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Review Article

Carbon Nanomaterials for Breast Cancer Treatment

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Currently, breast cancer is considered as a health problem worldwide. Furthermore, current treatments neither are capable of stopping its propagation and/or recurrence nor are specific for cancer cells. Therefore, side effects on healthy tissues and cells are common. An increase in the efficiency of treatments, along with a reduction in their toxicity, is desirable to improve the life quality of patients affected by breast cancer. Nanotechnology offers new alternatives for the design and synthesis of nanomaterials that can be used in the identification, diagnosis, and treatment of cancer and has now become a very promising tool for its use against this disease. Among the wide variety of nanomaterials, the scientific community is particularly interested in carbon nanomaterials (fullerenes, nanotubes, and graphene) due to their physical properties, versatile chemical functionalization, and biocompatibility. Recent scientific evidence shows the potential uses of carbon nanomaterials as therapeutic agents, systems for selective and controlled drug release, and contrast agents for diagnosing and locating tumors. This generates new possibilities for the development of innovative systems to treat breast cancer and can be used to detect this disease at much earlier stages. Thus, applications of carbon nanomaterials in breast cancer treatment are discussed in this article.

1. Introduction

Cancer is one of the main causes of human death and a major public health concern worldwide [1, 2]. Cancer refers to the uncontrolled growth and propagation of cells. It appears in almost any part of the body when a cell accumulates a set of mutations, generally during various years [3, 4]. Growth promoting genes in normal cells are duplicated several times in cancer cells and often become unstable acquiring lethal characteristics as they multiply [5]. The American Cancer Society estimates about 1,735,350 new cancer cases diagnosed and 609,640 cancer deaths in the US by 2018 [6]. According to the World Health Organization (WHO), there were about 14 million of new cancer cases and 8.2 million cancer-related deaths worldwide in 2012, and it is expected that annual cancer cases will rise from 14 million to 22 within the next two decades [3]. Breast cancer is the second most frequent cancer with 1.7 million diagnosed cases worldwide [2, 4] and is currently the main cause of death in women with an annual increase of 1 million new cases which lead to 450,000 deaths per year [2]. Breast cancer is an uncontrolled growth of cells that starts in the breast tissues and affects both women and, very rarely, men (less than 1% of all breast cancer cases) [7, 8].

In its initial stages, breast cancer can be detected by means of image studies (mammography, ultrasound, and magnetic resonance imaging) or, less often, clinical trials of palpable tumors. Recently, strategies to mitigate breast cancer have focused on prevention and its early detection and treatment. Breast cancer treatment depends on the type of cancer [9] and its grade, that is, size and extension of the tumor [7]. Surgery, radiotherapy, chemotherapy, and hormonal therapy are the main types of cancer treatments [7, 10].

Although survival rates of breast cancer patients are higher than to those of other types of cancer, in general, current treatments are not entirely effective in stopping the spread and/or recurrence of breast cancer. Furthermore, they are not specific and harm healthy tissues and cells [11–14]. Finding a solution to this problem would have a great repercussion on patient's lifestyle, especially for those suffering metastatic breast cancers.

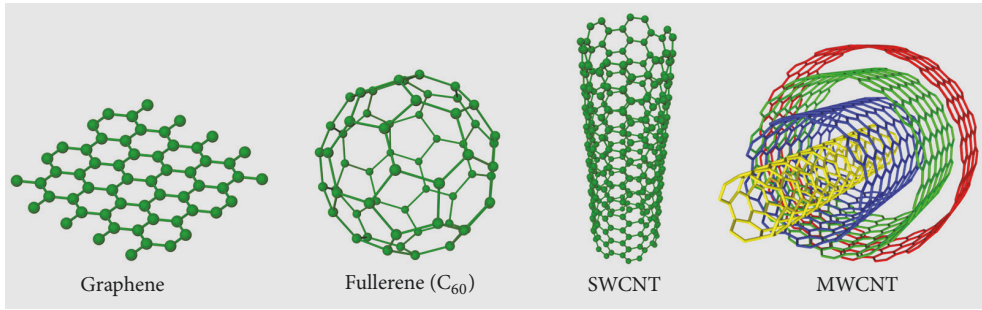

Figure 1: Structural representation of some allotropic forms of carbon.

