging equipment.

In the research of Mingming Luan et al.[42], a multicolor fluorescent nanoprobe based on AuNPs was designed and synthesized for simultaneously and visually detecting breast cancer cells' proliferation marker Ki-67 mRNA and invasion marker urokinase plasminogen activator (uPA) (Fig. 1). The fluorescence responses of the nanoprobe to Ki-67 and uPA targets were examined to experiment with the ability of the nanoprobe to simultaneously detect the respective targets. The

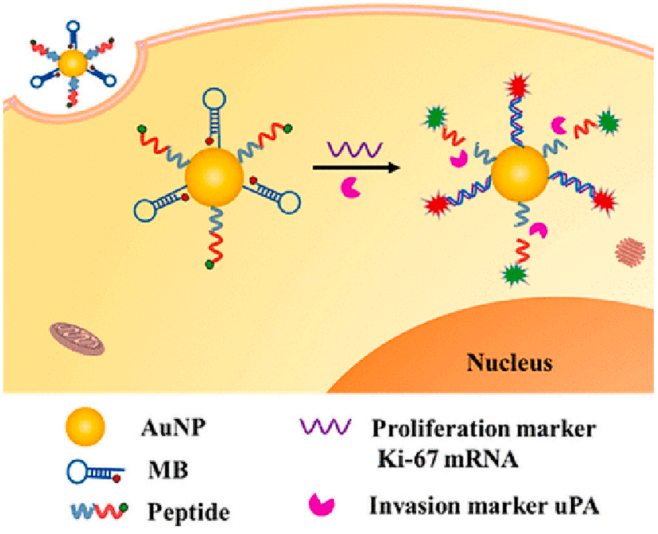

Fig. 1. Schematic Illustration of the Nanoprobe for Detection of Intercellular Ki-67 mRNA and uPA[42].

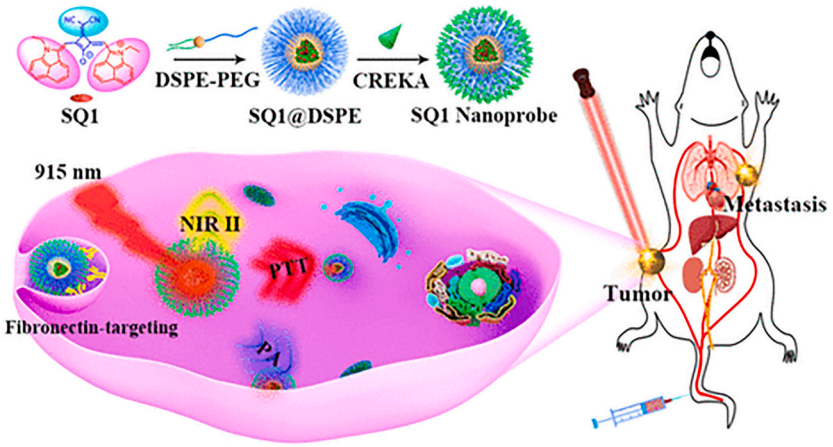

Fig. 2. Nanofunctionalization and molecular engineering of squaraine dye SQ1 for NIR-II/PA bimodal imaging and photothermal ablation of metastatic breast cancer[43].

fluorescence recovery and kinetic profile were observed and the nanoprobe could respond rapidly to the DNA targets in 10 min and uPA targets in 30 min (~~Fig. 2~~). The feasibility of the nanoprobe to detect Ki-67 mRNA and uPA in vivo was evaluated with the fluorescent imaging of the xenograft mouse models injected with the nanoprobe after the mice were treated with curcumin and tamoxifen and the results demonstrated that the nanoprobe was a convenient and reliable way to screen anti-tumor drugs.

Squaraine dyes are a class of organic dyes showing intense fluorescence, typically in the red and NIR region. Squaraines typically include two electron donors and an electron-accepting squaric acid in a donor−acceptor−donor (D − A − D) structure. Defan Yao et al.[43] used a molecular engineering strategy to develop squaraine dyes with NIR-II emission. The squaraine dye SQ1 can be encapsulated as SQ1 nanoprobe through facile nanoprecipitation and targeting peptide decoration, which shows NIR-II/PA bimodal imaging capabilities and favorable photothermal effects. NIR-II imaging in mice showed that the SQ1 nanoprobe was suitable for tumor-targeting and imaging angiography. Furthermore, in both PA imaging and PTT of solid tumors, the SQ1 nanoprobe achieved excellent photothermal conversion under NIR irradiation.

Due to the intrinsic advantages in both photothermal therapy and NIR-II/PA bimodal imaging, the SQ1 nanoprobe possesses good application potential in the theranostics of breast cancer and lung metastasis (Fig. 2).

Nuno Ferreira et al.[44] introduced a label-free nanosensor for the early detection of breast cancer. In this study, *nata de coco* was used to produce bacterial nanocellulose (BC) membrane, and then silver nanoparticles were in-situ-synthesized into BC as Surface-enhanced Raman spectroscopy (SERS) substrates. To examine the synthesized composites as SERS substrates, R6G was used as a test molecule. Rhodamine 6G (R6G) concentrations as low as 10^{-11} M were detected using enhancement factors of 10^4 to $10.^5$ Exosome samples from breast cancer cell cultures MDA-MB-231 and MCF-10A (nontumorigenic breast epithelium) were evaluated on the synthetic substrates, and the resulting Raman spectra were subjected to statistical principal component analysis (PCA). A low-cost, green, label-free diagnosis method with promising applicability in the clinical diagnosis of breast cancer was developed by combining PCA with Raman intravariability and inter-variability in exosomal samples. Using real-time in situ imaging of MMP-2 and uPA, Renhui et al. [45] constructed a fluorescent nanoprobe using a gold-selenium (Au—Se) bond to assess the invasive potential of breast cancer cells.

They functionalized Au NPs with two different selenol-modified short peptide chains via Au—Se bond formation. The other end of the peptide chains was labeled with rhodamine B (RhB) and fluorescein isothiocyanate (FITC), respectively. In the bound state, the two dyes were quenched by Au NPs. In the presence of uPA and MMP-2, the peptide chain labeled with RhB and the peptide chain labeled with FITC could be specifically cleaved by uPA and MMP-2, respectively, triggering fluorescence recovery. Compared with the Au—S nanoprobe, the Au—Se nanoprobe possessed better resistance to glutathione (GSH) interference, making the imaging results more reliable.

Ping Zhou et al.[46] developed a two-color nanoprobe based on Au NPs to screen the influence of different nutrient and oxygen conditions on the invasion and migration of breast cancer cells by detecting the changes in *MMP-2* and *RAB-22a* mRNA levels in living cells. This probe included Au NPs and two molecular beacons (MBs) labeled with two different dye molecules. To detect *RAB-22a mRNA* and *MMP-2 mRNA*, DNA1, and DNA2 were labeled with Alexa Fluor 488 (MB-RAB-22a) and Cy5 (MB-MMP-2), respectively. MCF-7 and MDA-MB-231 cells (human breast cancer cell lines) were incubated with different concentrations of oxygen and nutrients, and then fluorescence imaging assays were used to evaluate invasion and migration.

Leila Eskandari et al.[47] prepared DNA-functionalized AuNPs as the target-specific probes, for detecting RNA of activated leukocyte cell adhesion molecule (ALCAM) gene which is a detectable biomarker in the tumor of patients with breast cancer. Their result showed the detection of different concentraions of ALCAM target by the nanoprobes and the LOD of the method corresponded to 300 fmol/mL of synthetic ALCAM target which proves the method had a high sensitivity. Mohammad Keshtkar et al.[48] designed a nanoprobe with conjugation of AS1411 aptamer on the surface of Fe_3O_4@Au nanoparticles using the gold–sulfur chemistry for specific targeting of mouse mammary carcinoma (4 T1). Thiazolyl tetrazolium (MTT) assay of 4 T1 and HFFF-PI6 cells was used to assess in vitro cytotoxicity of the nanoprobe. For 4 T1 cells, at a concentration of 60 μg/mL, the nanoprobe had cytotoxicity effects, at concentrations from 10 to 45 μg/mL, cell toxicity was low or moderate. MTT results for HFFF-PI6 cells showed that up to 60 μg/mL, the nanoprobe had no cytotoxicity effects.

