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Review Article

Carbon nanomaterials: use in electrochemical biosensors for early diagnosis of cancer

Nanomateriales de carbono: uso en biosensores electroquímicos para el diagnóstico temprano del cáncer

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Abstract

Introduction: Cancer is one of the leading causes of mortality worldwide, and its early detection improves survival rates. Conventional methods are costly, invasive, and time-consuming. Electrochemical biosensors have emerged as an efficient alternative for rapidly and accurately detecting cancer biomarkers.
Objective: To review the use of carbon nanomaterials in electrochemical biosensors for early cancer detection, highlighting their properties, advantages, and challenges in biomedical applications.
Methodology: A search was conducted in Scopus and Web of Science for articles published in English since 2018. Search equations with key terms were used, and inclusion and exclusion filters were applied. The selected studies were systematically organized and analyzed according to the type of carbon nanomaterial used.
Results: Carbon nanomaterials enhance the sensitivity and selectivity of electrochemical biosensors, enabling biomarker detection at very low concentrations. Graphene and reduced graphene oxide stand out for their high conductivity and ease of functionalization.
Conclusions: The incorporation of carbon nanomaterials in electrochemical biosensors contributes to early cancer detection. However, further research is needed to improve the technology and facilitate its transition to clinical settings.

Keywords: Biomarker, Biosensor, Cancer Detection, Carbon Nanomaterials

Resumen

Introducción: El cáncer es una de las principales causas de mortalidad a nivel mundial, y su detección temprana mejora las tasas de supervivencia. Los métodos convencionales son costosos, invasivos y de largo tiempo de análisis. Los biosensores electroquímicos surgen como una alternativa eficiente para detectar biomarcadores de cáncer de forma rápida y precisa.
Objetivo: Revisar el uso de nanomateriales de carbono en biosensores electroquímicos para la detección temprana del cáncer, destacando sus propiedades, ventajas y desafíos en aplicaciones biomédicas.
Metodología: Se realizó una búsqueda en Scopus y Web of Science de artículos publicados desde 2018 en inglés. Se usaron ecuaciones de búsqueda con términos clave y se aplicaron filtros de inclusión y exclusión. Los estudios seleccionados fueron organizados y analizados sistemáticamente según el tipo de nanomaterial de carbono utilizado.
Resultados: Los nanomateriales de carbono mejoran la sensibilidad y selectividad de los biosensores electroquímicos, permitiendo la detección de biomarcadores a muy bajas concentraciones. El grafeno y el óxido de grafeno reducido destacan por su alta conductividad y facilidad de funcionalización.
Conclusiones: La incorporación de nanomateriales de carbono en biosensores electroquímicos contribuye en la detección temprana del cáncer. Sin embargo, se requiere más investigación al respecto para mejorar la tecnología y lograr su traslado a entornos clínicos.

Palabras clave: Biomarcador, Biosensor, Detección de cáncer, Nanomateriales de carbón

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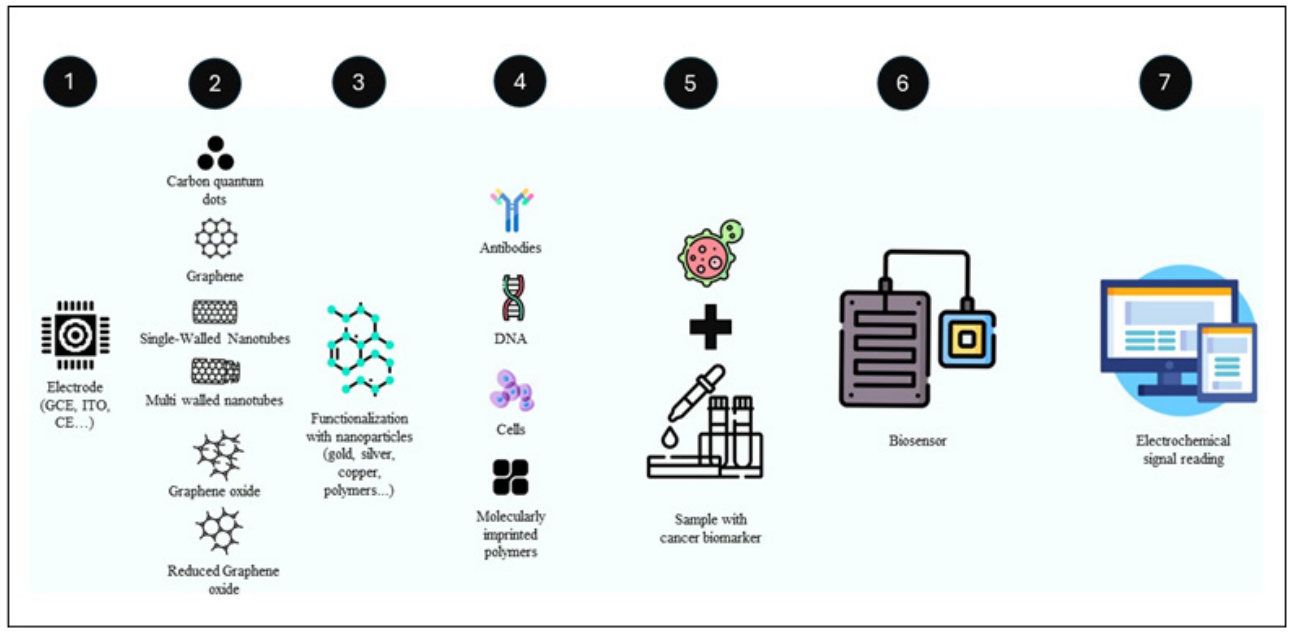
Contribution to the literature

Why was it done?
The review was carried out to address the need to detect cancer in its least invasive stages, and for these to be more sensitive and selective than current methods, which are often intrusive and carry side effects. Since early diagnosis is crucial to improving cancer survival rates, the review focuses on recent advances in the development of electrochemical biosensors. These biosensors, enhanced with carbon-derived nanomaterials such as graphene, carbon quantum dots, carbon nanotubes, graphene oxide, and reduced graphene oxide, offer an alternative for early cancer detection. The objective is to consolidate the existing information on these materials and their application in biosensors to provide a comprehensive and updated vision of the state of the art in this emerging field.

What were the most relevant results?
The identification of graphene oxide and reduced graphene oxide as the most studied nanomaterials due to their ability to significantly improve the sensitivity and selectivity of electrochemical biosensors.
The confirmation that the types of cancer most investigated with these biosensors were breast cancer, alterations related to the presence of tumors, and prostate cancer.
The exploration of various functionalization strategies, such as the use of gold and silver nanoparticles, organic components (amines and amides), and nanopolymers, which have been shown to improve the effectiveness of biosensors.

What do these results provide?
These results provide a greater understanding of the potential of carbon-derived nanomaterials in the development of electrochemical biosensors for early cancer detection. They provide a solid foundation for future research, highlighting the most promising materials and methods and pointing out areas that require further attention, such as the study of less investigated cancers (oral, colorectal, stomach, and bone cancers). Furthermore, they underline the importance of optimizing the detection limit and exploring new functionalization strategies to improve the sensitivity and specificity of biosensors, which is crucial for their practical application in cancer detection and monitoring in clinical settings.



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Introduction

According to the World Health Organization (WHO), cancer is the leading cause of death worldwide (1). In this context, the American Cancer Society (ACS) estimated that by 2023, the number of new cancer cases will rise to 1,958,310 in the United States alone (2) and global cancer deaths are expected to exceed 13 million by 2030 (3).

An early diagnosis of this disease is directly related to an increased 5-year survival rate of 27.4% for patients diagnosed at the metastatic stage and 70% for non-metastatic patients (4). For this reason, early detection becomes essential in minimizing the deadly consequences for those who suffer from it. The means used include mammography, X-rays, CT scans, biopsies, ultrasound, and blood tests. However, these methods have disadvantages such as high cost, long reaction times, harmful effects of radiation, the need to process large numbers of samples, and the use of expensive chemicals. This is evidence of the lack of an effective non-invasive tool for the early diagnosis of diseases (5). Because of this, the health system requires the development of new technologies that guarantee accurate and reliable results with low-cost methods compared to the traditional methods mentioned above due to their simplicity of operation that does not require specialized personnel, robust or highly complex equipment, and ease of sampling such as electrochemical biosensors (6–8).

Current research in accurate, efficient, cost-effective, and user-friendly diagnostics has focused on the development of biosensors, defined by the International Union of Pure and Applied Chemistry (IUPAC) as 'A device that uses specific biochemical reactions mediated by isolated enzymes, immune systems, tissues, organelles or whole cells to detect chemical compounds usually using electrical, thermal or optical signals' (9). Among their most notable features are the detection of deficient concentrations of target analytes, allowing the detection of diseases such as cancer in early stages, and their portability, as they are small devices that do not require extensive equipment for their operation (10).