In recent years, it has been observed that thanks to the nanotechnology advancements, it has been possible to improve the efficiency of conventional breast cancer treatments. One example of this is the release of chemotherapeutic drugs using nanomaterials [15–17]. Nanotechnology is considered one of the great emerging areas in science and technology that promises to make considerable advances in health. Nanotechnology can be defined as the science and engineering involved in the study, design, creation, synthesis, characterization, manipulation, and application of materials, devices, and functional systems through the control of matter at a nanoscale, that is, at the scale of atoms and molecules [18]. This also implies the use of phenomena and properties of matter at the nanoscale. According to the European Commission, the term "nanomaterial" refers to a natural, incidental, or manufactured material containing particles, in an unbound state or as an aggregate or as an agglomerate and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm [19].

Nanomaterials are promising tools that have been investigated for the advancement of current breast cancer treatment. Among these, carbon nanomaterials, fullerenes, nanotubes, and graphene, are of particular interest to the scientific community due to their unique physicochemical and biological properties. Many properties of carbon nanomaterials, such as size, shape, surface structure and charge, chemical composition, aggregation and/or agglomeration, and solubility, can greatly influence their interactions with biomolecules and cells. For example, carbon nanomaterials have been employed to produce exceptional images of tumor sites [20, 21], impressive potential as high-efficiency delivery transporters for drugs and/or biomolecules into cells [20, 22, 23]. Therefore, the main emphasis of this article focuses on the discussion of carbon nanomaterials and their current applications in the identification, diagnosis, and treatment of breast cancer.

2. Carbon Nanomaterials

Nanomaterials have interesting physicochemical and biological properties which depend on their structural characteristics. They have several uses for different biomedical applications [24], such as the development of innovative systems to treat breast cancer. There is a wide variety of nanomaterials synthesized and currently studied in the biology field; however, the scientific community is particularly interested on carbon nanomaterials due to their physical properties, chemical functionalization, versatility, and biocompatibility [16]. Although the properties of diamond and graphite have been extensively analyzed, other allotropic forms of carbon such as fullerene, carbon nanotubes (CNT), or graphene are of recent interest (Figure 1).

The first carbon nanostructure in closed cage-shaped (fullerenes) was discovered in 1985 by Kroto et al. (Nobel Prize in Chemistry 1996) by irradiating a graphite disc with a laser beam and mixing the resulting carbon gas with helium [25]. The fullerenes are either ellipsoidal or spherical, like a soccer ball (Figure 1), and are the third most stable carbon form after diamond and graphite. Fullerene (C_{60}) is better known as buckminsterfullerene in honor of Buckminster Fuller, an architect who successfully used the geodesic dome in architecture [25].

Although CNTs were observed decades ago, it was not seriously considered until the discovery of fullerene (C_{60}) [25] and the theoretical studies of other possible similar nanostructures. The attribution of the discovery of CNTs is controversial as a 1976 document reports the multilayer tubular structures identified with an electron microscope [26]. However, they were first experimentally observed in 1991 by Iijima, who used an insoluble material derived from the implementation of the arc-discharge synthesis technique [27].

CNTs have geometric structures which can be generated from graphite sheets. Graphene is defined as a single graphite layer (bidimensional), of finite size, constituted by a multitude of carbon atoms located in the vertices of a hexagonal net.

The structural formation of a CNT can be conceptualized as the envelopment of one graphite layer (graphene) resulting in a Single-Walled CNT (SWCNT). Multiple rolled layers of graphene result in a Multi-Walled CNT (MWCNT) (Figure 1). The diameter, internal geometry, and physicochemical properties of the CNTs depend on how the graphite layers are rolled (chirality vector dependence) [27] (Figure 2).

Currently, graphene is considered as the structural base of all the allotropic forms of carbon found since 1985 (Figure 1) and was synthesized in 2004 by Geim and Novoselov et al. (Nobel Prize in Physics 2010) by means of a very simple process which consisted in the exfoliation of graphite to obtain graphene layers using cellophane tape [28].