The cluster determinant 44 (CD44) antigen is a cell-surface glycoprotein involved in cell-cell interactions, cell adhesion, and migration. In humans, CD44, which is a receptor for hyaluronic acid and can also interact with other ligands, such as matrix metalloproteinases (MMPs), collagens, and osteopontin, is encoded by the CD44 gene in Chromosome.

Variations in CD44 are reported as cell surface markers for some breast and prostate cancer stem cells. In breast cancer research CD44+/CD24- expression is commonly used as a marker for breast cancer stem cells (CSCs) and is used to sort breast cancer cells into a population

enriched in cells with stem-like characteristics15 and has been seen as an indicator of increased survival time in epithelial ovarian cancer patients. In women with endometriosis, Endometrial cells show greater expression of splice variants of CD44 and enhanced adhesion to peritoneal cells.

Eunjung Kim et al.[49] used hyaluronic acid (HA)-based nanocontainers containing miR-34a beacons (bHNCs) to design a smart nanoprobe, which is used for the intracellular recognition of miR-34a levels in metastatic breast cancer (Fig. 3). These nanocontainers include 1) binding to CD44receptors, 2) internalization into an endosome, 3) disassembling under pH reduction, leading to the destabilization of endosome membranes, and 4) finally displacement of miR-34a beacons from the nanocontainer permitting them to transport into the cytoplasm and bind intracellular miR-34a. Specifically, HA as a non-immunogenic, nontoxic, and biodegradable biopolymer with a wide range of molecular weight (103 ~ 107 Da) has a high affinity for the cell surface adhesion molecule CD44. Since CD44 molecule is highly available in tumor cells with metastatic phenotype but hardly is seen in healthy tissue, is used as the determinant of progression to the metastatic breast cancer.

Table 2 also provides a summary of nanosensor applications in the early diagnosis of breast cancer.

In breast cancer, electrochemical methods can detect specific biomarkers in blood or tissue samples, aiding in early diagnosis and monitoring of treatment response. Fluorescence techniques enable targeted imaging of breast cancer cells or tumor markers, assisting in precise localization and characterization. Image-based methods assist in analyzing mammograms and other breast images to detect tumors, assess their size, location, and guide treatment planning.

2.3. Colorectal cancer

Colorectal cancer (CRC), also known as colon cancer, bowel cancer, or rectal cancer, is the development of cancer from the colon or rectum.

2.3.1. The biomarkers and detection targets for Colorectal cancer

In the case of colorectal cancer, several biomarkers and detection targets have been identified. Here are some commonly studied biomarkers and detection targets for colorectal cancer:

1. Carcinoembryonic antigen (CEA): CEA is a glycoprotein that is often elevated in patients with colorectal cancer. It can be measured in the blood and is used as a tumor marker to monitor disease progression and response to treatment.
2. Fecal occult blood test (FOBT): This is a non-invasive screening test that detects the presence of hidden blood in the stool, which may be an indication of colorectal cancer or other gastrointestinal disorders. FOBT can be used as an initial screening tool, but it is not specific to colorectal cancer.
3. DNA-based tests: Various DNA-based tests can be used to detect genetic alterations associated with colorectal cancer. These include:
   a. Microsatellite instability (MSI): MSI is a condition characterized by the presence of alterations in the length of microsatellite DNA sequences. It occurs in a subset of colorectal cancers and can be detected using PCR-based tests.
   b. DNA methylation markers: DNA methylation is an epigenetic modification that can be altered in colorectal cancer. Specific DNA methylation markers, such as the methylated form of the SEPT9 gene, can be detected in the blood or stool samples and used as a screening tool.
4. Immunohistochemistry (IHC): IHC involves the use of antibodies to detect specific proteins in tissue samples. In colorectal cancer, IHC can be used to assess the expression of proteins such as MLH1, MSH2, MSH6, and PMS2, which are associated with Lynch syndrome, a hereditary form of colorectal cancer.
5. Circulating tumor DNA (ctDNA): ctDNA refers to small fragments of DNA released into the bloodstream by cancer cells. Detection and analysis of ctDNA can provide information about the genetic alterations present in the tumor and can be used for monitoring disease progression and treatment response.

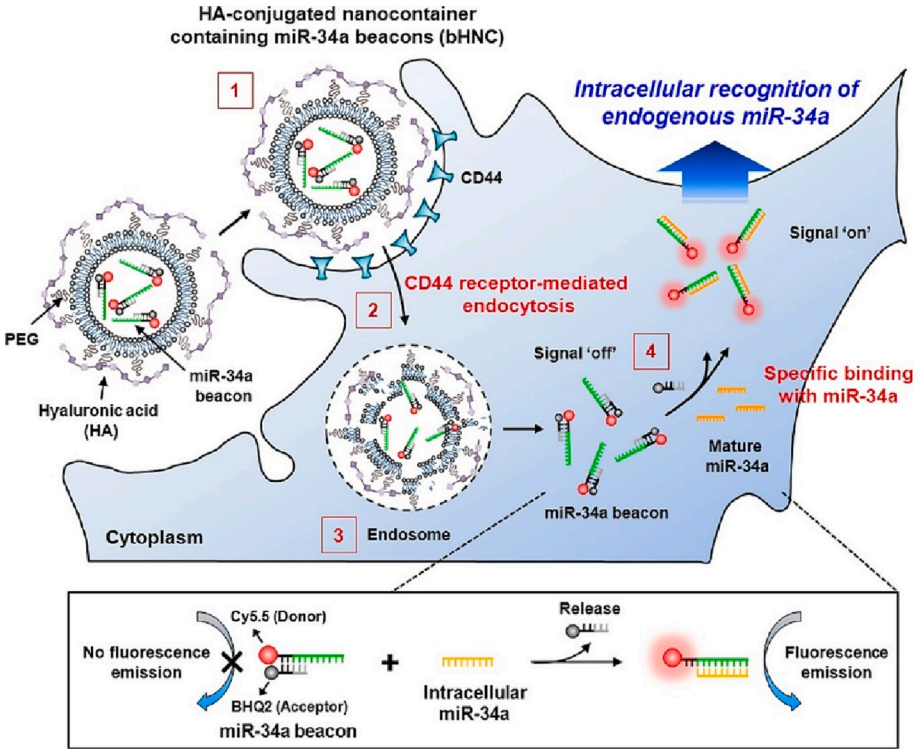

Fig. 3. Schematic illustration of miR-34a beacon delivery system for targeted intracellular recognition of miR-34a based on HA-coated nanocontainers that encapsulate the miR-34a beacons (bHNCs)[49].

Table 2
Applications of nanosensors in the early detection of breast cancer.