All these advantages are achieved through research into novel nanomaterials, which, in conjunction with an appropriate detection technique, improve clinical diagnosis (11). The main types of biosensors studied for cancer detection are electrochemical, which measure the voltage change resulting from the chemical reaction between analyte and biomarker (12,13), amperometric, which measures the faradaic current generated by the oxidation-reduction reaction of the biological system under study, and amperometric, which measures the voltage change resulting from the chemical reaction between analyte and biomarker (14,15) and optical biosensors, which generate a fluorescence, colorimetric, or surface plasmon resonance signal, depending on the type of biomarker used (15,16). Among the various classes, electrochemical biosensors have proven to be highly effective (17,18) due to their accuracy, selectivity, fast response, low detection limit, and low cost (13).

The principle of detection in electrochemical biosensors is shown in Figure 1. It is based on the conversion of biological and chemical interactions into measurable electrical signals using redox

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reactions on the surface of an electrode, where specific biomolecules (bioreactors) are immobilized and selectively interact with the biomarker (analyte) of interest, which is associated with cancer. The resulting changes in electrical current or electrochemical potential are directly related to the concentration of the biomarker, allowing detection and quantification with high sensitivity and selectivity (19).

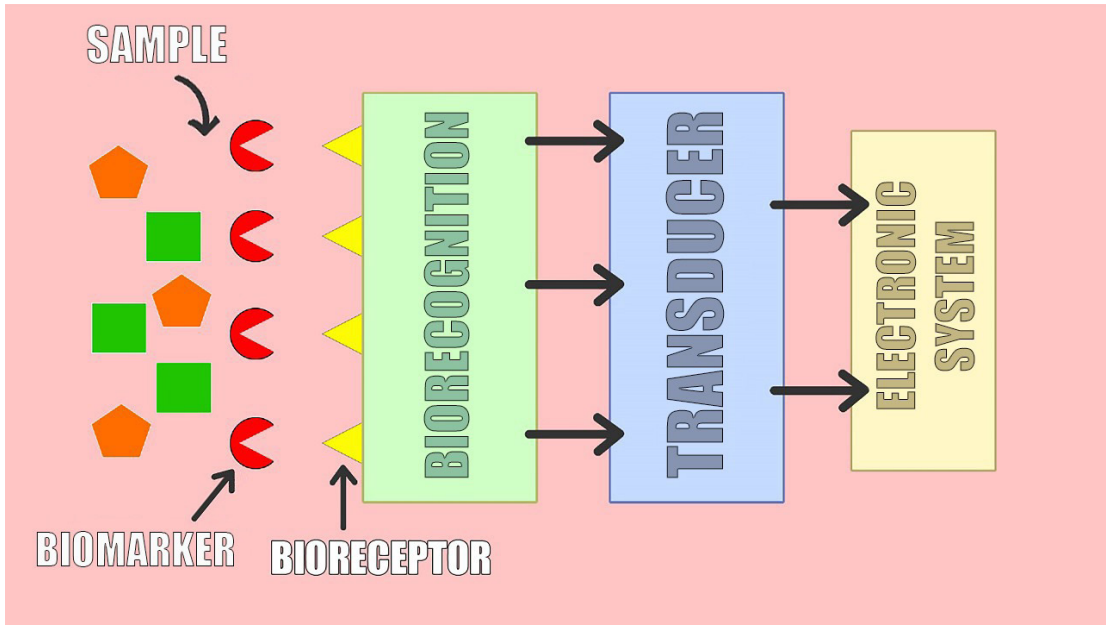

Figure 1. Diagram of the elements and functioning of biosensors

Among the biomaterials investigated for the improvement of cancer detection in electrochemical biosensors, carbon-derived nanomaterials have been the subject of numerous studies due to their remarkable mechanical properties, biocompatibility, ease of functionalization, and excellent electrical conductivity (20,21)This review shows the most recent advances in using carbon-based nanomaterials in electrochemical biosensors to detect different types of cancer. It provides a comprehensive and up-to-date overview of a constantly evolving field of research with the potential to impact cancer detection and treatment positively.

To achieve this goal, a review of carbon-based nanomaterials is carried out, including carbon quantum dots (CQDs), structures with dimensions smaller than 10 nm; two-dimensional carbon nanosheets arranged in a honeycomb structure, such as graphene; graphene functionalized with hydroxy, carboxy and peroxy groups, known as graphene oxide; reduced graphene oxide, which contains fewer functional groups than graphene oxide; single-layer carbon nanotubes, consisting of rolled-up graphene sheets; and multilayer carbon nanotubes, consisting of concentrically rolled-up graphene sheets. These nanomaterials provide different properties such as high surface area, chemical stability, ease of synthesis, and optical activity (22–25) which will be further developed and specified in each section.

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Methodology

This section describes the process followed for the search, selection, and analysis of the scientific literature used in this bibliographic review. Scopus and Web of Science were used as databases due to their broad scope and high impact on scientific literature. A search equation was designed based on the use of Boolean operators (AND, OR, NOT), combining the following keywords: "carbon nanomaterials," "electrochemical biosensor," cancer, "carbon quantum dot," "carbon nanotubes," Graphene, "Graphene oxide," and "reduced graphene oxide." Additionally, filters were applied to restrict results to research papers published from 2018 onwards in English, aiming to include only recent and relevant studies in this field.

In selecting documents, inclusion and exclusion criteria were established. Only papers addressing the use of carbon nanomaterials in electrochemical biosensors for cancer detection were considered. Reviews and papers in which carbon nanomaterials were not specifically used in electrochemical biosensors for cancer applications were excluded.

The selection process was carried out in four phases. First, the titles and abstracts of the retrieved articles were reviewed, eliminating those that did not align with the study's objectives or were duplicates. Next, the carbon-derived materials used in electrochemical biosensors for early cancer diagnosis were identified, grouping the documents by nanomaterial type (carbon quantum dots, carbon nanotubes, graphene, graphene oxide, and reduced graphene oxide). Subsequently, the search was expanded by focusing on each type of nanomaterial identified in the previous phase to increase the number of relevant documents for each category. Finally, a full-text reading of the selected studies was conducted, extracting methodological information, reported results, relevance, and key findings from each study.

To ensure a clear synthesis of the information, the extracted data were organized into comparative tables by nanomaterial type, allowing for a systematic analysis of trends in the development of electrochemical biosensors based on carbon-derived nanomaterials. This approach facilitated the identification of patterns in the evolution of these technologies, their advantages and limitations, as well as opportunities for improvement in detecting different types of cancer. In this way, an updated overview of the state of the art in using carbon nanomaterials in electrochemical biosensors for early cancer diagnosis was obtained.

Biosensor specificity

Electrochemical biosensors require a biosensing platform with nanomaterials that ensure efficient conduction of the electrochemical signal. They also need receptors to ensure that the biosensor only detects the specific biomarker associated with the target disease, in this case, cancer. A proper choice of functionalization and assay performed on the bioreceptor avoids false results that could lead to misdiagnosis and unnecessary or inappropriate treatment.

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A commonly used functionalization is through aptamers, single-stranded nucleic acid (DNA or RNA) sequences that can fold into specific three-dimensional structures and selectively bind to the biomarker under study. Choosing an appropriate sequence is critical in these cases. In a particular case, Park et al. (26) used the aptamer sequence 5′-NH_2-AUG CAG UUU GAG AAG UCG CGC AU-3′ to detect vascular endothelial growth factor ($VEGF_{165}$), an indicator of tumor cells. Immobilization of the aptamer on the carbon nanotube-polyaniline-based biosensor used the deposition of a mixture of anti-$VEGF_{165}$ RNA aptamer (10 nM) and 4-(4,6-dimethoxy-1,3,5-triazin-2- Se incubated in -4-methyl-morpholinium chloride (DMT-MM) solution (1% wt; 40 µl) with the SPCE surface for 12 h. Devices have also been developed for the detection of prostate cancer using the sequence (5′-Thiol - (CH_2)6-TTTTTA ATT AAA GCT CGC CAT CAA ATA GCT TT-3′)(27), the detection of circulating tumor DNA (28), (29).