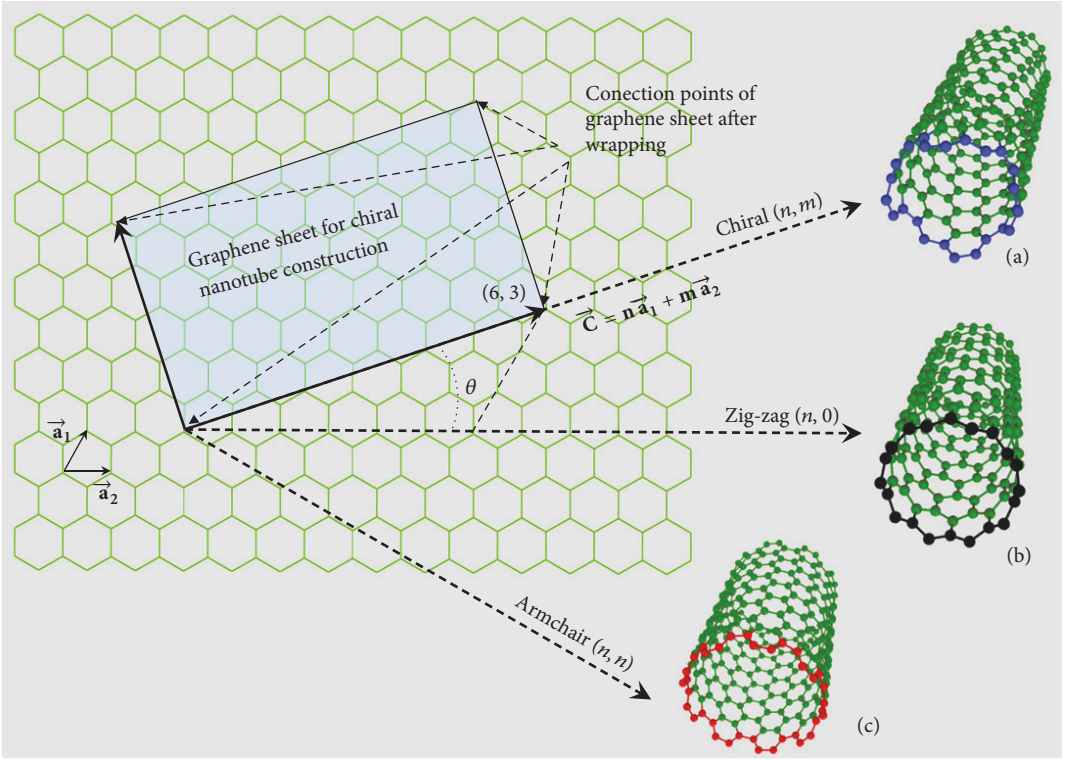

Figure 2: Representation of the chirality vector dependence with the generation of CNT species or types: (a) chiral, (b) zig-zag, and (c) armchair.

3. Studies Regarding Carbon Nanomaterials and Breast Cancer

The physicochemical properties and novel techniques of the synthesis of fullerenes, CNTs, and graphene have originated new research fields in biomedicine which aim to study and treat pathologies such as cancer with these carbon nanomaterials [16]. Several reports towards the application of carbon nanomaterials to diagnose and treat cancer (especially breast cancer) have been performed. Figure 3 shows the number of articles reporting the implementation of carbon nanomaterials for different applications to diagnose and treat cancer, such as breast cancer. The dates in the figure below are the results of a query in the Thomson Reuters database (Web of Science™ website) including studies from 2001 and 2017.

As indicated in Figure 3, the number of studies on the implementation of carbon nanomaterials for diagnosing and treating cancer worldwide has an exponential growth trend. There were more than 968 publications on breast cancer treatment until 2017, representing 14.4% of all the international publications on cancer until that year.