No.	Biomarker/Target	Nanomaterials/Methods	Sensitivity/LOD[a]	Specificity	Reference
1	HER2[b]	SPR[c] using signal enhancement with AuNPs[d]	180 pg mL^{-1}	ND[e]	Unai Eletxigerra et al.[50]
2	HER2	SPIO-3-5MF[f]: For HER2 imaging, multifunctional superparamagnetic nanoparticles modified with fluorescein-5-maleimide-labeled DARPin G3 (SPIO-G3-5MF) were produced. Ankyrin repeat protein (DARPin) G3 was constructed as a binding protein with picomolar affinity for HER2.	ND	ND	Dong-Li Li et al. [51]
3	EpCAM[6]	GQDs[g] and MoS_2 nanosheets: A "turn-on" fluorescence biosensor based on GQDs and MoS_2 nanosheets	450 pM	Good	Jingyu Shi et al. [52]
4	HER2	WS_2 NW/TM[h]: The tungsten sulphide nanowire array on Ti mesh (WS_2 NW/TM) was used to create the biosensor.	0.36 ng/mL	1 ng/mL	Xiaoxi Guo et al. [53]
5	MicroRNA159c	Ti_3C_2:CdS nanocomposite: The fluorine-doped tin oxide (FTO) electrode's surface was first covered with Ti3C2:CdS nanocomposite. The SH-miRNA were attached to the electrode surface via the S—Cd bond after the chitosan was removed.	33 fmol.L^{-1}	Good	Shen-Ting Liu et al. [54]
6	HER2	AgNCs[i]: DNA2 containing G-rich sequences and the HER2-binding aptamer (HApt) served as templates for AgNCs.	0.0904 fM	High	Manman Zhang et al.[55]
7	HER2	MnCuInS/ZnS QDs[j]-loaded BSA fluorescence nano-probe: Near-infrared (NIR) emission from a MnCuInS/ZnS QDs-encapsulated BSA nano-probe coupled to the HER2 antibody.	ND	Good	Tianxiang Wei et al.[56]
8	BRCA1 Gene	DNA-mediated Au − Au dimer based SPC-ECL[k]: Au—Au dimer-based SPC-ECL sensor with DNA-mediated surface plasmon coupling.	0.83 fM	Good	Qian Zhang et al. [57]
9	HER2	DNA Ab/AuNPs: Immobilizing polycytosine DNA sequence (dC20) for electrochemical current generation and anti-HER2 antibodies using AuNPs as a supporting matrix.	0.5 pg mL^{-1}	High	Xiaoqing Li et al. [58]
10	MicroRNA-155	H1 and H2 linked to AuNPs: The two hairpin DNA strands, H1 and H2, and PEG were joined to the surface of AuNPs to create the photoacoustic nanoprobes (Au-H1/PEG and Au-H2/PEG).	0.25 nM	Superior	Wenhua Cao et al. [59]
11	MicroRNA-21 MUC1	ECL sensor using H1 and H2 incubated on the TiO_2@Pt	MicroRNA-21: 0.1 fM MUC1: 2.4 fg·mL^{-1}	Remarkable	Yamin Nie et al. [60]
12	CD44	MNFs[l] modified with AgNPs: MNFs were made by self-assembling peptide probes that attracted AgNPs to produce electrochemical signals and offered a significant number of reaction sites to enhance signals.	6 cells/mL	High	Yingying Tang al. [61]
13	MDA-MB-231 and MCF-7	SERS[m] nanoprobes using AuNFs[n] modified with silica and PEG[o]: Gold nanoflowers (AuNFs), which acted as the Raman signal enhancer, were coated with three bioorthogonal Raman reporters having alkyne, azide, or nitrile groups.	Down to fM concentrations	High	Jing Wang et al. [62]
14	H_2O_2 in BT20 and 4 T1	PB/ZnO/COOH-MWNT[p] composite: To improve the signal, PB was electrostatically linked with an electrocatalyst composite made of refluxed zinc oxide nanoparticles coupled to carboxylic acid-	1–21 μM	High	Raja Ram Pandey et al.[63]

(*continued on next page*)

Table 2 (*continued*)

No.	Biomarker/Target	Nanomaterials/Methods	Sensitivity/LOD[a]	Specificity	Reference
		functionalized multiwalled carbon nanotubes (ZnO/COOH-MWNTs).			
15	4 T1 cells	A-ZGCN[q] NPs: The NIRPL imaging is based on Cr^{3+}/Nd^{3+} codoped A-ZGCN nanoparticles	High	ND	Hanghang Liu et al. [64]
16	MicroRNA-21	cDNA[r]@ PDDA[s]@PAA[t]@UCNPs[u]: A dual dye acceptor-based LRET-based upconversion luminescence (UCL) nanosensor.	11.2 pM	Excellent	Lin Yang et al.[65]
17	CA15–3	GO[v]-PEI[w]-CQDs[x]-AuNPs nanocomposite: Ag + and dopamine were subjected to a redox reaction to form the AgNPs-PDA nanocomposite. CQDs were adhered to graphene oxide using polyethylenimine functionalization (PEI-GO) using amide bonds. Au nanoparticles were modified on CQDs-decorated PEI-GO substrates.	0.0017 U/mL	Outstanding	Dongmiao Qin et al.[66]
18	Estrogen receptor alpha (ERα)	AuNPs-based colorimetric aptasensor: Using the aptamer-functionalized aunps' color transition property to detect and measure ER.	0.64 ng/mL	ND	Rajesh Ahirwar and Pradip Nahar[67]
19	BRCA1	Bi_2Se_3-AuNPs biosensor: Bi_2Se_3-AuNPs and GO-AuNPs nanocomposites were synthesized by in situ reduction of $HAuCl_4$ on the surface of 2D nanomaterials.	10^{-18} M	High	Yunfei Bai et al. [68]
20	HER2	MSN–AuNC[y]: Gold nanoclusters confined in mesoporous silica nanoparticles (MSNs) offer an amplified signal system.	Down to 10 cells	Excellent	Mingqiang Li et al. [69]
21	Protein C receptor (PROCR)	TAMRA[z]-AN33/MoS_2 TAMRA-AN33/GO: A 2D fluorogenic material made of a synthetic peptide ligand and self-assembling.	0.76 nM 1.26 nM	Good	Wei-Tao Dou et al. [70]
22	MicroRNA	QDs–AuNP: A biosensor built on the strand-displacement characteristic of polymerase-assisted cycles and functionalization of a quantum dot and Au nanoparticle combination.	33 aM	High	Dongli Chen et al. [71]
23	MicroRNA-21	DNA- AuNPs nanocomposites: A biosensor based on the isothermal strand-displacement polymerase reaction (ISDPR) and DNA-AuNPs nanocomposites bridge.	3.2 aM	Good	Aiping Cui et al. [72]
24	MicroRNA-21	Graphene, polypyrrole, and AuNPs, modified onto a SPCE[aa]: An electrochemical sensor was created by modifying a graphene, polypyrrole, and AuNPs nanocomposite onto an SPCE.	0.020 fM	High	Chammari Pothipor et al.[73]
25	MUC1	Zn-Bp-MOFs[ab]: To improve the ECL responses of zinc meso-tetra(4-sulfonatophenyl) porphine (Zn-TP), Zn-Bp-MOFs were synthesized through coordination.	0.23 pg mL^{-1}	Good	Li-Yan Huang et al. [37]
26	Megestrol acetate (MGA)	FAB-CeO_2NPs/GCMPE[ac]: A functionalized acetylene black-CeO_2NPs nanohybrids modified glassy carbon microspheres paste electrode (FAB-CeO_2NPs/GCMPE) was used to create an electrochemical sensor.	1.30 nM	Good	Hossieny Ibrahim et al.[74]
27	Vascular endothelial growth factor (VEGF)	AP-UCNPs[ad]: Thermal breakdown of the corresponding rare-earth stearate produced UCNPs of the Type α-$NaYF_4$:Yb^{3+}, Er^{3+} with a typical diameter of 6–7 nm. The oleic acid on the UCNPs' surfaces was then replaced with aptamer DNA.	6 pM	95.1%	Jianming Lan et al. [75]
28	MicroRNA	CNPs[ae]: The coupling use of of CNPs resulted in the	3.2 pM	Good	Hongfeng Li et al. [76]

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Table 2 (*continued*)