Other common bioreceptors, such as antibody-based bioreceptors, called immunobiosensors, are based on proteins the immune system produces in response to specific antigens, such as cancer-associated proteins. To use these antibodies, first, the conductive probe of the biosensor is prepared based on nanomaterials, and then a solution containing the antibody is prepared, as in the specific case of the research conducted by Purohit et al. (30) in which they designed a biosensor based on graphene oxide, chitosan, and 3D gold dendrites where, after preparing the conductive layer, they prepared a 5 µl solution of carcinoembryonic antigen-antibody (anti-CEA) with (10 µl) N-(3-dimethyl aminopropyl)-N′-ethyl carbodiimide hydrochloride solution (50 mM) and N-hydroxysuccinimide (50 mM) for 15 minutes at room temperature to activate the primary carboxylic groups of the protein. This solution was deposited on the modified electrode at ambient conditions for 60 minutes to establish a covalent interaction with the primary amino group of chitosan. Finally, a 10 µl (1 mg/ml) bovine serum albumin (BSA) solution was additionally treated for 15 minutes to block unspecified sites and avoid non-specific interactions.

This method is commonly used for functionalization with antibodies, as is the case of Ren et al. (31) for identifying cancer antigen 125 by their antibody. Although these chemical bonds are very stable, conduction layer/antibody binding can also be done by physical adsorption, which allows direct binding of antibodies to a surface without requiring complex chemical reactions or additional reagents thanks to Van der Waals-type interactions, hydrophobic effects, electrostatic forces, solvation, and hydrogen bonding (31). An example of such a case is the biosensor developed by Echeverry et al. (32). They fabricated a biosensor of laser-etched reduced graphene oxide electrodes decorated with gold nanoparticles to identify the cancer indicator glycoprotein CA-19-9 by its antibody. The addition of the antibody to the biosensor was performed, on the one hand, by binding to the gold nanoparticles via Au-S bonds, specifically with the thiol groups of the exposed cysteine residues of the anti-CA-19-9 and, on the reduced graphene oxide side, through electrostatic, π-π stacking and hydrophobic interactions, due to the characteristic sp^2 carbon structure of graphene.

Another technique used for biomarker recognition is molecular polymer imprinting, known as MIP. This technique creates a polymeric matrix around the target biomarker through

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electropolymerization. Subsequently, the target biomarker is removed, leaving a vacancy designed explicitly for the selective capture of the cell or molecule to be identified (33). Researchers Carvalho et al. (34) used pyrrole monomer to synthesize the STEAP1 enzyme template for prostate cancer detection. Printing was performed by applying potential variations for 10 cycles with a possible range between -0.8 and 1.1V at 0.02 V/s, the solution of pyrrole monomer, STEAP1, and phosphate-buffered saline (PBS) and subsequently removing the biomarker template by dropping 5 µl of 100-fold diluted trypsin on the modified biosensor and incubating at 37 °C for 1 h, followed by an electrochemical procedure with PBS to remove unreacted amino acids or monomers from the electrode surface by CV for 10 cycles at a potential between - 0.4 and 0.5 V at a scanning rate of 0.05 V/s. Another example of this method is the investigation of (35) using an alpha-fetoprotein as a template in a graphene and gold nanoparticle-based device to detect tumor lesions.

The above are the most common methods used to identify specific biomarkers, which are usually identified with different signals depending on the type of biosensor. The main types include amperometric, voltammetric, and impedimetric biosensors. Amperometric biosensors detect the electrical current generated by an electrochemical reaction between the biomolecule of interest and an electrode, allowing quantification of the analyte (36). On the other hand, voltammetric biosensors measure the electrical current as a function of the potential applied to the electrode, providing information about the chemical oxidation-reduction process with the analyte (37) (38). Finally, impedimetric biosensors quantify changes in the electrical impedance of the system, allowing the detection of biomolecular interactions (39). The standard conditions of these assays consist of a three-electrode system: platinum auxiliary electrode, Ag/AgCL reference electrode, and the working electrode. The latter is the electrochemical biosensor developed for each study, and the way to determine its effectiveness is to compare the signals obtained when subjected to different concentrations of solutions containing the biomarker under study (40,41).

Another influential factor in determining which biosensor to develop is the type of sample to work with, since for diagnostics with electrochemical biosensors, a variety of biological fluids or cellular samples containing the analyte of interest are required. These may include sera, plasma, saliva, urine, and interstitial fluid. For specific diseases, such as cancer, tumor tissue samples or isolated cancer cells may also be used. In addition, in research studies, simulated or artificial fluids at different concentrations are used to evaluate the sensitivity and detection limit of electrochemical biosensors (42–44).

Economic perspective

The medical and diagnostic fields are emerging as highly profitable market segments, driven by a growing interest in monitoring devices, rapid point-of-care testing, and the demand for modern diagnostic methods. This momentum is supported by significant advances in manufacturing methodology, which has enabled the development of sensitive, selective, and efficient electrochemical sensors for clinical analysis. Integrating biosensors into various diagnostic medical equipment adds a new market opportunity to the projected horizon. In addition, massive

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investment in research and development to improve medical technology reflects the continued growth of this sector (45).

The biosensors market, segmented into various applications such as healthcare, agriculture, and food toxicity, will experience significant growth. Healthcare is expected to generate the largest revenue share due to its use in drug delivery and disease detection areas. The food toxicity category is expected to see rapid revenue growth. Projections indicate that the global biosensors market will reach USD 41.48 million by 2029, up from USD 20.75 million in 2020, where the most significant contributing country to this growth is the US, followed by China (46,47). With the cost of cancer diagnosis projected to reach $266 billion by 2030, biosensors emerge as a much more cost-effective alternative as they do not require specialized personnel or robust or complex equipment (48).

The market for biosensors is booming thanks to their diversification across multiple sectors, with a particular emphasis on healthcare, where they are used for a wide range of applications, from disease detection to drug discovery. Promising growth is observed, with projections suggesting an even more expansive outlook in the coming years.

Carbon Quantum Dots (CQD)

The quasi-spherical structure of carbon quantum dots (CQDs) can be amorphous or crystalline as well as graphitic or turbostratic sp^2-based or of graphene and graphene oxide sheets fused by diamond-like sp^3 hybridized carbon inserts (49). The distinguishing feature of CQDs is their ability to exhibit quantum properties due to their small size. These quantum properties can include electronic confinement effects that give them unique electronic properties. CQDs have attracted considerable research attention because of their potential application in electronics, optoelectronics, and as contrast agents in biomedical imaging due to their unique optical properties (50,51).

The interest in these nanomaterials lies in the possibility of replacing traditional semiconducting CQDs with low biocompatibility properties, which, although possessing good conductive properties, have been little explored in electrochemical biosensors (52). However, these nanomaterials have disadvantages that limit their use, such as their synthesis in a multi-step process, harsh chemical conditions, and poor size control (53). According to the information reported in Table 1, most of the research on CQDs in electrochemical biosensors has focused on breast cancer diagnosis (54–63) and found that the presence of CQD favors the interaction of thionin with the dsDNA to detect the BRCA1 gene, obtaining a detection limit of 0.003 µmol L^{-1}(54). The strong electrical conductivity and large specific surface area of carbon quantum dots have enabled their use as a substrate for metal ions in breast cancer detection (60). Abdel-aal et al. (56) found detection limits similar to those reported by Garcia et al. (54) with a polypyrrole nanocomposite and carbon quantum dots.
In addition, wireless bio-devices have been developed for the detection of breast cancer-related cells (62) using ureidopyriminone-conjugated gelatin hydrogel (Gel-UPy) incorporating diselenide-containing carbon dots when reacting with MDA-MB-231 cells or the nanocomposite of carbon, hyaluronic acid, titanium oxide, and Cu^{2+} ions for differentiation of cancer cell pyrophosphatase and

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alkaline phosphatase, achieving a minimum detection limit of 2.31 cells/mL (64).
The use of CQD in electrochemical biosensors for cancer types other than those already mentioned has not been pervasive, but related research was found for the detection of specific malignant tumors (65), ovarian cancer (66), pancreas (67) and prostate (68).