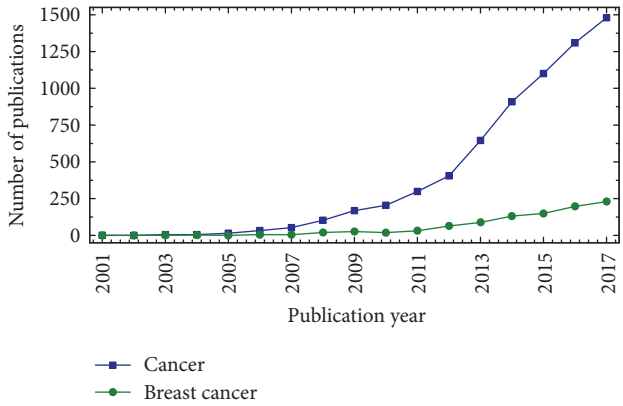

Figure 3: Annual trend in the number of international scientific publications related to the use of carbon nanomaterials for different applications to diagnose and treat cancer, such as breast cancer. Source: authors' calculations based on the data obtained in the Thomson Reuters database (Web of Science) in the period from 2001 to 2017.

4. Advances towards the Application of Carbon Nanomaterials for Breast Cancer Treatment

Literature data taken from the Thomson Reuters database (Web of Science website) suggest that carbon nanomaterials have potential uses as devices for selective and controlled drug delivery and/or release, contrast agents for diagnosing and locating breast tumors, and biosensors. They have also applications in photodynamic therapy.

4.1. Drug Release. Chemotherapy and hormonal therapy are the main cancer treatments used to destroy or control cancer cells in the entire body [7, 10]. Chemotherapy refers to the intravenous or oral administration of chemotherapeutic drugs. Although their very high efficiency, chemotherapeutic

drugs are not specific for cancer cells and, therefore, diverse side effects may emerge during treatment including hair loss, nausea, vomiting, fatigue, and risk of developing infections [13]. Anthracyclines (doxorubicin and epirubicin) and taxanes (paclitaxel and docetaxel) are the most common chemotherapeutic drugs [7]. About 60–70% of all breast cancer cases receive hormonal therapy, which refers to the blocking of hormones that promote the growth of cancer cells by means of pharmaceuticals [10] such as estrogen. The efficiency of this type of treatment depends on the biological characteristics of patients with hormone receptor-positive (estrogen-receptor-positive or ER+). Tamoxifen (TAM), aromatase inhibitors, and fulvestrant [7, 12–14] are common pharmaceuticals. TAM is an "antiestrogen", that is, a Selective Estrogen Receptor Modulator (SERM) that binds to estrogen receptors of cancer cells in the breast, blocking the action of this hormone. Currently, most of the ER+ breast cancers are treated with TAM whose efficiency has been tested during the initial and advanced stages in women of all ages [12, 13]. However, TAM has also side effects [12, 13].

One of the main problems associated with conventional drugs for breast cancer treatment is the unfavorable pharmacokinetics of their solubility, their limited biodistribution, their lack of selectivity, and the harm they produce to tissues. These drawbacks could be avoided if drugs were positioned in specific regions of the body. This would allow for reducing the drugs dosage, their concentrations on sites that are not of interest, and the side effects associated with chemotherapy and hormonal therapy [15, 16]. In this regard, carbon nanomaterials with potential uses for the administration of drugs against cancer and breast cancer are being analyzed [17, 22, 23, 29–31]; they are considered as advantageous systems to control drug release in the organism and increase the efficiency of treatments and reduce their toxicity [17, 32, 33]. However, carbon nanomaterials have some disadvantages including their lack of solubility and low reproduction rate through their chemical functionalization and structural characterization. Furthermore, their use in medicine is widely tested due to their potential toxicity [32–39].

Carbon nanomaterials have a very low solubility in aqueous or biological media when they are in their native form or are not chemically functionalized. In the latter case, the nanomaterial lacks the molecular aggregates (simple or complex) that provide its specific activities. Insolubility is very relevant in toxicology studies as the excessive accumulation of conventional drugs inside of biological environment, along with a high stability to enzymatic oxidation, hinders their elimination from the body. Therefore, the increase in chemical functionalization of carbon nanomaterials (fullerenes, CNTs, and graphene) favors their solubility and reduces the toxicity in the organism, increasing their viability for the administration and delivery of drugs (Figure 4) [40, 41].