No.	Biomarker/Target	Nanomaterials/Methods	Sensitivity/LOD[a]	Specificity	Reference
		development of a fluorescence amplified sensing technique for miRNA analysis.			
29	microRNA-21	Cu NCs as luminophore and TiO_2 as coreaction accelerator: An ECL biosensor based on in-situ generation of Cu NCs as luminophore and TiO_2 as coreaction accelerator.	19.05 aM	Excellent	Hongxia Liao et al. [77]
30	MUC1	Colorimetric aptasensor based on trivalent peroxidase-mimic DNAzyme and magnetic NPs.	5.08 nM in buffer and 5.60 nM in 10% serum system	High	Shuwen Liu et al. [78]
31	MDA-MB-231	Photoelectrochemical antifouling immunosensor using BiOBr/FeTPPCl/BiOI as matrix and PAA/ PEG as hybrid antifouling interface.	30 cells·mL^{-1}	Good	Xin Liu et al.[79]
32	HER2	MnO_2 Nanosheets/Au NPs: The dual-mode electrochemical immunosensor was created to use Au@Ag NRs as double signal labels and MnO_2 NSs/Au NPs as substrate materials.	16.7 and 33.3 fg/ml through differential pulse voltammetry (DPV) and chronoamperometry (CA)	High	Qing Ma[80]
33	MicroRNA-21	CDs-CH[af]: Carbon dots-chitosan nanocomposite hydrogels were created by combining carbon dots synthesized from different aldehyde precursors with chitosan and then functionalizing them with a ssDNA probe.	0.03 fM	Good	Susan Mohammadi et al.[81]
34	MCF-7	Bipolar electrode modified with AS1411 aptamer and AuNPs	About 10 cells	High	Hasan Motaghi et al.[82]
35	SKBR-3 cells	silica-based mesoporous material-modified electrode: In situ electrosyntheses of mesoporous silica were used to create a silica-based electrode.	20 cells/mL	Good	Hassan Nasrollahpour et al.[83]
36	MicroRNAs (miRNA-133a, miRNA-10b, let-7b, miRNA-143, miRNA-126, miRNA-1, miRNA-21, miRNA-155, and miRNA-125b)	 Silicon SERS chip: AgNPs in situ grown on silicon wafer (AgNPs@Si)	~1 aM	>85%	Sifan Meng et al. [84]
37	MicroRNA-21	Electrochemical nano-genosensor based on sandwiched AgNPs in PANI[ag] and N-doped graphene	2.5 μA.cm^{-2}/ 0.2 fM	High	Razieh Salahandish et al.[85]
38	HER2	AntiHER2-Fe_3O_4 NPs laid on GCE as platform and antiHER2/Hyd@AuNPs-Fe_3O_4 NPs as label	2.0 × 10^{-5} ng/mL	ND	Mojtaba Shamsipur et al.[86]
39	E-cadherin (sE-cadherin) and soluble N-cadherin (sN-cadherin)	SERS Nanotags using AuNPs	sE-cadherin: 8 cells mL^{-1} sN-cadherin: 4 cells mL^{-1}	Good	Zhen Zhang et al. [87]
40	HER2	BSA-AuNCs-LPs-anti-HER2: The extrusion process was used for producing AuNCs-LPs.	5 cells	Excellent	Yu Tao et al.[88]
41	poly(ADP-ribose) polymerase-1 (PARP-1) in human breast cancer cells of SK-BR-7	CTAB coated AuNRs: An enzyme-free colorimetric technique based on counterion-mediated AuNR aggregation.	0.006 U (0.261 ng)	Good	Shuangshuang Wu et al.[89]
42	CEA	SPR using a Ti_3C_2-MXene-based sensing platform and MWCNTs-PDA-AgNPs signal enhancer.	0.07 fM	Good	Qiong Wu et al. [90]
43	BRCA1	CuS/Eu[ah]: PEG-NH2 was coated on the Ni foam/Eu: Co_3O_4/CuS electrode to provide an antifouling interface for high-sensitivity BRCA1 detection.	0.38 fM	Great	Rui Xu et al.[91]
44	MCF-7	CNSs/P0-FAM[ai] nanocomplex: Fabrication of a fluorescence "turn off/on" aptasensor for the selective detection of MCF-7 breast cancer cells using carbonised glucose CNSs.	25 nM	High	Dandan Yang et al. [92]
45	MUC1	Cy5-tagged S2.2-functionalized silicon nanodot (SiND-S2.2-Cy5) aptasensor: The aptasensor was built by covalently attaching cyanine (Cy5)-tagged aptamer S2.2 to fluorescent silicon nanodot (SiND).	1.52 nM	Remarkable	Yanan Zhang et al. [93]
46	MicroRNA-21	L-Au NPs@ZnO luminol-functionalized Au NPs: An ultrasensitive ECL biosensor was developed for the detection of miRNA-21 using L-Au NPs@ZnO	18.6 aM	Superior	Xiaoli Zhang et al. [94]

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Table 2 (*continued*)

No.	Biomarker/Target	Nanomaterials/Methods	Sensitivity/LOD[a]	Specificity	Reference
		nanoparticles as an ECL probe and dissolved O2 as an endogenous coreactant.			
47	MUC1	AuNPs@Cu_7S_4@Cu/Mn-AzoPPOP-HP2: An inorganic-organic polymer hybrid mimic peroxidase (AuNPs@Cu7S4@Cu/Mn-AzoPPOP) and catalytic hairpin assembly (CHA) were used to provide a label-free and dual-amplified electrochemical bioanalysis for ultrasensitive detection of mucin 1 (MUC1).	0.72 fg/mL (DPV) and 0.82 fg/mL (CA)	High	Huijuan Zhao et al. [95]
48	CA15–3, CA125 and CEA	Ag NPs immobilized onto the microfluidic channels: A microfluidic biosensor using immobilized Ag NPs on the microfluidic channels to generate a SERS-active substrate.	0.0001 U/mL	Excellent	Zhihua Zheng et al. [96]
49	CA15–3	Enzyme-mimetic AuNCs[aj]: AuNCs were attached on the outer layer antibody to catalyse the decomposition of hydrogen peroxide used to convert HAuCl4 into AuNPs.	7.52×10^{-14} U/mL	ND	Qian Zhao et al. [97]
50	microRNA-21 and microRNA-34a	AuNS@Ag[ak]: The "OFF-to-ON" SERS inverse Molecular Sentinel (iMS) nanoprobe is being used as a homogenous assay for multiplexed detection of miRNAs in a single sensing platform.	ND	ND	Hsin-Neng Wang et al.[98]
51	EpCAM	AgNPs-PVA[al]: Silver nanoparticles coated with polyvinyl alcohol (AgNPs-PVA) were created and employed as a trapping agent in a microfluidic immunosensor based on anti-EpCAM recombinant antibodies. The concentration of captured EpCAM is then electrochemically measured using an anti-EpCAM antibody coupled with HRP.	0.8 pg/ml	High	Karina Bravo et al. [99]
52	Let-7a and miRNA-21	Nucleic acid-functionalized MOF-based homogeneous electrochemical	Let-7a: 3.6 fM miRNA-21: 8.2 fM	High	Jiafu Chang et al. [100]
53	mRNAs[am]	A four-color nanoprobe based on AuNPs and molecular beacons	ND	ND	Wei Pan et al.[101]
54	CD24	CD24-PEGylated AuNPs: To increase the stability of the Au NPs and to provide bio modification sites for antibody immobilization, Au NPs were synthesized and coated with PEG chains.	ND	ND	Mona Fazel-Ghaziyani et al. [102]
55	PSA and CA15.3	Label-free nanosensors: In <20 min, two model cancer antigens were specifically and quantitatively detected from a 10 ml sample of whole blood.	0.9 pg/ml	Good	Eric Stern et al. [103]

[a] LOD: Limit of Detection.
[b] HER2: Human Epidermal Growth Factor Receptor-2.
[c] SPR: Surface Plasmon Resonance.
[d] AuNPs: Gold Nanoparticles.
[e] ND: Not-determined.
[f] SPIO-3-5MF: Superparamagnetic nanoparticles modified with fluorescein-5-maleimide-labeled DARPin G3.
[g] EpCAM Epithelial cell adhesion molecule.
[h] WS_2 NW/TM: Tungsten sulfide nanowire array on Ti mesh.
[i] NCs: Nanoclusters.
[j] QDs: Quantum dots.
[k] SPC-ECL: surface plasmon coupling electrochemiluminescence.
[l] MNFs: Multifunctional nanofibers.
[m] SERS: Surface-enhanced Raman scattering.
[n] AuNFs: gold nanoflowers.
[o] PEG: polyethylene glycol.
[p] PB/ZnO/COOH-MWNT: Refluxed ZnO NPs tethered to carboxylic acid functionalized multiwalled carbon nanotubes.
[q] A-ZGCN NPs Cr^{3+}/Nd^{3+} codoped $ZnGa_2O_4$.
[r] LRET: luminescence resonance energy transfer, ^{18}cDNA: Complementary DNA
[s] PDDA: poly(diallyldimethylammonium chloride).
[t] PAA: poly(acrylic acid).
[u] UCNPs: Upconversion nanoparticles.
[v] GQDs: Graphene Quantum Dots.
[w] PEI: Polyethylenimine.
[x] CQDs: Carbon Quantum Dots.