Table 1. Research on the use of carbon quantum dots (CQD) in electrochemical biosensors for the detection of different types of cancer

Type of cancer	Functionalization	Biomarker / Bioreceptor	Electrode type	Detection limit	Range	Ref.
Breast	Thionine as a hybridization indicator and CQD as a nano substrate for direct immobilization of the DNA probe	BRCA1/Thionine	Gold	55.0 pg µL-1		(54)
Breast	sulfur/nitrogen, polypyrrole, cobalt phthalocyanine	HER2/HB5	GCE	0.00141 ng/mL	1–10 ng/mL	(55)
Breast	cobalt tetraphenoxyacetic acid phthalocyanine (CoTAPc), S- and N-doped graphene QDs, gold nanoparticles, and cerium oxide nanoparticles	HER2/HB5	GCE	6.0 pg/mL	1–10 ng/mL	(56)
Breast	pencil graphite electrode/ carbon points/overoxidized polypyrrole (Ov-Ox PPy/CD/ PGE)	tryptophan (Trp)/Ov-OX PPy	PGE	0.003 µmol L−1	0.01 - 0.09 µmol L−1 and 0.5 - 9.0 µmol L−1	(57)
Breast	graphene quantum dots (GQDs)	differentiation antigen-44 (CD44)/Anti-CD44	GCE	2.71 fg/mL	1.0 pg/mL - 100.0 ng/mL	(58)
Breast	Graphene quantum dots (GQDs) rich in carboxylic acid groups modified with gold nanoparticles and a binuclear porphyrin (CoP-BNF) structure	HER2/HB5	GCE	0.0489 ng/mL	Does not report	(59)
Breast	antimonene nanoflakes (AMNF) and carbon quantum dots (CQD) as substrate for cadmium ion (Cd2+)	miRNA-21/ss-RNA	GCE	9pm	100aM-100nM	(60)
Breast	sulfur/nitrogen-doped graphene quantum dots and a cobalt phthalocyanine	HER2/HB5	GCE	1.41 pm/mL	1–10 ng/mL	(61)
Breast	Nitrogen-doped graphene quantum dots	MCF-7 cells/ phytohemagglutinin-L (PHA-L	SPE	1 cells mL-1 in PBS and 2 cells mL-1 in human serum	5 to 106 cells ml-1 in PBS and 20-106 cells ml-1 in human serum	(62)

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Breast	ureidopyriminone-conjugated gelatin (Gel-UPy) hydrogels that incorporate diselenide-containing carbon dots (dsCD)	/				(63)
Breast	gold nanoparticles/graphene quantum dots/graphene oxide film	miRNA-21, miRNA-155, and miRNA-210/		0.04, 0.33, and 0.28 fM	0.001 to 1000 pM	(65)
Ovary	zinc oxide, carbon ink	CA-125/CA125 antibodies	ITO	0.1 fg·mL−1	1 ag·mL−1 − 100 ng·mL−1	(66)
Pancreas	Single-stranded DNA (thiol-ss-DNA) modified and thiolated with graphene oxide quantum dots	miR-141/Modified and thiolated single-stranded DNA (thiol-ss-DNA)	SPCE	0.091 pM	2.3 to 6.1 nM	(67)
Prostate	gold nanoparticles, multi-walled carbon nanotubes and graphene quantum dots	PSA/Anti-PSA	GCE	0.48 pg/ml	1 - 10,000 pg/ml	(68)

Carbon nanotubes

Carbon nanotubes (CNTs) are graphene sheets rolled to form a cylinder with a high length/diameter ratio. According to the number of carbon sheets, they are classified as single-layer, or single-wall, and double-wall, or multilayer, nanotubes (69). Nanotubes stand out for their high functionalization capacity and good conductive properties (70). However, some studies report that in their pristine state, they have a level of toxicity that is risky to health (71–73). Although the reason has not been determined precisely, the causes point to the heterogeneity of its surface that can induce its reaction with plasma proteins and the production of reactive oxygen species (ROS), which activate an inflammatory response through the release of cytokines and cause the release of apoptotic factors that lead to cell death (74).
Other research shows that functionalized nanotubes or in the form of structured aggregates do not reveal evidence of toxicity since the modification of the surface of carbon nanotubes reduces their reactivity and improves their biocompatibility (75,76). Furthermore, the formation of structured aggregates can minimize the exposure of carbon nanotubes' active surface, reducing the potential for interaction with biomolecules and consequent toxicity.

Monolayer nanotubes

In Table 2, we observe that single-walled CNTs functionalized with single-stranded DNA have been used for the diagnosis of bladder cancer (77) and breast cancer (78–80) taking advantage of the excellent affinity of different nanostructures combined with a high surface area of carbon nanotubes (81).

Cancer detections are possible thanks to the fact that carbon nanotubes provide conductivity and the ability to functionalize with other nanomaterials and with bioreceptors such as

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carcinoembryonic antigen (CEA) (82), p-type glycoprotein (P-gp) (83) or exosomes derived from A549 cells (84).

Table 2. Research on the use of monolayer carbon nanotubes in electrochemical biosensors for the detection of different types of cancer

Type of cancer	Functionalization	Biomarker / Bioreceptor	Detection limit	Range	Ref.
Changes generated by tumors	DNA/ferrocene	exosomes derived from A549 cells/Epidermal growth factor receptor (EGFR)	9.38×10^{4} exosomes/ mL	4.66×10^{6}- 9.32×10^{9} exosomes/mL	(84)
Changes generated by tumors	three-dimensional hierarchical nanohybrid based on bimetallic Cu-Au nanocrystals embedded in carbon nanotube arrays grown vertically on carbon spheres	CEA/anti-CEA	0.5 pg/mL	0.025^{-25} ng/mL	(82)
Breast	antimonide quantum dots (AMQDs), aromatic heterocyclic dyes and single-walled carbon nanotubes (SWCNTs)	microRNA-21and miRNA-155 / ss-RNA(1 5 5)	64 am and 89 am	0 - 1 pM	(78)
Breast	palladium (Pd) nanostructures supported on oxidized carbon nanotubes	HER2/Anti-HER2	1ng/mL	10 - 100ng/ml	(81)
Breast	single-walled carbon nanotubes (SWCNTs) incorporating the polymerization of an oxiran-2-ylmethyl 3-(1H-pyrrol-1-yl) propanoate monomer (Pepx)	calreticulin (CALR) / anti-CALR	4.6 fg/mL	0.015 - 60 pg/mL	(79)
Breast	electrochemically reduced graphene oxide and single-walled carbon nanotubes	HER2/Anti-HER2	50 fg/mL	0.1 pg/mL - 1 ng/ mL	(80)
Bladder	single-stranded DNA	miRNA-21/ssDNA	3.0 fM		(77)
Leukemia	No functionalization other than the antibody	P-glycoprotein (P-gp)/anti-P-glycoprotein	19 cells/mL	1.5×10^{3}cells/mL – 1.5×10^{7}cells/mL	(83)

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Table 3. Research on the use of multilayer carbon nanotubes in electrochemical biosensors for the detection of different types of cancer

Type of cancer	Functionalization	Biomarker / Bioreceptor	Detection limit	Range	
Changes generated by tumors	Copper Cobalt Spinel ($CuCo_2O_4$)/N-Doped Nonotubes	25(OH)D3 / G-quadruplex aptamer VDBA14-35	0.063 pM	$1x10^{-13}$ - $1x10^{-6}$ M	(85)
Changes generated by tumors	mesoporous carbon functionalized with multilayer carbon nanotubes and gold nanoparticles	Cancer exosomes extracted from cell line MCF7/CD9 protein	70 exosomes/µL	$1x10^{2}$ - $1×10^{7}$ exosomes/µL	(86)
Breast	gold nanoparticles	HER2-ECD/anti-HER2-ECD	0.16ng/mL	7.5 - 50 ng/mL	(87)
Breast	Double-layer nanotubes, tungsten disulfide semiconductor nanosheets, silver nanoparticles	miRNA-21/complementary DNA	1.54 am	10^{-18}- 10^{-11} M	(88)
Breast	Carboxy and activators regenerated by electron transfer atom transfer radical polymerization (ARGET ATRP) into a highly conductive poly(3,4-ethylenedioxythiophene): polystyrene sulfonate (PEDOT). :PSS) PEDOT:PSS and Gold Nanoparticles	HER2 / HER2 aptamer-antibody (Apt-HER2-Ab*)	1.979 fg mL^{-1}	10^{-2} - 10^{3} ng mL^{-1}	(89)
Breast	gold nanoparticles (GNPs) and multi-walled carbon nanotubes (MWCNTs)	HER2/aptamer, MCH	4.4 µg/mL	1 Pg/mL - 25 ng/mL	(90)
Breast	multi-walled carbon nanotubes (MWCNT) deposited on electrode needle	4T1 and MC4L2	In vivo detection in biomodels		(91)
Ovary	AuNPs@MWCNTs	CA125/acid treatment (H_2SO_4 and HNO_3) of CBNs resulted in surface modification and ended up with oxygen-containing functional groups that are essential for binding with biomolecules	Does not report	0.001 - 10 µg/ mL	(92)
Ovary	Amine-Modified Multi-Walled Carbon Nanotubes (MWCNT)	squamous cell carcinoma antigen (SCC-Ag)/anti-SCC-Ag antibody	80 pM	60 - 120 pm	(93)
cervical	reduced graphene oxide nanocomposite and multi-walled carbon nanotubes	HPV-18/ssDNA	0.05 fM	0.01 fM and 0.01 nM	(94)
Prostate	polymerization of the monomer such as pyrrole-2-carboxylic acid (PY-COOH) with a nanocomposite of dendritic platinum nanoparticles aminated with carbon nanotubes (CNTs-PAH/Pt).	Prostate epithelial antigen 1 STEAP1 / Molecular imprinting on polymer	Does not report	130 pg/mL - 13 µg/mL	(95)
Prostate	Carboxyl-functionalized multi-walled carbon nanotubes (MWCNT) and Fe_3O_4 nanoparticles	PSA/anti-PSA	0.39 pg/mL	2.5 pg/mL - 100 ng/mL	(96)
Prostate	multi-walled carbon nanotubes (MWCNT) modified with gold nanoparticles (AuNPs)	Self-assembled PSA/thiolated single-stranded DNA	1 pg/mL	1–100 ng/mL	(97)
Pancreas	carboxyl group	miRNA/ss-DNA	3 pm	1.3^{-12} nM	(98)
Pancreas	multi-walled carbon nanotubes and gold nanoparticles	microribonucleic acid (miR-21)	3.68 fM	Does not report	(99)