CNTs are particularly of scientific interest due to their chemical stability, mechanic resistance, high electrical and thermal conductivity, high surface area, and tubular structure, as well as their ability to pass through the membranes of endothelial, vascular, and tumor cells [32, 38, 42–44]. The surface and high electrical and thermal conductivity of CNTs

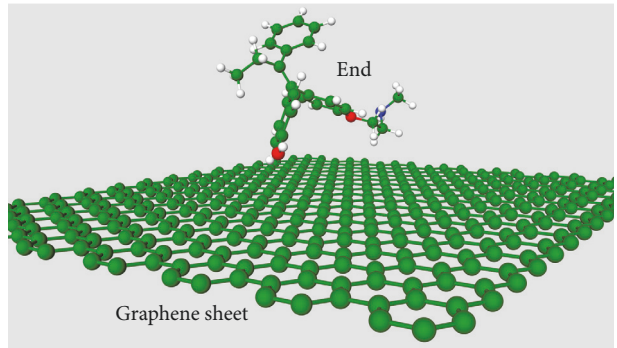

Figure 4: Schematic representation of graphene sheet functionalization with a chemotherapeutic drug (endoxifen).

allow other molecules (drugs, peptides, and nucleic acids) to be attached to their walls and extremities. Therefore, CNTs are considered as a viable alternative for the administration and delivery of drugs. Even chemical functionalization can increase the solubility of the extreme insoluble and hydrophobic fullerene. For instance, cationic-functionalized fullerenes have a stable solubility and are more able to bind anionic residues of cancer cells, which enable a targeted and controlled delivery of drugs [45, 46].

Graphene is a bidimensional carbon nanomaterial characterized by its simple synthesis [28]. It can be easily functionalized due to its high surface area and has a high electrical and thermal conductivity and a high flexibility and mechanical resistance [47, 48]. However, recent research shows that graphene is a very hard nanomaterial to be manipulated and synthesized in a controlled way. Furthermore, in the context of biomedical applications, graphene is lower toxic than CNTs and fullerenes [49].

Recent studies in nanomedicine concluded that fullerenes, CNTs, and graphene have favorable properties for the carriage, targeted, and controlled delivery of chemotherapeutical drugs including taxol (paclitaxel), docetaxel (DTX), doxorubicin (DOX), and others [22, 29, 31, 32, 44, 50–53]. Raza et al. [22] reported that the system conformed by the fullerene C_{60} and DTX (C_{60}/DXT) is able to improve up to 4.2 times the bioavailability of DTX and decreases the clearance of DTX by 50%. In addition, C_{60}/DXT system showed an effective controlled release of ~84.32% of DTX during a period of 120 hours, as well as compatibility with erythrocytes. Furthermore, an in vitro cytotoxicity assay revealed that, compared to free DTX, C_{60}/DTX system exhibits significantly increased cytotoxicity on human breast cancer cell lines (MCF-7 and MDA-MB-231). Zhang et al. [54] developed a multifunctional tumor-targeting drug delivery system (HA-MWCNTs/Tf@ART) for the in vitro treatment of breast cancer cells (MCF-7), by means of hyaluronic acid functionalized MWCNTs as drug carrier (HA-MWCNTs), with the transferrin as the targeting ligand (Tf) and the artemisinin (ART) as the drug, that showed synergistic antitumor efficacy due to the enhanced intracellular accumulation of ART in cancer cells and the simultaneous delivery of Tf and ART. Also, under radiation, this nanomaterial led to improved inhibition efficacy against tumors.

On the other hand, there is even experimental evidence of their pharmacokinetics and toxicity profiles which are favored when carbon nanomaterials are functionalized [22, 44, 45, 51]. Hence, carbon nanomaterials have biochemical characteristics that allow them to pass through cell membranes and release the drugs in specific tissues [43, 45].