[y] MSN: Mesoporous silica.
[z] TAMRA Tetramethyl-rhodamine.
[aa] SPCE: screen-printed carbon electrode.
[ab] Zn-Bp-MOFs: Zn-based metal organic frameworks with pyridine.
[ac] FAB-CeO_2NPs/GCMPE: functionalized acetylene black–CeO_2NPs nanohybrids modified glassy carbon microspheres paste electrode.
[ad] AP-UCNPs: UCNPs modified with auxiliary probe.
[ae] CNPs: Carbon nanoparticles.
[af] CDs-CH: CDs-chitosan nanocomposite hydrogel.
[ag] PANI: Polyaniline.
[ah] CuS/Eu: Co3O4/Ni foam electrode.
[ai] CNSs/P0-FAM Carbon nanosphere-based fluorescence aptasensor.
[aj] AuNCs gold nanoclusters.
[ak] AuNS@Ag: silver-coated gold nanostars.
[al] PVA: polyvinyl alcohol.
[am] mRNA: Messenger RNA.

6. Other biomarkers: Several other biomarkers are being investigated for their potential role in colorectal cancer detection and monitoring. These include microRNAs, long non-coding RNAs, and specific proteins like Guanylyl Cyclase C (GCC) and KRAS mutations.

The main methods for diagnosis of colon cancer are serological markers, radiological techniques, endoscopy and biopsy. These strategies have several advantages but they are not able to achieve very early diagnosis, which requires very sensitive and specific analytical methods.

Based on a covalently modified anti-human epithelial cell adhesion molecule (EpCAM) antibody nanoparticle, Liang Tao et al. [104] created a sensitive and specific sensor for colon cancer colo205 cells combining fluorescence microscopy imaging and flow cytometer (FCM). They used $NaIO_4$ oxidation and the conventional glutaraldehyde methods for the covalent immobilization of anti-EpCAM monoclonal antibodies onto core-shell silica nanoparticles. To compare these two methods, they used fluorescence microscopic imaging. Their result showed that the $NaIO_4$ oxidation approach preserves antibody activity better than the glutaraldehyde procedure. Their results also showed that the nanosensor could increase the signal intensity obviously and distinguish three kinds of target cells (colo205, sw480, and NCM460) well.

Kelly E. van Keulen et al.[105] reported that VOCs in breath could potentially serve as a noninvasive diagnostic biomarker for the detection of advanced CRC and adenomas. They collected five hundred and eleven breath samples using an e-nose from adult colonoscopy patients, without inflammatory bowel disease or (previous) malignancy.

Cytidine has been recognized as an early biomarker of colon cancer. Yuan Xiang et al.[106] developed a highly sensitive Fe_3O_4/Au/Ag_5 NPs-based SERS method to determine cytidine in urine for screening colon cancer risk in an early stage. First, they removed urea using the adopted diazo chemical reaction because it would interfere Raman's detection of cytidine. According to their result, the lowest detectable concentration of cytidine could reach 1 nM.

Payal Gulati et al.[107] fabricated a genosensor using vertically-aligned multiwall carbon nanotubes (VA-MWCNTs)-based electrodes for an early diagnosis of CRC by targeting a specific DNA sequence, carcinoembryonic antigen-related cell adhesion molecule (CEACAM5) which is a glycoprotein, a specific tumor marker for colorectal cancer. In this study, chemical vapor deposition was used to synthesize VA-MWCNTs and the nanotube patterns were transferred from solid Si/SiO_2 substrate to flexible polyethylene terephthalate (PET) substrate by hot compress method. They also optimized the probe binding conditions and the electrode's electrochemical condition to improve the efficiency of the genosensor. To investigate the hybridization event on the electrode material, the cyclic voltammetry was obtained by changing the concentration of the target DNA and the sensor showed a LOD of 920 nM concentration of DNA.

Ayemeh Bagheri Hashkavayi et al.[108] developed electrochemical aptasensor by fabricating an aptamer–cell–aptamer sandwich architecture on an SBA-15-3-aminopropyltriethoxysilane (SBA-15-pr-NH_2) and AuNPs modified graphite screen printed electrode (GSPE) surface for the early diagnosis of CT26 cancer cells. In this study, SBA-15, a kind of mesoporous silica was synthesized and functionalized with 3-aminopropyltriethoxysilane and AuNPs were electrochemically deposited on the SBA-15-pr-NH_2 modified GSPE surface. The results of cyclic voltammetry and electrochemical impedance spectroscopy demonstrated that the nanosensor could detect CT26 cells in the concentration ranges of 10–1.0×10^5 cells/ml and 1.0×10^5–6.0×10^6 cells/ml, respectively.

Mucin-1 (MUC1), an essential transmembrane glycoprotein, was regarded as a promising biomarker for colon, breast, ovarian, and lung cancers and can strongly hybridize with aptamer DNA (aptDNA) of double-stranded DNA (dsDNA, generated by aptDNA and linked DNA (L-DNA)) to rerelease free L-DNA. In a study by Li-Yan Huang et,[37] altrimeric acid and 4,4-dipyridyl were used as the linking agent, to chelate Zn^{2+} with trimeric acid to form Zn-based metal-organic frameworks with pyridine (Zn-Bp-MOFs), which were then aminated with APTES and finally grafted with zinc meso-tetra(4-sulfonatophenyl) porphine (Zn-TP) by sulfonamide bonds. This biosensor was used for detetction of MUC1 and showed a broad dynamic linear range (1 pg mL^{-1}–10 ng/mL), the LOD down to 0.23 pg mL^{-1}, excellent stability, and selectivity, as well as great recovery in the diluted serum samples.

In colorectal cancer, electrochemical methods can detect specific biomarkers in blood or fecal samples, aiding in early diagnosis and monitoring of treatment response. Fluorescence techniques enable targeted imaging of colorectal cancer cells or tumor markers, assisting in precise localization and staging. Image-based methods assist in analyzing colonoscopy or imaging studies to detect tumors, assess their size, location, and guide treatment planning.

2.4. Other cancers

Liver cancers are malign tumors that grow inside or on the surface of the liver. Liver tumors are discovered by medical imaging (often by accident) or present themselves symptomatically as abdominal pain, abdominal mass, nausea, jaundice, or liver dysfunction. It is important to distinguish liver cancers from liver metastases, which originate in another organ of the body and migrate to the liver. Liang Tao et al.[109] developed an ultrabright fluorescent mesoporous silica nanoparticle (FMSN) combined with anti- CD112 monoclonal antibodies and with anti-CD155 monoclonal antibodies by the $NaIO_4$ oxidation method to detect liver cancer SMMC-7721 and HHCC cells, respectively. A three-step hydrolysis method was used to synthesize the FMSNs. Based on fluorescence microscopy imaging, modified FMSNs were able to clearly distinguish between CD112 and CD155 on the surface of liver cells. Furthermore, in vivo imaging in mice was used to evaluate the performance of the modified FMSN and the results demonstrated that the nanosensors could target tumor tissue in mice.

