

Detection of Molecular Markers of Cancer Through the Use of Biosensors

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Abstract

This review covers the literature published in recent years for current molecular markers detected by different types of biosensors; with the purpose of identifying the approaches that need to be concentrated. The review remarks that a great number of molecular markers can be used in the detection and monitoring of cancer, its detection can be the key for an early diagnosis of this disease, which would lead to a decrease in its mortality rate. However, molecular markers have presented some challenges to be applied clinically; this is due to the lack of reproducibility, sample variability, poor accessibility to patients with the same clinical conditions and other variables that have made them difficult to study. Furthermore, the use of biosensors has been increasing for the detection of molecular markers associated with some types of cancers; such devices have shown great potential for the study of molecular markers that are well known. These devices combine a biochemical recognition/binding element (ligand) with a signal conversion unit (transducer). Among the benefits that can provide the biosensors for the study of cancer it is that they are highly sensitive, reproducible, easy to use, do not use invasive samples (usually serum or plasma), are economic, portable (it provides the ability to monitor a patient during its treatment), among other advantages. Therefore, although there is much to be done in the study of molecular markers of cancer, it is necessary to design biosensors that support its detection and monitoring, to facilitate its study and provide both doctors and patients more tools to fight this disease.

Keywords: Biosensors; Cancer; Diagnosis; Molecular markers

Introduction

The United States National Cancer Institute, has developed a series of statistical data that has allowed to visualize how lethal can be this disease. Among the most significant data from the institute, we can highlight the prediction of an estimated of 1,658,370 new cases of cancer that will be diagnosed only in the United States, because its population is the most studied for monitoring and tracking the factors that are known to cause the development of this disease. Another prediction of the institute states that 589,430 people will die of the disease in 2015. Among the most prevalent ones here is to enlist the breast, lung, bronchus, prostate, colon, rectum, skin melanoma, Hodgkin lymphoma, thyroid, liver, renal pelvis, endometrial, leukemia and pancreatic cancer [1].

This text is focused on looking at molecular markers of cancer that may be excellent candidates for designing a biosensor that can monitor and detect early development of the disease. Since there are a variety of cancer types, this work focuses only on five, which are the most common in Mexico, they are breast, lung, prostate, ovarian and cervical cancer.

Advantages of Designing a Biosensor for Early Detection of Cancer

A biosensor is a bioanalytical device, which incorporates a molecular recognition together with a physicochemical transducer, providing us with more advanced tools for the analysis of biomarkers. To detect cancer antigens, monoclonal antibodies and aptamers are often used to capture agents and capture micro Ribonucleic acids (miRNAs) corresponding single stranded Desoxyribonucleic acid (ssDNA). A transducer is a device that converts the molecular recognition signal to an electrical signal. The transducer may be electrochemical (by potentiometry, amperometry, conductometry / impedimetry), optical (fluorescence, luminescence, colorimetric and interferometry), calorimetric (thermistors) or based on mass changes (piezoelectric / acoustic waves),

and are required because they offer high performance, high noise ratios and signals, have relatively low costs of instrumentation, have good resolution and with reproducible results (Table 1) [2]. It has been reported that several molecular markers have been successfully detected by different types of biosensors. The most commonly used are electrochemical biosensors and less explored are the calorimetric (Figure 1).

Electrochemical Biosensors

These types of biosensors are most commonly used because of its portability, low cost, easy to use and small size. Such biosensors can be used from home or in the doctor's office. The potentiometers and amperometric biosensors are two of the most common types of electrochemical biosensors. Potentiometric biosensors utilize ion selective electrodes that detect an electrical response when there is a molecular recognition of a specific element. Such biosensors have great potential for the use in the detection of cancer. For example, their use has been reported by detecting the cancer marker hPRL-3 in breast cancer cells MDA / MB231 with a high sensitivity [14].