4.2. Contrast Agent. Currently, the timely identification of breast cancer tumors is relevant for medical community as it allows, in the vast majority of cases, the eradication of the disease. The contrast agent technique has been of particular interest since it enables real-time identification of breast tumors. This technique uses specific antibodies for recognizing antigens which are expressed in the surface of certain tumors. These specific antibodies are added to fluorescent molecules or fluorophores which enable them to absorb electromagnetic radiation (light) under specific wavelengths and emit it under longer wavelengths. However, common contrast agents (CAs) used in the magnetic resonance imaging (MRI), such as gadolinium complexes and superparamagnetic iron oxides, generally cannot pass through the cell membrane. In this sense, the packaging of CAs onto or inside of carbon nanomaterials enables them to be internalized by cells. Even though gadolinium is the most used contrast agent in MRI, in recent years, research has focused on reducing the side effects and needed dose of this lanthanide metal, as well as enhancing the selectivity of desired organs and tissues. It has been shown that carbon nanomaterials could be more effective than common CAs by 2–100 times in their activity and lead to dose reductions by 1-2 orders of magnitude [55]. Moreover, carbon nanomaterials can penetrate cell membranes as well as couple with drugs. Therefore, the development of efficient contrast agents coupled with powerful medical imaging techniques is needed for increasing the sensitivity and specificity in breast cancer diagnosis.

Carbon nanomaterials have been found to be an excellent scaffold for contrast agents since they can be used to carry imaging agents, such as fluorescent labels and radionuclides, contributing to the generation of high-quality images and the early detection of breast cancer [20, 21, 49, 56–58]. Experiments have demonstrated that CNT can carry imaging agents [57] and demonstrated great potential of using functionalized MWCNT as efficient cell probes for MRI [59]. In vivo MRI on mice showed that CNTs functionalized with Gd (Gd-CNTs) have the ability to act as a good contrast agent [60]. Moreover, when CNT is functionalized with phospholipids, the biocompatibility increases, making it more stable while circulating in the reticuloendothelial system [61, 62].

In recent years, fullerene and their derivatives have been considered as one of the most promising agents for cancer imaging due to their specific physicochemical properties. In this regard, polyhydroxy fullerenes (PHF) have shown their potential use for cancer imaging [63]. In addition, it was observed that PHF nanoparticles functionalized with amines (PHF-NH_2) were soluble in water and exhibited green emission with a quantum yield of ~17%. Also, due to their high surface charge, PHF-NH_2 nanoparticles present excellent fluorescence properties and are able to easily penetrate cell lines, such as breast cancer cells (MCF-7) in vitro [64]. Furthermore, endohedral fullerenes (enclosed cage-shaped carbon structures that contain simple or complex molecules) have been successfully implemented as contrast agents for MRI [58].

Chelates are common in MRI studies due to their good contrast properties. These compounds have heavy metal ions in their structures such as gadolinium (Gd^{+3}). However, they frequently lose the metal or suffer transmetalation processes (release of Gd^{+3} in the organism), which severely affects patients with renal or hepatic dysfunctions [65, 66]. Recent studies indicate that this can be avoided by introducing the Gd^{+3} molecules inside the cavity of the fullerene cage and then functionalize it. This allows for a good solubility and a low toxicity of the chelate contained in the nanomaterial [67]. One of these fullerenes, the metallofullerenol $Gd@C_{82}(OH)_{22}$ is a potent activating agent of T Lymphocytes of the immune system when used as contrast agent in MRI. Metallofullerenol can efficiently inhibit the growth of tumors and is less toxic than some usual antitumor drugs to treat breast cancer such as taxol (paclitaxel) [57, 67].

Through their functionalization, fullerenes, graphenes, and CNTs are capable of carrying imaging agents or chemotherapeutic drugs for diagnosing and treating breast cancer [20, 67, 68]. This confers these systems an additional advantage and allows them to contribute to cancer detection and also to the targeted and controlled administration of drugs.

4.3. Photodynamic Therapy. Surgery and radiotherapy are breast cancer treatments commonly used to remove, eliminate, or control cancer cells in a specific area [7, 10]. Surgery allows for identifying the extension of the tumor and is commonly used to extirpate the part of the breast containing the cancerous tumor (breast-conserving surgery) or the whole breast (mastectomy) [7], unlike radiotherapy (destruction of cancer cells by means of high-energy rays or particles) which is usually recommended after surgery to reduce the risk of recurrence [7]. However, both surgery and radiotherapy are treatments that require invasive procedures; therefore, side effects are common.