>238,000 patients are diagnosed with ovarian cancer worldwide, a disease that is responsible for >151,000 deaths each year. In the United States, this disease ranks top among gynecologic malignancies and is the sixth most common cause of cancer-related deaths in females. These terrible statistics are because the majority of cases are discovered at an

advanced stage. >60% of diagnoses are at stage III or later which is higher than any other form of cancer. The average 5-year survival rate across all populations is only 46%. If the diagnosis occurs at stage I, however, the 5-year survival rate is 92%. Current screening methods include transvaginal ultrasonography and cancer antigen 125 [CA-125 or mucin 16 (MUC16)] serum testing. However, the U.S. Preventive Services Task Force recommends against these methods because of poor sensitivity, and high false-positive rates for detecting small lesions. These methods neither reduce mortality nor change the patient outcome.

Patients with high-grade serous ovarian carcinoma (HGSC) exhibit poor 5-year survival rates, which may be remarkably improved by early-stage diagnosis. The U.S. Food and Drug Administration–approved biomarkers for HGSC, HE4 (human epididymis protein 4) and CA-125 (cancer antigen 125) do not generally appear at detectable levels in the serum until the advanced stages of the disease. Consequently, new methods are needed for early-stage detection to reduce the burden of ovarian cancer. In the research of Ryan M. Williams et al.[110], a carbon nanotube-based sensor to noninvasively detect the ovarian cancer biomarker HE4 in vivo was prepared (Fig. 4). SWCNTs was used to transduce the binding of HE4 to an immobilized antibody via modulation of the intrinsic NIR emission of the nanotubes. The nanotube-antibody complexes could detect HE4 in ascites and serum from patients with ovarian cancer.

Sibel Büyüktiryaki et al.[111] applied an imprinting method for the detection of CA 125. Methacryloyl antipyrine terbium (III) [$(MAAP)_2$-Tb (III)] and methacryloyl antipyrine europium (III) [$(MAAP)_2$-Eu(III)] were used as new metal-chelating monomers by metal coordination. To find CA 125, phosphoserine (PS) was used as a template. PS imprinted CNT and Fe_2O_3 nanoparticles (SPN) have cavities that are selective for CA 125. LOD of PS imprinted CNT nanosensor for PS and CA 125 were 1.77 10^{-10} M and 0.49 UmL^{-1}, respectively. The feasibility of the nanosensors for clinical applications has been investigated by spiked human serum samples with different concentrations of CA 125 (in pH 7.4 PBS).

Prostate cancer (CaP) is the third most common type of cancer in men with the age over 50 years and one of the major health concerns in the world. Screening and early diagnosis methods such as prostate-specific antigen (PSA) are one of the common methods to reduce the mortality rate of prostate cancer, but there is a need for improved biomarkers that can identify aggressive disease. Zahra Akbari jonous et al.[112] designed an electrochemical biosensor for the detection of PSA using a sandwich-type electrode composed of anti-total PSA monoclonal antibody, reduced graphene oxide/ gold nanoparticles (RGO/AuNPs), and anti-free PSA antibody. The nanosensor showed excellent selectivity for PSA in comparison to the other tumor markers such as CEA, BHCG, CA125, Alb, and CA19–9. The LOD was 0.2 and 0.07 ng/mL for total and free PSA antigen, respectively.

The work presented by Lingyun Xu et al.[113] developed a magneto-nanosensor (MNS) based multiplex assay to measure protein and auto-antibody biomarkers from human serum for CaP diagnosis. They selected 4 candidate autoantibodies against 4 proteins (PARK7, TARDBP, TLN1, Talin 1, and CALD1) that were shown to be associated with CaP and paired them with total PSA (includes both complexed and uncomplexed forms) and free- PSA (uncomplexed to chaperone proteins) to develop a panel for the detection of CaP. As a class of enzymes, proteases play a key role in every hallmark of cancer; their activity might be used as a biomarker. Jaideep S. Dudani et al.[114] designed an injectable activity-based nanosensors (ABNs) to measure protease activity in vitro using in vivo urinary readouts and fluorescence. They applied this nanosesnor array in xenograft mouse models to classify aggressive CaP.

Thyroid cancer incidence rates have increased rapidly worldwide in the past few decades in comparison with other types of cancers. The most common type of thyroid cancer is papillary thyroid carcinoma (PTC) followed by follicular thyroid carcinoma (FTC). While FTC accounts for just 10%–15% of thyroid cancer cases, it is a more aggressive disease than PTC and is associated with poorer long-term patient survival, necessitating timely diagnosis and treatment. Epidermal growth factor receptor (EGFR) is a cell surface tyrosine kinase receptor that is responsive to extracellular growth factors, regulating key oncogenic processes including survival, proliferation, migration, and metabolic activity. EGFR dysregulation is a hallmark of many cancer types including head, breast, neck, lung, and pancreatic cancer, and it is thus a valuable biomarker that can help discriminate between malignant and benign lesions. Importantly, FTC nodules exhibit increase EGFR expression relative to follicular thyroid adenoma (FTA) nodules. Yang Gui et al.[115] prepared a targeted affibody-Au-Tripod nanoprobe to facilitate the targeted photoacoustic imaging (PAI) of epidermal EGFR-positive cells and tumors in vivo in mice and yielded strong PA signals.

Pancreatic cancer begins in the tissues of the pancreas, an organ in your abdomen behind the lower part of the stomach. In addition to assisting digestion, the pancreas releases hormones that regulate blood sugar level. Mingmin Wu et al.[116] designed a nanosensor for the detection of trypsin as a biomarker of pancreatic diseases or pancreatic cancer based on the fluorescence resonance energy transfer (FRET) between UCNP and AuNP. A trypsin-sensitive peptide DDDDARC was used to link UCNP and AuNP and form the non-fluorescent UCNP-peptide-AuNP nanosensor. The nanosensor showed great selectivity and sensitivity for trypsin and its inhibitors with a LOD of 4.15 ng/mL for trypsin.

Other applications of nanosensors in the detection of cancer biomarkers are also summarized in Table 3.

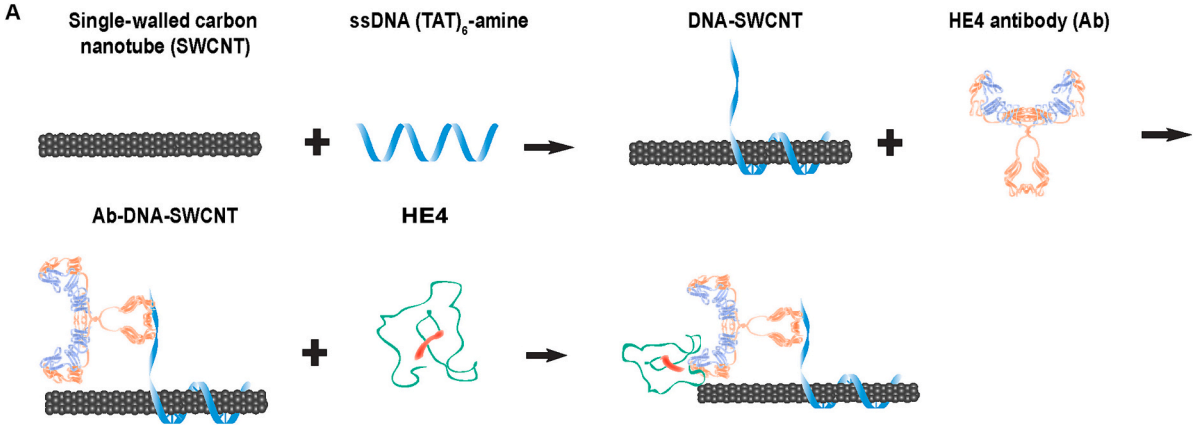

Fig. 4. Design and in vitro characterization of optical nanosensor for HE4.[110].