In addition, amperometric transducers measure the current that is produced when the potential is placed between two electrodes. The oxidation and reduction reactions produce current, which can

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Methods	Disadvantages	Advantages	Ref
Biosensors	Not clinically used	No need of an aseptic working area	[3,4]
	Molecular markers are not reproducible in cancer diagnosis applications	No need of trained personnel	
		Fast	
		Easy to perform	
		<i>In situ</i> simple preparation	
		High analytical specificity	
		Reduction of reagents consumption	
		Decrement the analysis time	
		Increasing reliability	
		Sensitivity through automation.	
		Integration of multiple processes in a single device.	
		Portable electronic characterization unit.	
ELISA	Requires highly qualified personnel	Selectivity and sensitivity	[5-9]
	Consumes a lot of time	Improving the time required to yield results	
	Needs a Laboratory	Work well for samples without interfering molecules	
	Expensive		
Quantitative PCR	Expensive	Selectivity and sensitivity	[5,9]
	Needs a Trained personnel	Improving the time required to yield results	
	Need a Lab		
Microarrays	Difficult to perform		[10]
	Oxidation of tissue	Examination of expression of thousands of genes simultaneously	
	Expensive	Discrimination between RNA expression levels of different genes.	
	Limited by access	Detection of almost indistinguishable tumors.	
	Destructive testing		
	Lack of rigorous standards for data collection, analysis and validation		
	Quality and amount of RNA samples		

PCR: Polymerase chain reaction

Table 1: Biosensors comparison with other molecular techniques for the detection of cancer.

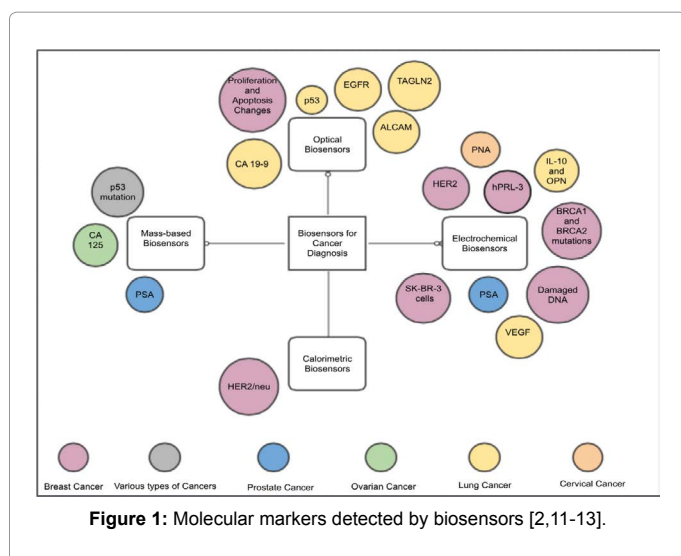
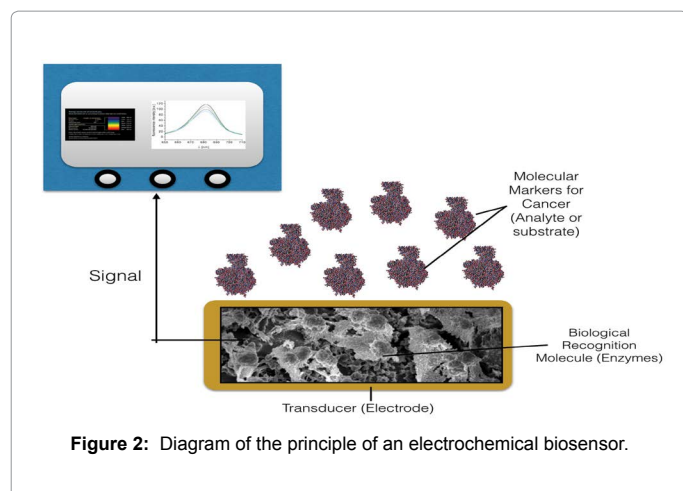


Figure 1: Molecular markers detected by biosensors [2,11-13].

be measured. It has been reported that amperometric biosensors used for detecting cancer, which utilize specific DNA sequences for recognizing elements useful for the diagnosis of cancer. These sensors

can detect the presence of cancer conjoined with genetic mutations; the chemical recognition strategy is through hybridization of specific DNA sequences that are being present in the genome of cancer cells. With this type of biosensors it has been possible to determine the BRCA1 and BRCA2 mutations which are associated with hereditary breast cancer [15]. Electrochemical biosensors offer the ability to detect damaged DNA and carcinogens that are causing the damage. In Figure 2, It can be seen that the electrochemical transducers can be functionalized with a molecule that allows the recognition a molecular marker for cancer. This recognition generates chemical reactions that create a potential difference, which sends a signal to a processor that is interfaced to quantify and / or detect the presence of a molecule of interest. Electrochemical transducers are also used in immunoassays and protein scans. The immunosensor, which use antibodies that are anchored to an electrochemical transducer, are also useful for the detection of cancer [15].