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Lung	composite of UiO-66-NH2 and carboxylated multi-walled carbon nanotubes (CMWCNTs) and chitosan functionalized with gold nanoparticles	cytokeratin fragment 19 antigen 21-1 (CYFRA 21-1) / Anti-CYFRA 21-1	1.15 pg/mL	0.005–400 ng/ mL	(100)
Lung	amidated multi-walled carbon nanotubes (Au NCs/MWCNT-NH_2)	Long non-coding RNAs (lncRNAs) MALAT 1	42.8 fM	10^{-7}– 10^{-14}M	(101)
Liver	Fe3O4/MWCNTs-COOH/Gold Naoparticles	Alpha-fetoprotein (AFP)/Anti-AFP	1.09034 pg mL^{-1}	1 pg mL^{-1}– 10 µg mL^{-1}	(102)
Liver	multi-walled carbon nanotubes (MWCNT) with chitosan film	OV6/Anti-OV6	100 cells/mL	$1x10^2$ - $5×10^5$ cells/mL	(103)
colorectal, pancreatic lung	multi-walled carbon nanotubes/chitosan ionic liquid/gold nanoparticles	KRAS gene/T7E1 enzyme mutation	11.89 fM	100 fM - 1 µM	(104)

Multilayer nanotubes

As shown in Table 3, the functionalization of these materials with gold nanoparticles has achieved the development of electrochemical biosensors for breast cancer detection (87) where they reached a low detection limit of 0.16 ng/mL. The above was achieved thanks to the contributions of the high sensitivity of the nanotubes and the properties of gold nanoparticles for effective immobilization of HER2 antigen used as biomarkers in this assay. Most biosensors based on multilayer nanotubes have been used in the diagnosis of breast cancer (87–91), using functionalization with metal nanoparticles, mainly gold and silver.

Other cancers studied with these nanomaterials are prostate cancer (100,101), pancreatic cancer (99) (98), colorectal cancer (104), ovarian cancer (88,93), liver cancer (102) or biomarkers related to tumor cells (85).

Graphene

Graphene is a two-dimensional allotrope of carbon, one atom thick with sp^2 hybridization (105). It is a nanomaterial with a large surface area, good biocompatibility, and superior electrical conductivity compared to other carbon derivatives, which make it ideal for detecting and quantifying cancer biomarkers (106,107). Graphene has notable potential for its functionalization with different types of drugs, biological agents (proteins and nucleic acids), metals, and fluorescent probes intended for the detection of intracellular components, thanks to its flat geometry (108).

The simplicity of its functionalization combined with its excellent electrical properties has driven many investigations into using this nanomaterial in electrochemical biosensors to detect malignant tumors, prostate, breast, and liver cancer (Table 4).

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Table 4. Research on the use of graphene in electrochemical biosensors for the detection of different types of cancer

Type of cancer	Functionalization	Biomarker / Bioreceptor	Detection limit	Range	Ref.
Changes generated by tumors	aptameric graphene-based field effect transistor with buried gate geometry with HfO_2 as a dielectric layer and online signal processing circuits to measure the signals	interleukin-6 (IL-6) / Unlabeled	12pm	Does not report	(109)
Changes generated by tumors	antibody-modified graphene ^{field} effect transistor	Carcinoembryonic Antigen (CEA) / Unlabeled	100 pg/mL	100 pg/mL - 100 ng/mL	(110)
Changes generated by tumors	Laser-etched graphene electrodes on a polyimide sheet	eIF3d protein biomarker / Anti-eIF3d	50.4 ng/mL	75–500 ng/mL	(111)
Changes generated by tumors	graphene foam Functionalized with pyrene carboxylic acid	IL-10/Anti-IL-10	7.89 fg/mL	10 fg/ml and 100 fg/ml	(112)
Changes generated by tumors	graphene nanosheets decorated with Ag nanoparticles (GNSs@Ag NPs)	carcinoembryonic antigen (CEA)	0.5 fg/mL	0.001 pg/mL - 10 pg/mL	(113)
Changes generated by tumors	uniform thin films of amine-functionalized graphene (f-graphene) and Ti3C2-Mxene nanohybrid	carcinoembryonic antigen (CEA) / anti-CEA	0.30 pg mL^{-1}	0.01 pg mL^{-1} - 2000 ng mL^{-1}	(114)
Changes generated by tumors	large size (~ 2.5 × 1.0 cm2), uniform, continuous, single-layer graphene films on copper (Cu) substrate using	carcinoembryonic antigen (CEA) / anti-CEA	0.23 ng mL^{-1}	1.0 - 25.0 ng mL^{-1}	(115)
Changes generated by tumors	graphene-zirconia nanocomposite	carcinoembryonic antigen (CEA) / anti-CEA	4.25 pg/mL	0.01 - 10ng/ mL	(116)
Changes generated by tumors	Amine functionalized graphene	microRNA-155 /anti-microRNA-155	12.5 fM mL^{-1}	30 fM mL^{-1} - 1 pM mL^{-1}	(117)
Changes generated by tumors	cubic dendritic gold/platinum nanomaterials functionalized with nitrogen-doped graphene loaded with copper ions	carcinoembryonic antigen (CEA) / anti-CEA	0.167 pg/mL	0.5 pg/ml - 50 ng/ml	(118)
Changes generated by tumors	graphene field effect transistor	human chorionic gonadotropin (hCG) / anti-hCG	pg/mL	1 pg/mL - 1 ng/mL	(119)
Breast	Polypyrrole, gold nanoparticles	miRNA-21/Unlabeled	0.020 fM	1.0 fM - 1.0 nM	(120)
Breast	Nanostructured Gold Modified Laser Etched Graphene (LSG)	HER2	0.008 ng/mL	0.1 - 200 ng/ mL	(121)
Breast / Ovary	electrospun graphene-doped manganese III oxide (GMnO) nanofibers	BRCA1/single-stranded DNA	0.8 ± 0.069 pM	10 pM - 1 µM	(122)
Prostate	3-aminobenzoic acid (ABA), porous gold and silver nanoparticles.	PSA/Anti-PSA	50 amol/L	0.0001 and 1000 pmol/L	(123)
Prostate	Chitosan	Sarcosine oxidase (SOx) / Sarcosine	0.001 µM	0.001–100 µM	(124)
Prostate	iron oxide Fe3O4	PSA/anti-PSA	0.38ng/mL	1 - 150 ng/mL	(125)

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Prostate	carbon fabric modified with gold nanoparticles	microRNA-141/ aptamer 1 (APT1)	50 AM	0.1 fM - 1 nM	(126)
Prostate	3D graphene airgel (GA)/AuNPs/Nafion	PSA/Anti-PSA	0.0306 ng·mL^{-1}	0.05 - 50 ng·mL^{-1}	(127)
Prostate	graphene nanoplatelets with diblock copolymers	PSA/anti-PSA	40 fg mL^{-1}	0.1 pg mL^{-1} - 100 ng mL^{-1}	(128)
Liver	gold nanoparticles	Alpha-fetoprotein (AFP) / Molecular imprinting on polymer	3.7 pg/mL	0.001 ng/mL - 1000 ng/mL	(129)
Lung	3D graphene functionalized with Ag nanoparticles	CYFRA21-1/ssDNA	1.0×10^{-14} M	1.0×10^{-14} - 1.0×10^{-7} M	(130)

According to Table 4, 50% of the research has aimed at the development of biosensors for the diagnosis of non-specific malignant tumors (115) (116) (117) (118) (119) through the detection of carcinoembryonic antigen, a normal glycoprotein in fetuses but which indicates the presence of tumors in adults (131). An example of this is the biosensor developed with graphene nanosheets decorated with silver nanoparticles (113), which achieved a low detection limit of 0.5 fg/mL and a linear detection range of 0.001 pg/mL to 10 pg/mL. For this same biomarker, thin graphene sheets have been functionalized with amine and Ti_3C_2-Mxene nanohybrid with a low detection limit of 0.30 pg mL^{-1} and detection range of 0.01 pg mL^{-1} to 2000 ng mL^{-1}(114). This biomarker has also been detected using graphene-zirconia compounds (116), graphene-copper (115) or cubic dendritic gold/platinum nanomaterials with sulfur and nitrogen functionalized graphene (118) with detection limits of less than 4 pg/mL.