Photodynamic therapy (PDT) is a clinically approved, minimally invasive treatment that can exert a selective cytotoxic activity towards malignant cells. PDT requires light, a photosensitizer, and molecular oxygen. The procedure involves the topically or intravenously administration of a photosensitizer to cancerous cells, followed by irradiation with a light of specific wavelength (inside of absorbance band of the sensitizer). The electronically excited photosensitizer transfers energy to ground state of molecular oxygen to produce excited singlet oxygen, which is cytotoxic, thus leading to direct tumor cell death via apoptosis or necrosis and damage of the tumor microvasculature and dramatic changes in tumor microenvironment [69].

Recently, the properties of carbon nanomaterials and their potential applications in PDT have been analyzed in an attempt to substitute current invasive thermal procedures that remove tumors or cancer cells of breast cancer [70–81]. Due to the carbon nanomaterials presence in the PDT,

cancer cells accumulate light-sensitive molecules (carbon nanomaterials) which, in the presence of oxygen, absorb the radiation of an infrared camera and turn it into heat. This induces cytotoxic effects that lead to an irreversible photodamage of cancer cells [71–74, 77]. In this regard, carbon nanomaterials have been used successfully to cause thermal ablation of solid tumors in breast cancer studies [16, 68, 74–76, 79–82]. Ogbodu et al. [74] reported for the first time the synthesis, photophysical properties, and PDT activity of ZnMCPPc-spermine-SWCNT (zinc monocarboxy phenoxy phthalocyanine upon conjugation to spermidine, as a targeting molecule, and then adsorbed onto SWCNT) on breast cancer cells (MCF-7). The in vitro cytotoxicity test of ZnMCPPc-spermine-SWCNT in cancer cells (MCF-7) proved to be relatively nontoxic in the absence of light. In addition, the results showed that the presence at 40 mM of spermine improves the effect of PDT, with up to 97% decrease in cell viability. Shi et al. [80] developed a multifunctional system based on the fullerene C_{60}, iron oxide nanoparticles, polyethylene glycol, and folic acid that offers a combination of advantages including cancer diagnosis, radiofrequency-assisted thermal therapy, PDT, and magnetic targeting applications. Furthermore, experimental results did not reveal any remarkable toxicity in vitro or in vivo. On the other hand, Nurunnabi et al. [81] developed a carboxyl functionalized graphene nanodots that act as a potential agent for the imaging of cancer in deep tissue/organs through a noninvasive technique and can efficiently kill breast cancer cells (>70% of MDA-MB231 cell line) through combined photodynamic and photothermal effects.

The results of the above studies reveal the potential uses of carbon nanomaterials in the photodynamic therapy and there were several challenges that must be overcome before being used as a standard technique for breast cancer treatment.

4.4. Biosensors. The generation of biosensors capable of detecting cancer tumors is very important, particularly for breast cancer whose detection during the early stage is a key factor for its eradication. Biosensors are able to identify tumor markers at such a low concentration (traces) where other techniques, such as image studies, may fail. Therefore, the numbers of studies towards the use of carbon nanomaterials as biosensors have increased [16, 82–84].

Engineers of the University of California in San Diego developed a graphene sensor capable of detecting mutations and early-stage breast cancer [85]. Also, researchers at the University of Manchester found that graphene oxide is not toxic to healthy cells and can act as an anticancer agent selectively targeting cancer stem cells [86]. Although these techniques are still new, their results are promising for preventing and treating breast cancer.

5. Conclusion

The study, design, creation, synthesis, manipulation, and application of carbon nanomaterials are an emerging technology with promising applications in the biomedicine field, particularly for detecting, diagnosing, and treating breast cancer. However, there is no carbon nanomaterial that presents simultaneously the desirable traits for therapeutic use in humans (nontoxic, good solubility, high specificity, easy functionalization, targeted and controlled delivery system, etc.). Furthermore, more research is needed to avoid potential side effects. Currently, the studies on toxicological properties and biomedical applications of carbon nanomaterials have a trend to increase, but these studies are still inconclusive for the implementation in human's traits. Research findings commented here are part of human efforts that contribute to the future implementation of nanotechnology-assisted solutions to treat breast cancer, the control of propagation and recurrence of breast cancer, and the reduction of toxic effects of conventional treatments.

Conflicts of Interest

All authors declare that they do not have any conflicts of interest to report.

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