The making of multiple sensors that can detect many varieties of cancer can be the key to a greater method of prevention and detection that could reduce the death rate from this disease. Such biosensors with multiple transducers are individually functionalized for the detection of specific proteins or antigens. Such biosensors are reliable, can be inexpensive and are designed using semiconductor materials. It can be found in the literature the viability of electrochemical cell-based



biosensors, as these measures the changes in the impedance of the cell in response to the analyte. Such sensors may be called cytosensors since these utilize living cells as a biological recognition element, whose purpose is to monitor changes that are induced by various stimuli coming from the analyte [16].

Optical Biosensors

Optical biosensors are based on light, in other words, it measures the changes in specific wavelengths of light. The transducers may be luminescent, fluorescent, colorimetric, or interferometric. Optical transducers convert changes of the wavelengths in response to the recognition of the analyte and provide digital / electrical readings [17].

Biosensors with photonic crystals are a new class of biosensors using an optical transducer. Such biosensors are designed to capture the light areas or very small volumes, allowing measurements at a higher susceptibility, and then transmit the light to a high electromagnetic field to display the result. Through measuring the light reflected in the crystal, this technique can detect when and where the cells or molecules bind or dissociate from the crystal surface. It has been reported that this type of biosensors have been implemented for monitoring changes in proliferation and apoptosis of breast cancer cells that were exposed to doxorubicin, these measurements were used to determine the rate of drug cytotoxicity. This is important to monitor the effectiveness of the treatment [15].

Another example of optical biosensor is based on laser-induced fluorescence for the diagnosis and monitoring of cancer in the throat. After the biosensor is swallowed by the patient, the device directs a laser beam emitting at specific wavelengths of light on the surface of the esophagus. The walls of the esophagus reflect light to very specific wave lengths, and the difference in the visualization of different wavelengths is determined by the presence of normal cells or the presence of cancer cells. This sensor has been tested on over 200 patients and found adequately findings that correspond to a 98% of cases compared with other conventional methods. The use of biosensors prevents surgical biopsies and the pain associated recovery [15].

Biosensors Based on Changes of the Mass

Piezoelectric and acoustic biosensors are the two kinds of sensors that are based on a change of mass. Piezoelectric sensors are based on changes in the mass of a quartz crystal when the potential energy

is applied to them. These mass changes generate frequencies, which can be converted to signals. Immunosensors and microcantilever biosensors that are based on piezoelectric technologies have proven useful for the detection of cancer biomarkers. It has been shown that using piezoelectric biosensors coupled with PCR amplifications, can detect point mutations in the human p53 gene, which is overexpressed in most types of cancer. This is why mutations of p53 are critical to the development of cancer [17].

Calorimetric Biosensors

Calorimetric biosensors are less common in the diagnosis of cancer, and are based on measuring exothermic reactions. Many enzymatic reactions generate heat, and these changes in the temperature can be used to measure the concentration of the analyte. The reactions are monitored by measuring changes in the enthalpy, which indirectly provide the information necessary to calculate the concentration of the analyte. These biosensors are not commonly used for the diagnosis or forecast of cancer, but, there have been some features of these potential biosensors for their use in the detection of cancer. For example, in the use of calorimetric biosensors with gold nanoparticles based aptamers for the detection of cancer, the research group successfully detected two different types of cells, these include: acute leukemia cells and cells of Burkitt's. The authors argue that this strategy can discriminate between normal and cancerous cells [18].

Molecular Markers of Some Cancers

Because of the wide variety of cancers this review is focused on five of the most common cancers in America. Similarly, this text mentions just a few molecular markers that may be useful for the diagnosis of cancer.