The protein interleukin-6 (IL-6) (109), the D subunit of eukaryotic translation initiation factor 3 (eIF3d) (111), the carcinoembryonic antigen (CEA), microRNA-155 (117), and human chorionic gonadotropin (hCG) (119), are related to the presence of different types of cancer and have been detected only with graphene nanoparticles functionalized with their respective antibodies, reaching detection limits of 12 pM, 50.4 ng/mL, 100 pg/mL, 12.5fM mL^{-1} and 1 pg/mL, respectively, demonstrating the ability of graphene to conduct the biochemical signal produced by the biomarker-bioreceptor interaction.

Graphene nanocomposites with gold nanoparticles have been studied for the diagnosis of prostate cancer (126) reaching detection limits of 50 aMol/L (S/N = 3) and a detection range between 0.0001 and 1000 pmol/L when an oxidation reaction occurs between the glucose oxidase aptamer and the prostate-specific antigen analyte. The same detection limit was obtained by adding silver nanoparticles and 3-aminobenzoic acid to the graphene nanocomposite and gold nanoparticles to detect microRNA-141, also related to prostate cancer (123). Other types of functionalization with nanoparticles, such as iron oxide (125), biopolymers such as chitosan (124) and even synthetic polymers such as polystyrene and polyacrylic acid (128) have achieved detection limits lower than 0.001 µM when detecting biomarkers related to prostate cancer (132).

According to Table 4, the third most studied type of cancer in detection with graphene-based biosensors is breast cancer. For this, biosensors based on electrospun graphene and manganese III oxide nanofibers have been developed (122) where the inherent electrical properties of the electrospun nanofibers are taken advantage of to achieve superior reaction kinetics, reaching

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a minimum detection limit of 0.8 pM and a range of 10 pM to 1 mM. Nanostructured gold-functionalized graphene biosensors (121) and gold and polypyrrole nanoparticles (120) have reached detection limits of 0.008 ng/ml and 1.0 fM, respectively, thanks to the graphene in the nanocomposite, which increases both the surface area and the conductivity of the electrode.

Other cancers, such as lung and liver, have been investigated through the detection of the CYFRA21-1 gene with a 3D graphene biosensor functionalized with Ag nanoparticles (130), obtaining a minimum detection limit of 1.0×10−14 M, thanks to the fact that these nanocomposites provide a favorable microenvironment to retain the bioactivity of the DNA of the immobilized probe and effectively promote the transfer of electrons due to their excellent biocompatibility and good conductivity. Liver cancer (129) It has also been detected through the functionalization of graphene with gold nanoparticles and through the detection of alpha-fetoprotein, a protein whose presence is normal in the development of the fetus but which in adults can indicate the presence of malignant tumors. The limit of detection is 3.7 pg/mL, and the range is 0.01 ng/mL to 1000 ng/mL.

Graphene oxide and reduced graphene oxide

Graphene oxide (GO) and reduced graphene oxide (rGO) are derivatives of graphene, which are composed of a layer of graphene with hydroxyl, carbonyl, peroxide, and carbonyl functional groups (133). A known, but not definitive, model for GO is that of Lerf and Klinowski, which postulates a random distribution of hydroxyl and epoxy groups throughout the graphene oxide layer, while the carboxyl and carbonyl groups are located at the edge of the graphene oxide layer (134). This layer consists of an unoxidized benzene ring region (planar hexagonal structure) and an oxidized six-membered aliphatic ring region (carbon atoms in this region can form open chains instead of closed structures as in benzene), which vary according to the degree of oxidation and the random distribution of GO (134). In addition to these areas with different degrees of oxidation, they also present gap defects due to over-oxidation and exfoliation from the synthesis process (135).
The reduction of GO to rGO is carried out to obtain properties like those of graphene, improving, for example, its conductive properties (35). rGO has the advantage that the synthesis of GO is much easier and cheaper, considering that graphene requires liquid media with meager yields or high-cost equipment in demanding conditions such as type of substrates or high temperatures (20,136).
Both GO and rGO have been widely used in electrochemical biosensors for specific detection of cancer cells due to their large surface area, good electrical conductivity, immobilization of biomolecules such as DNA, protein mutations, and microRNA with great sensitivity and selectivity (106).

As shown in Table 5, tumor-associated changes have been detected thanks to the implementation of GO in a sandwich structure based on Prussian blue/graphene oxide (GO/PB) and pointed gold-oxide nanoparticles. of iron to detect exosomes derived from tumors (MCF-7), thanks to the fact that the combination of Prussian blue/GO has excellent electrochemical properties, favoring efficient electron transfer, reaching a minimum detection limit of 80 particles·μL^{-1}(137).

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GO has been implemented to a greater extent in biosensors for the detection of breast cancer (138–142) through different types of functionalization, such as with gold nanoparticles and graphene quantum dots (63), gold nanoparticles, and molybdenum disulfide (140), different metal ions (142), bimetallic gold-platinum nanoparticles (141) with detection limits lower than 1.5 µg/mL, thanks to the fact that GO sheets can improve the electrochemical signal and sensitivity by increasing conductivity and specific surface area.

Table 5. Research on the use of graphene oxide (GO) in electrochemical biosensors for the detection of different types of cancer

Type of cancer	Functionalization	Biomarker / Bioreceptor	Detection limit	Range	Ref.
Changes generated by tumors	sandwich platform based on Prussian blue/graphene oxide (GO/PB) and pointed Au@Fe3O4 nanoparticles	Tumor-derived exosomes (MCF-7)/ EpCAM Antibody	80 particles μL^{-1}	2.0×10^{2}- 5.0×10^{5} particles·μL^{-1}	(137)
Breast	different metal ions (Co^{2+}, Ni^{2+}, Mn^{2+}, Zn^{2+}, Fe^{3+}, Cr^{3+}, La^{3+})	miRNA-21	1.18 am	10^{-17}-10^{-12} M	(141)
Breast	two-dimensional (2D) functionalized graphene oxide (FGO)	HER2/anti-HER2	0.59 ng/mL	0.5 ng/mL 25 ng/mL	(139)
Breast	two-dimensional (2D) poly(3-amino benzylamine)/molybdenum selenide/ graphene oxide nanocomposite modified with two screen-printed carbon electrodes (dual-electrode), individually functionalized with 2,3-diamino phenazine-gold nanoparticles and toluidine blue nanoparticles gold	15-3 (CA 15-3) and microRNA-21 (miRNA-21)/anti-CA 15-3 and DNA capture probes-21	0.14 U mL^{-1} and 1.2 fM	0–500 U mL^{-1} and 0–1000 pM	(140)
Breast	Carboxylated graphene oxide followed by deposition of bimetallic gold-platinum nanoparticles	miRNA-21/streptavidin and a biotinylated capture probe	1 fM	1 fM - 1 µM	(142)
Breast	composed of ionic liquid and graphene oxide (GO-IL-PGE)	BRCA1 / Unlabeled	1.48 µg/mL	2–10 µg/mL	(138)
Cervical	Silver-coated gold nanoparticles	human papillomavirus-16 (HPV-16) / HPV-DNA	100aM	100aM - 1 µM	(143)
Colorectal	polypropylene-imine (PPI)	carcinoembryonic antigen (CEA) / anti-CEA	0.3 pg/mL	0.001 - 2000 ng/mL	(144)
Colorectal	Graphene oxide (GO) decorated with gold (Au) nanoflower nanostructures (GO@Au-NS)	miR-223/thiolated DNA probes (Cap-223)	0.012 aM	zM - nM	(145)
Liver	graphene oxide modified screen-printed carbon electrode with the N-hydroxy-succinimide ester of 1-pyrene-butyric acid	Anti-HepG2 human hepatoma HepG2 cells	1 × 103 cells/mL	$1x10^{3}$ - 3×10^{5} cells/mL	(146)