Table 3
Other applications of nanosensors in the detection of cancer biomarkers.

No.	Biomarker/Target	Nanomaterials/Methods	Sensitivity/LOD[a]	Specificity	Reference
1	MT1-MMP activity[b]	AuNRs[c]-ActFP[d]	Good	NA[e]	Minhee Ku et al.[117]
2	Sialoglycan	The coupling of fluorescent proteolytic enzyme-specific cleavable peptides with gold nanorods results in an NIR fluorogenic nanosensor based on the nanoparticle surface energy transfer effect. MPBA[e] decorated AgNPs	8.9 μg/mL	NA	Lijia Liang et al.[118]
3	Cancer exosomes	Based on chemical recognition between phenylboronic acid and sialoglycans at physiological conditions, an MPBA-based SERS nanosensor was developed to analyze sialoglycan levels and dynamic expression processes of distinct cell types in situ. The MPBA adorned AgNPs were used to create this nanosensor. ASP[f]	0.24 μg/mL	NA	Yan Lyu et al.[119]
4	HE4, CA-125, and YKL-40	A luminescent nanosensor made up of a quenchertagged aptamer electrostatically complexed with an NIR ASPN. DNA-SWCNT-based photoluminescent A DNA-SWCNT-based photoluminescent sensor array was utilised to train machine learning models to identify gynecologic cancer biomarkers HE4, CA-125, and YKL-40 in laboratory-generated samples and patient fluids.	100% for HE4 and CA-125 91% for YKL-40	Moderate	Zvi Yaari et al.[120]
5	Single-Nucleotide Polymorphism	QD-mediated FRET	5.41×10^{-20} M	Good	Chen-chen Li et al.[121]
6	HepG2-MVs[g]	A QD-mediated FRET nanosensor with multipleprimer generation rolling circle amplification (MPG-RCA) for sensitive SNP detection in cancer cells. AAP-GFET[h]	84 particles/μL	High	Ding Wu et al.[122]
7	MT1-MMP Activity	A dual-aptamer modified RGO field-effect transistor (AAP-GFET) nanosensor coated with AuNP for the label-free, selective, and sensitive quantification of HepG2-MVs (HepG2-MVs). QD-FRET[i]	High	High	Eddie Y. Chung et al.[123]
8	Fe^{3+}	A QD-FRET nanosensor for observing MT1-MMP activity at the cell membrane. A bended peptide with several motifs was created to place the FRET pair near enough together to facilitate energy transfer, which can then be cleaved by active MT1-MMP, resulting in FRET alterations and the exposure of cell penetrating sequence. RBD-GQDs[j]	0.02 μM	High	Ruihua Guo et al.[124]
9	GSH[k]	A turn-on orange-red fluorescent nanosensor based on RBD-GQDs functionalized with rhodamine B derivatives ACD-AuNPs[l]	6 nM	Very High	Krishnendu Das et al.[125]
10	Thioredoxin Reductase	Nanohybrid made of ACD-protected AuNPs. ACD directly capped AuNP by anionic surface functionalization, resulting in stable aqueous AuNP dispersion. Naphthalimide Coupled FRET	7.2×10^{-8} M	High	Jagpreet Singh Sidhu et al.[126]
11	Tumor-derived exosome	To monitor the activity of thioredoxin reductase, the FRET mechanism was built between CDs and naphthalimide. hMFEX[m] This hMFEX nanosensor includes two critical modules: target exosome separation using antibody-functionalized magnetic beads and improved fluorescence measurement using supramolecular interactions of aptamer-induced DNA three-way junctions with AIEgens and GO in a homogeneous solution.	6.56 × 104 particles/μL	High	Bo Li, et al.[127]
12	EV-miRNAs[n]	DNA nanowire guided-catalyzed hairpin assembly	95.2%	86.7%	Ye Zhang et al.[128]
13	mRNA	A nanoprobe for profiling EV-miRNAs based on DNA nanowire guided-catalyzed hairpin assembly (NgCHA). Dextran-coated GO nanocolloid	169 pM	High	Seong Min Ahn et al.[129]
14	Leaky vasculature	A fluorescent nanosensor for monitoring cancer-related mRNAs in live cells via the Wnt/−catenin signalling pathway. Fluorescent Nanoprobes	High	NA	Britto S. Sandanaraj et al.[130]
15	Cyt c[o]	A fluorescent nanoprobe used as a functional biomarker to detect increased vascular permeability in cancer/arthritis disease models. N-doped CD[p] A new label-free N-doped CD-based nanosensor for fluorescence activation imaging of Cyt c release during cell death.	0.3 nM	High	Haijuan Zhang et al.[131]

(*continued on next page*)

Table 3 (*continued*)

No.	Biomarker/Target	Nanomaterials/Methods	Sensitivity/LOD[a]	Specificity	Reference
16	PTMs[q]	Peptide-templated AuNP A peptide-templated AuNP nanosensor for the detection of numerous posttranslational modification (PTM) enzymes at the same time.	28 pM for histone deacetylase (HDAC) 0.8 pM for protein tyrosine phosphatase 1B (PTP1B)	Good	Dandan Zhang et al. [132]
17	Exosomes	MoS_2–MWCNT Using molybdenum disulfide-coated MWCNTs (MoS2-MWCNT) as a fluorescence quenching material and an exosome protein biomarker (CD63) as a target element.	14.8×10^5 particles per mL	High	Mahnoush Tayebi et al. [133]
18	GSH	CNPs[r]@MnO_2–AgNPs The CPs@MnO_2 nanocomposite was created by capping MnO_2 onto carbon nanoparticles using an ultrasonic in situ redox process. AgNPs with fluorescence were produced in a silver-mirror-like reaction utilizing BSA as both a template and a reductant, and then electrostatically attached onto the surface of CPs@MnO_2 to form the CPs@MnO_2-AgNP nanocomposite.	0.55 μM	High	Qi Wang et al.[134]
19	Fe^{3+}	Silicon-doped CQDs In vitro and in vivo, an on-off-on fluorescent nanosensor based on CDs was developed for Fe^{3+} detection and selective imaging of malignant cells.	16 nM	High	Ge Gao et al.[135]
20	Epidermal Growth Factor Receptor	GMR[s] A giant magnetoresistive (GMR) nanosensor-based circulating tumor DNA (ctDNA) Epidermal Growth Factor Receptor (EGFR) mutational test.	87.5%/ 0.01%	100%	Jared C. Nesvet et al. [136]
21	miR-21, miR-155	AuNP A rapid and colorimetric nano-biosensor that does not require amplification and is based on non-crosslinking Aunanoprobes.	1 ng/μL	High	Hamidreza Mollasalehi and Elmira Shajari[137]
22	PSA[t] and CEA[u]	AuNPs Cancer biomarkers in serum may be detected at ultralow concentrations using a sandwich test that combines mechanical and optoplasmonic transduction.	1×10^{-16} g ml^{-1}	Good	P. M. Kosaka et al.[138]
23	CD133	Anti-CD133 mAb-nano-MSN[v] Based on the particular interaction between glioblastoma CSCs' cell-membrane marker antigen CD133 and its increased anti-CD133 monoclonal antibody (mAb), a smart immunomagnetic nanosensor for molecular imaging of targeted glioblastoma cancer stem cells (CSCs) has been created.	ND	ND	Xueqin Wang et al.[139]
24	p53 gene and PSA	MOF[w]@AuNP@GO[x] FAM-labeled single-stranded DNA (ssDNA) was used to test the MOF@AuNP@GO's ssDNA absorption affinities and fluorescence quenching abilities. Then, for the identification of the p53 gene and prostate specific antigen (PSA), two unique dye-labeled ssDNA and aptamer probes were created.	p53 gene: 0.005 nM PSA: 0.01 ng/mL	High	Xiaolin Huang et al. [140]
25	HE4, CA-125, and YKL-40	DNA-SWCNT–based photoluminescent A perception-based platform based on an optical nanosensor array that detects numerous protein biomarkers in biofluids using machine learning techniques.	High	High	Zvi Yaari et al.[120]
26	AA[aa] and GSH	SiNP[z]/$Fe3^+$ A fluorescent nanosensor for imaging intracellular reducing chemicals such as AA and GSH at the same time.	Excellent	High	Chunrong Li et al.[141]
27	Exosomes	Au NBP[ab]@MnO_2 nanosheets Exosome-triggered competitive reaction and etching of gold nanobipyramid@MnO2 nanosheet nanostructures (Au NBP@MnO2 NSs) are the major steps in the sensing technique.	1.35×10^2 particles μL^{-1}	Good	Yingzhi Zhang et al. [142]
28	CEA	TiO_2 Nanotubes Functionalized Paper-Based A cascaded photoactive interface made of tidy TiO_2 nanotube arrays, Pt NPs, and N-CDs was inserted into paper fibres, resulting in a signal-on PEC state.	0.48 pg mL^{-1}	High	Li Li et al.[143]
29	H_2O_2	v-AuNWs/PDMS[ac] v-AuNWs/PDMS is a stretchable electrochemical cell-sensing platform based on vertically aligned gold nanowires embedded in PDMS.	250 mA/cm^2M^{-1}/ ~12 μM	Good	Quanxia Lyu et al.[7]
30	PSA	TPE[ad]-In-PSA@Au A novel tetraphenylethylene (TPE) appended organic fluorogens and reveal their unique Raman fingerprinting reflected by SERS upon adsorption on nanoroughened gold surface as a new insight in addition to their prevalent aggregation-induced emission (AIE) and aggregation-caused quenching (ACQ) phenomena were discovered.	0.5 ng	ND	Adukkadan N. Ramya et al.[144]