Ovarian cancer

Ovarian cancer kills about 125,000 women worldwide each year and it is the second most lethal cancer and the fifth leading cause of death in women. Therefore, its early detection is very important between stages (I/II) because it causes a survival rate above 90%. Despite this, approximately only 20% of these cases are detected in this stage. This cancer exhibits a wide range of morphologies and variations in a clinical and genetic way during the process of tumor progression. Among the most commonly used methods of detection, we have the transvaginal sonography, a method that is designed to provide information on the size of the ovaries using medical imaging technology. However, the method lacks specificity and sensitivity to reveal cancer in early stages, and even in later stages the tumor may go unnoticed [19]. Over the past 20 years we have identified more than 200 potential molecular markers for the diagnosis of ovarian cancer. Among tumor markers can find the B2M, which is a beta-2-microglobulin and is overexpressed in the serum with 87% sensitivity. The B2M is a useful tool for monitoring the progress of the disease when used in combination with CA125 [19]. For several years, efforts have been made to identify suitable prognostic factors based on molecular markers. A large number of these markers have been further investigated up to this day, usually by immunohistochemically methods. Given the large number of candidates published, it is interesting that none of them has been approved for clinical use. Clearly, the literature shows that the use of a single molecular marker is not enough for the detection and progress of the disease [20].

This is due to the lack of reproducibility, since no one has the access to appropriate groups of patients for experimental studies, most studies that have analyzed such markers have managed only a small number

of samples. Biological variability and heterogeneity of tumor tissues in the ovary, do not allow patient groups exceeding 100 samples, so the reproducibility is precluded. Other reported issues in many studies state that the sample is heterogeneous with different histological subtypes, with different treatments applied, as well as with different levels and stages of the disease. In fact, ovarian carcinoma subtypes are immunophenotypically different and have different clinical features, such as the stage of the disease where symptoms and associated biomarkers are presented. Also, when a biomarker is compared with different proportions, and it's necessary to predict the next stage of the disease, this appears to be irreproducible [20].

Study quality is also a strong parameter which can influence the interreproducibility of biomarkers that may be analyzed. These studies include an inclusion and exclusion criteria, detailed tumor characteristics, patient selection, time tracking, additional treatments and specificity of the assay used. A particular technical challenge is the reproducibility associated with protein expression using specific antibodies to identify different epitopes. Some antibodies may recognize several different epitopes that are located in post translational modified regions in proteins, therefore, these epitopes are not expressed or detected in different conditions. Moreover, technical problems can be found in the same use of antibodies, for example, using the same antibody with different concentrations can potentially give different results. That is, low concentrations of antibody will detect higher expression of the markers. Conversely, high concentrations of antibody will quantitatively detect low concentrations of the biomarker and equivalent marker levels between antibodies and the results may not be quantifiable [20].

The ability to build tissue microarrays (TMA) has pointed to a new area of analysis that shall help in the validation of biomarkers based on tissue. A key benefit is the ability to analyze hundreds of patients while reducing costs, time, and increasing the reproducibility of the results by staining samples simultaneously. However, these advantages have their flaws. Since the tissue analyzed through microarrays is small samples derived from biopsies, the heterogeneity of each tumor can influence in the interpretation of results. Fortunately, in some studies, this sampling variability is reduced by the size of the sample set. Moreover, since microarrays often use hundreds of specimens collected through decades, the time between the collection of tumors and the construction of microarrays can influence the antigenicity of biomarkers. Finally, in the construction of microarrays, it can occur a tissue oxidation and induce a loss of antigenicity of some antibodies [20].

There is a great need for diagnosis with biomarkers for cancer subtypes and predictive biomarkers to identify women with severe carcinomas that are not helped by conventional therapies. For other subtypes, the development of new treatments will require the co-development of predictive biomarkers [20].

Breast cancer

Some biomarkers have been identified for the detection of breast cancer as hormone receptors, such as estrogen (ER), progesterone (PR) receptor 2 and the epidermal growth factor; these are routinely used for the prognoses of breast cancer and therapeutic purposes [21]. The estrogen receptors are members of the superfamily of nuclear transcription receptors that are activated by steroid hormones such as estrogen. This hormone and its receptors are involved in various processes including cell proliferation, inhibition of apoptosis, invasion and angiogenesis. The estrogen has two isoforms, ER- α and ER- β , both expressed in normal mammary glands; ER- α is directly involved in

disease processes, including breast cancer. Expression of estrogen receptor is clinically used to detect amplification and overexpression of HER2 in a routine assay [21]. The IHC is a quantitative method to detect the expression of HER2 receptors on cell surfaces using a gradual system (0: no, 1 β : Negative, 2 β : wrong, 3 β : over-expressed). It is also the most used method on a routine basis to detect levels of HER2, however, it has some disadvantages (different fixing protocols, registration systems and placement levels, the selection of antibodies) that compromise the its reproducibility and validity. The quantitative FISH method measures the number of gene copies, which is more reproducible and accurate than the IHC. To obtain valid results, the American Society of Clinical Oncology and the College of American Pathologists recommendations published a guide for assessing HER2 [21].