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Lung	two layers of graphene oxide-chitosan@polyvinylpyrrolidone-gold nanocomposite (GO-CS/PVP-AuNUs)	miRNA- 141 and miRNA-21/dhDNA-based probe thiolated methylene blue-labeled hairpin capture probe (MB-HCP) as internal reference probe and a ferrocene-modified anti-miRNA-21 DNA probe (Fc-AP -21) as signal marked with Fc	0.89 and 1.24 fM	2.0 - 105 fM	(147)
Lung	Two-layer nanocomposite film graphene oxide-chitosan polyvinylpyrrolidone-gold nano urchin	miR-141/hematoxylin	0.94 fM	2.0 –5.0×10^5 fM	(148)
Lung	porous zinc oxide/graphene oxide (ZnO/HGO) composites	carcinoembryonic antigen (CEA) and CA153 / anti-CEA and anti-CAI153	0.07 ng/mL and 0.22 U/mL	0.1 - 20 ng/ml and 0.5 - 70 U/ml	(149)
Lung	Functionalized with label	Lung cancer DNA/peptide nucleic acid (PNA)	0.213 aM	1.0 aM to 100 fM	(150)
Oral	gold nanoparticles, redox-active gadolinium hexacyanoferrate (GdHCF)	cyfra-21-1 / Anti-cyfra- 21–1	0.039 (±0.01) ng/mL	2–50 ng/mL	(151)
Oral	aptamer-conjugated graphene oxide with methylene blue and graphene oxide covalently linked with methylene blue	TNF-α/methylene blue (MB)	1 pg mL^{-1} and 10 pg mL^{-1}	1-400 pg mL^{-1} and 10-300 pg mL^{-1}	(152)

The second most studied type of cancer for detection by GO-based biosensors is lung cancer, with nanocomposites such as graphene oxide-chitosan, polyvinylpyrrolidone-gold nanourchin for the detection of related miRNA-141 and miRNA-21. with this type of cancer (147,148), porous zinc oxide/graphene oxide composites (149) and only functionalization with the bioreceptor (150). Likewise, the detection of other types of cancer has been studied, such as cervical cancer (143), colorectal cancer (144,145), oral cancer (151,152), prostate cancer (153) and liver cancer (146), through the use of biosensors based on GO nanoparticles.

Table 6 summarizes the research reported on the use of rGO-based electrochemical biosensors for the detection of different types of cancer; It is striking that rGO has been investigated for the detection of various types of cancer, including breast cancer with some functionalization such as nickel-iron, graphene quantum dots conjugated with silver and gold nanostars (154), rGO/amino substituted polypyrrole polymer nanocomposite (155), ordered mesoporous carbon and gold nanoparticles (156), copper sulfide (157), gold-palladium nanotubes (158), gold nanoparticles (159–161), conductive polymers (162–164), rhodium nanoparticles (165), $ZnMn_2O_4$ (166) or the research conducted by Xia et al. (164) where they functionalized a carbon electrode with 3D rGO nanosheets and polyaniline nanofibers, which resulted in a synergistic effect on biosensing, reaching a minimum detection limit of 3.01×10^{-16} M (3S/m).

Another investigation focused on detecting this type of cancer is that of Sadrabadi et al. (167) In this case, the researchers developed a biosensor composed of a magnetic carbon paste electrode, a metal-organic nanostructure (called MOF) of copper, carbon nanofibers, and sheets of rGO functionalized with iron. This composition reached a low detection limit of 0.08 fM, thanks to the

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addition of metallic and carbon-derived sites that provided good electron transfer and the analyte immobilization capacity of magnetic rGO.

Table 6. Research on the use of reduced graphene oxide (rGO) in electrochemical biosensors for the detection of different types of cancer

Type of cancer	Functionalization	Biomarker / Bioreceptor	Detection limit	Range	Ref.
Breast	Nickel-iron (Fe-Ni@rGO), silver-conjugated graphene quantum dots (GQD-Ag), and gold nanostars (GNS)	miR-155/hematoxylin-ssDNA and scDNA	20.2 am	0.05 fM - 50.0 pM	(154)
Breast	Reduced Graphene/Amino Oxide Substituted Polypyrrole Polymer Nanocomposite	calreticulin (CALR)/anti-CALR	10.4 fg/mL	0.025 - 75 pg/mL	(155)
Breast	Thionine (TH), reduced graphene oxide (rGO), ordered mesoporous carbon (CMK-3), and gold nanoparticles (AuNPs)	miRNA-21/methylene blue (MB)	0.046 fM	0.1 fM - 1 pM	(156)
Breast	Reduced graphene oxide (RGO) and copper sulfide (CuS)	tumor marker carbohydrate 15-3 (CA15-3) / Anti-CA15–3	0.3 U/mL	1.0–150 U/mL	(157)
Breast	Au-Pd and rGO nanocubes	$h_2EITHER_2$	4nM	0.005 µM - 3.5 mM	(158)
Breast	Reduced graphene oxide (rGO) decorated with gold nanoparticles (AuNPs)	ds-methylated MGMT gene/peptide nucleic acid (PNA)	0.86 pM	1 pM - 50 µM	(159)
Breast	rGO and gold nanoparticles	Vascular endothelial growth factor A (165) (VEGF-A (165)) / Without bioreceptor	0.007 pg/mL	20 - 120 pg/mL	(160)
Breast	Reduced graphene oxide (rGO) and AuNPs modified with pyrene carboxylic acid (PCA) and 6-ferrocenyl hexane thiol (Fc-SH)	miRNA-21/RNA-21 capture probes	5 fM	Does not report	(161)
Breast	Graphene oxide/poly(2-amino benzylamine)/gold nanoparticles and adopting hollow and porous gold-silver nanoparticles	miRNA-155, miRNA-16 and miRNA-21 / Hybrid (DNA)-RNA Antibody [S9.6]	0.98 fM, 3.58 fM, and 0.25 fM	1 fM - 10 nM	(162)
Breast	Polypyrrole/reduced graphene oxide	BRCA1 / Unlabeled	3 fM	10 fM – 0.1 µM	(163)
Breast	Polyaniline (PANI)	BRCA1/ssDNA	3.01×10^{-16}M	1.0×10^{-15}–1.0×10^{-7}M	(164)
Breast	Reduced graphene oxide nanosheets (rGON) and rhodium nanoparticles (Rh-NP)	HER2/anti-HER2	1.0 cells/mL	5.0 - 10.0 × 104 cells/ mL	(165)
Breast	Reduced graphene oxide-wrapped ZnMn2O4 microspheres ($ZnMn_2EITHER_4$ @ rGO)	$h_2EITHER_2$ / electrocatalyst	0.012 µM	0.03-6000µM	(166)
Breast	Carbon nanofibers, CuBTC-AIA (CuMOF), and magnetic graphene oxide Fe@rGO	microRNA 155 / 1-pyrene-butyric acid N-hydroxysuccinimide ester	0.08 fM	0.2 fM – 500 pM	(167)
Malignant tumors	Cysteine-coated gold nanoparticles (Cys-AuNP)	Interleukin 8 (IL-8) / Anti-IL-8	0.589 pg/mL	1–12 pg/mL	(168)