[a] LOD; limit of detection.
[b] MT1-MMPs: Membrane-anchoredmembranetype1-matrixmetalloproteinases.
[c] AuNRs: gold nanorods.
[d] ActFP: activatable fluorogenicpeptide.
[e] NA: not applicable.
[f] MPBA 4-ercaptophenylboronic acid.
[g] ASP afterglow semiconducting polyelectrolyte.
[h] HepG2-MVs: Hepatocellular carcinoma-derived cancerous microvesicles.
[i] AAP-GFET AuNP-decorated dual-aptamer modified reduced graphene oxide field-effect transistor.
[j] QD-FRET: quantum-dot-based fluorescence resonance energy transfer.
[k] RBD-GQDs: Rhodamine B derivative-functionalized graphene quantum dots.
[l] GSH: Glutathione.
[m] ACD-AuNPS: anionic carbon dots protected gold nanoparticle.
[n] hMFEX: Homogenous magneto-fluorescent exosome.
[o] EV-miRNAs: Extracellular vesicle-associated miRNAs.
[p] Cyt c: cytochrome *c*, ^{17}N-doped CD Nitrogen doped carbon quantum dots.
[q] PTMs Protein post-translational modifications.
[r] CNPs: carbon nanoparticles.
[s] GMR: Giant magnetoresistive.
[t] PSA: prostate specific antigen.
[u] CEA: carcinoembryonic antigen.
[v] mAb-nano-MSN: mAb-conjugated nanoscale magnetic sensor.
[w] MOF: Metal-organic frameworks.
[x] GO: graphene oxide.
[z] SiNP: silicon nanoparticles.
[aa] AA: Ascorbic acid.
[ab] Au NBP: gold nanobipyramid.
[ac] v-AuNWs/PDMS: vertically aligned gold nanowires embedded in PDMS.
[ad] TPE: tetraphenylethylene.

3. Conclusions and future directions for nanosensors

This study provides a summary of recent developments in cancer diagnostics using nanotechnology. The development of nanotechnology-based tests for cancer diagnosis has received a lot of attention over the past ten years. A variety of NP-based assays demonstrated improvements in terms of selectivity and sensitivity compared to the currently available cancer diagnostics in the clinic or provided completely new capabilities that were not possible with conventional methods. By enabling early detection, these developments will increase the survival rate of cancer patients. These developments could also be used to track the growth of cancer and how it responds to therapy, which could aid in the creation of more effective cancer treatment plans. The last ten years have seen significant advancements in the field of nanotechnology-based cancer diagnostics, and our knowledge of it has grown significantly. Nanotechnology-based cancer detection is about to enter the clinic, even though only a small number of NP-based assays have progressed to clinical trials. This is due to strong cooperation among researchers, engineers, and physicians. Nanotechnology offers excellent prospects to enhance cancer diagnosis, which will ultimately increase the survival rate of cancer patients because of its high sensitivity, specificity, and multiplexing measuring capacity. In conclusion, the expanding field of study focused on the creation of nanodevices is having and will continue to have a major influence on the creation of nanosensors for the early detection of cancer and the monitoring of therapeutic drugs. Nanosensors have made significant advancements in various fields, including healthcare, environmental monitoring, and industrial applications. However, they still face several challenges that limit their widespread adoption. Here are some of the main challenges associated with current nanosensors and potential ways to improve them:

- Sensitivity and Detection Limits: Enhancing the sensitivity and detection limits of nanosensors is crucial for detecting low concentrations of analytes. Improvements can be made by optimizing the choice of materials, developing novel transduction mechanisms, and exploring advanced signal amplification techniques.
- Selectivity and Specificity: Nanosensors often encounter challenges in distinguishing between similar analytes or suppressing interference from the sample matrix. Incorporating highly selective recognition elements, such as specific biomolecules or functionalized nanoparticles, can improve selectivity and specificity.
- Stability and Durability: Nanosensors should be stable and durable, especially in harsh environments or during long-term use. Researchers can focus on developing robust nanomaterials, protective coatings, or encapsulation strategies to enhance the stability and lifespan of nanosensors.
- Scalability and Cost-Effectiveness: Manufacturing nanosensors on a large scale with consistent performance and at a reasonable cost is a challenge. Streamlining fabrication processes, exploring scalable nanomaterial synthesis techniques, and leveraging economies of scale can help address these challenges.
- Integration and Miniaturization: Integrating nanosensors into complex systems or devices, and achieving miniaturization, is essential for their practical applications. Advances in microfabrication techniques and nanomaterial integration methods can facilitate the seamless integration of nanosensors into various platforms.
- Biocompatibility and Safety: In biomedical applications, ensuring the biocompatibility and safety of nanosensors is crucial. Conducting comprehensive toxicity studies and utilizing biocompatible materials are important steps towards addressing these concerns.
- Power Supply and Energy Efficiency: Nanosensors often require a power source, and optimizing power supply and energy efficiency is essential for their long-term operation, especially in remote or implantable applications. Exploring low-power design strategies and energy harvesting techniques can help mitigate power-related challenges.
- Data Handling and Interpretation: Nanosensors generate large volumes of data, requiring efficient data handling, processing, and interpretation. Developing advanced algorithms, data analytics tools, and machine learning techniques can facilitate real-time analysis and extraction of meaningful information from nanosensor data.

- Standardization and Regulatory Frameworks: Establishing standardized protocols and regulatory frameworks for nanosensors is crucial for ensuring their reliability, reproducibility, and safety. Collaborative efforts among researchers, industry, and regulatory agencies can help in defining guidelines and standards for nanosensor development and deployment.
- Real-World Integration: Bridging the gap between laboratory research and real-world applications remains a challenge. Collaborations between academia, industry, and end-users can facilitate the translation of nanosensor technologies into practical solutions addressing specific societal needs.

By addressing these challenges, researchers and engineers can continue to improve nanosensors, expanding their capabilities and enabling their broader adoption in various fields.

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Consent for publication

Consent for publication has been obtained.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

Data availability

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