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Malignant tumors	Mxene Gold Nanoparticles	mi-RNA21 / Without bioreceptor	0.418 fM	1 fM - 1 nM	(169)
Malignant tumors	Bipolar Exfoliated Reduced Graphene Oxide (rGO) (BPE)	Platelet-derived growth factor-BB (PDGF-BB) / Bioreceptor-free	0.75 pM	1 pM–10 nM	(170)
Malignant tumors	Polyethylene terephthalate (PET/Au) coated with gold and decorated with bipolar exfoliated graphene	platelet-derived BB growth (PDGF-BB) / Without bioreceptor	0.65 pM	0.0007–20nM	(171)
Malignant tumors	Reduced graphene oxide nanosheets coated with highly charged poly diallyldimethylammonium chloride	h_2EITHER$_2$ / gold/ platinum/silver trimetallic nanoalloy	1.2nM	0.05 µM to 5.5 mM	(172)
Malignant tumors	Reduced graphene oxide nanohybrid grafted with molybdenum disulfide	EpCAM/Anti-EpCAM epithelial cells	44.22 fg/mL	0.001 - 20 ng/mL	(173)
Prostate	Reduced graphene oxide/gold nanoparticles	PSA/anti-PSA total and anti-free PSA antibody	0.2 and 0.07 ng/mL	Does not specify	(153)
Prostate	Prussian blue, reduced graphene oxide (P-rGO) nanosheets dispersed in polymer and sarcosine oxidase (SOx)	SAR/Sarcosine Oxidase	0.66 µM	10 – 400 µM	(174)
Prostate	Hybrid TiO nanosheets$_2$(200)-rGO	PSA	1 pg/mL	0.003 – 1000 ng/mL	(175)
Lung	Reduced graphene oxide (rGO), polypyrrole (PPy), silver nanoparticles (AgNPs), and single-stranded DNA (ssDNA as capture probe)	CYFRA21-1/ssDNA for guanine oxidation signal	2.14 fM	1.0×10^{-14} M - 1.0×10^{-6} M	(176)
Lung	Reduced molybdenum disulfide (r-MoS) multilayer nanosheet-based matrix$_2$) modified with rGO	Neuronal specific enolase (NSE)/anti-NSE	1ng/mL	1–200 ng/mL	(177)
Lung	Reduced graphene oxide nanosheets modified with gold nanoparticle hybrid structures	miRNA-155 and miRNA-21/ complementary DNA	12.0 and 25.7 nM	12.0 - 25.7 nM and 51.6 - 59.6 nM	(178)
Cervical	DNA	Human papillomavirus 16 (HPV 16) / HPV-DNA	2:00 p. m.	1 pM - 1 µM	(179)
Cervical	Nano-copper functionalized with perylene tetracarboxylic acid	Human papillomavirus 16 (HPV 16) / HPV-DNA	2.15 fM	10 fM - 10 µM	(180)
Ovary	Silver nanoparticles, cysteamine-coated gold nanoparticles	Mucin 16 or carcinoma antigen 125 (CA 125) / anti-CA 125	0.78 U/mL	0.78–400 U/mL	(181)
Liver	Flexible hybrid film of reduced graphene oxide and carbon nanotubes (rGO-CNT) with MnO nanoflowers$_2$ and Co nanospheres	h_2EITHER$_2$ / Without label	66.7nM	0.2 µM – 18.0 mM	(182)
Leukemia	Gold/magnetite/reduced graphene oxide nanoparticles (AuNPs/Fe_3EITHER$_4$/RGO)	miRNA-128/ hexacyanoferrate and methylene blue	0.05346 fM and 0.005483 fM	0.1–0.9 fM and 0.01–0.09 fM	(183)
Gastric	Polymeric gold nanostars wrapped in graphene oxide and l-arginine (rGO-AuNS)	PIK3CA gene / Unlabeled	1.0×10^{-twenty} M	1.0×10^{-twenty} - 1.0×10^{-10} M	(184)

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Oral	Cerium oxide nanocubes ($ncCeO_2$) and reduced graphene oxide (RGO)	Cyfra-21-1/anti-Cyfra-21-1	0.625 pg/mL	0.625 pg/mL - 0.01 ng/mL	(185)

For biological changes generated by the presence of a tumor, such as the level of EpCAM epithelial cells (173) or the overexpression of enzymes such as glucose oxidase and peroxidase, leading to an increase in H_2O_2 levels (172), functionalization has been carried out with gold nanoparticles (168,169,171), and even biosensors without bioreceptors that detect platelet-derived growth factor-BB (PDGF-BB) have been developed by using bipolar exfoliated rGO due to the increase in surface area and conductivity provided in the bipolar electrochemistry process (170).
Other case studies have focused on the detection of prostate cancer (153,174,175), lung (176–178) and cervical (179,180) and with less abundant results related to ovarian cancer (181), liver (182), leukemia (183), gastric (184) and oral (185).

Challenges and projections

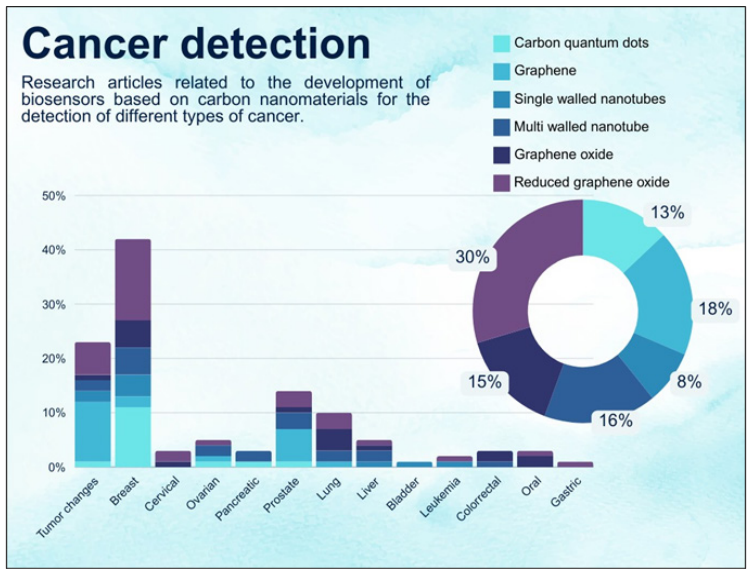

Figure 2. Statistics against research on electrochemical biosensors for cancer screening.

Figure 2 summarizes the amount of research into the detection of different types of cancer and the carbon-derived nanomaterials used. It can be seen that some types receive more research attention, such as breast and prostate cancer and the identification of cells related to malignant tumors in general. These cancers have been extensively studied due to their high incidence and interest in developing early detection and effective treatment methods.

However, it is essential to mention that other cancers are equally important to detect, although they do not receive the same amount of research. Examples of these are cervical, ovarian, and colorectal cancer, among others, and we even find that cancers such as bone cancer may lack significant research in the specific context of this article.

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This is important as, according to the World Health Organization, high-cost non-communicable diseases such as cancer continue to represent a global public health problem, causing around 41 million deaths annually, with low- and middle-income countries being the most affected (186). The identification of this disease is of vital importance and, within the category mentioned above, is primary bone cancer (PBC), studied in our research group, which consists of the mutation of bone cells and their high rate of cell division (187) a high prevalence of mortality and metastatic potential (188).

Among the factors hindering early diagnosis of HCC is the lack of coverage of medical centers with the required equipment and their high cost of operation and maintenance, and less access to specialized medical controls, which represent an increase in the survival rate, a lower risk of metastasis and a greater possibility of not losing limbs in advanced stage treatments (20). In addition, 20 out of 100 lesions caused by primary bone cancer have already had effects such as wounds, fractures, and infections when the presence of cancer is determined, but due to the difficulties of the procedure and turnaround time, treatment time is hampered (21).

A pressing challenge in these cases is related to the three types of samples used for bone cancer screening: serological, genetic, and histological, as their collection can be invasive and painful for patients, limiting the availability of samples for research and the development of screening systems (132). This highlights the need for non-invasive and sensitive screening methods for bone cancer. Despite the many advantages of biosensors, they have disadvantages that include limitations in stability and shelf life, susceptibility to sample interferences, challenges in sensitivity for detecting low concentrations, specific storage and operational requirements, high production costs, need for periodic calibration and maintenance, and concerns about specificity and selectivity. In addition, the development of specific biomarkers can be challenging. Although progress is being made to address these limitations, it is essential to keep these issues in mind when considering the implementation and application of biosensors in various areas (24).

Conclusions

Among the carbon-derived materials, graphene and reduced graphene oxide emerge as the most studied, probably due to their versatility and higher electrical conductivity that improve the sensitivity of biosensors. In the case of rGO, the presence of oxygen-rich functionalities facilitates functionalization with other particles, making them more suitable and promising in electrochemical biosensors for the detection of various types of cancer.

The most studied cancer types with carbon-based electrochemical biosensors are breast cancer, non-specific malignancies, and prostate cancer, suggesting the need for future studies in less explored types such as oral cancer, colorectal cancer, stomach cancer, and cancers without specific reports such as bone cancer.

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Among the various functionalization options, metallic gold and silver nanoparticles have been widely explored due to their good biocompatibility and excellent electrical conductivity, which makes them naturally able to improve the sensitivity of biosensors.

The detection limit is crucial to the efficacy of these devices as it defines the minimum concentration of a biomarker that the biosensor can reliably detect, and its optimization is essential to ensure rapid and accurate detection of cancer biomarkers. In general, the studies analyzed in this research presented low detection limits; however, due to the close relationship between early cancer detection and patient life expectancy, it is necessary to investigate new alternatives that offer the possibility of significantly reducing the current limits and thus achieve a significant impact on the health and prognosis of patients.

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