Cervical cancer

Cervical cancer is one of the most common cancers. Patients have an average surviving period of 5 years of recurrent cervical cancer and only about 5% survive and this is caused by a lack of effective therapy system. Epidemiological studies have shown that the primary risk factor is the development of a pre-invasive cervical intraepithelial neoplasia (CIN) and invasive cervical carcinoma which is related to infection with HPV [22]. The continued expression of the E6, E7 and E5 of the high-risk subtypes of HPV oncoproteins also seems to require maintenance of malignant phenotypes in patients with cervical cancer. The detection of infection with known HPV subtypes is considered to be used as useful markers for the diagnosis of cervical cancer. However, the malignant transformation of cervical epithelial cells requires long periods of latency. It is estimated that the average duration of preclinical lesions can exceed 16 years. It has been suggested that most infections with known HPV subtypes typically last less than one year. Furthermore, subtypes of HPV can also be found in healthy women without any clinical evidence of cervical lesions. Hence, the lack of markers to monitor the progression in cervical cancer has meant that patients receive a poor treatment. It has been estimated that over 75% of reported cases of cervical cancer are squamous cell carcinomas [22].

Prostate cancer

Prostate cancer is the second cancer with the highest incidence on the world; therefore, its diagnosis in early stages has become very important. Usually the detection includes a digital rectal examination and quantification of prostate specific antigen (PSA) in blood samples. In addition, transrectal biopsies are performed causing side effects such as bleeding and infection. All these procedures are not 100% reliable and may cause a misdiagnosis, leading to incorrect treatment which causes complication and death [22,23]. Histopathological analysis of biopsies using a needle is also performed; however, there are still some drawbacks that must be solved, such as small sample size, tumor location and the pathologist's subjective evaluation. The linear discriminatory analysis, microarrays and Real-Time Quantitative Reverse Transcription PCR (Real-Time qRT-PCR) have been used for the diagnosis of prostate cancer. These molecular methods provide 100% accuracy [24,25].

Between the molecular markers for the detection of prostate cancer that has been reported in the literature, we can find AMARC (methylacyl alpha CoA racemase), which is an enzyme involved in the oxidation of branched-chain fatty acids, which is overexpressed in prostate and other types of cancers. AMACR can be detected in tissue by immunohistochemistry antigen P504S, similar to AMACR. The blood and urine samples are also useful for detection of gene mRNA of AMACR using qRT-PCR [25,26].

Furthermore, the nuclear matrix protein EPCA (Early Prostate carcinoma antigen), is found increased in prostate cancer and can be detected in a blood analysis by using ELISA or tissue immunohistochemistry [25,27].

Lung cancer

Lung cancer is a disease with the highest record of deaths in the world. It has been reported that only in 2008 were recorded 1.6 million new cases of lung cancer, from which, 1.4 million people died around the globe [28]. It is said that the mortality rate has not decreased over the last 10 years by the lack of clinical symptoms early, which causes the disease is diagnosed in later stages [29]. Among the subtypes of lung cancer, we can find the non-small cell lung cancer (NSCLC). This cancer has a survival rate of 15% in 5 years. However, this is caused because 75% of patients detected with NSCLC are performed in advanced stages and surgery is no longer feasible [30]. Therefore, it is necessary to detect lung cancer in early stages, ideally before cell invasion. Unfortunately, the aggressive and heterogeneous nature of this cancer has limited and blocked the efforts to reduce mortality using scanning techniques [31].

Among the scanning techniques for the detection of lung cancer can be found the chest radiography and sputum cytology, however, these have not been helpful in reducing the mortality. Currently, it can be found more sophisticated techniques such as low-dose computed tomography (LDCT) which is widely used, and it reduces mortality by 20% compared with to the chest radiography [32].

It is still possible to find more complex methods, such as computed tomography and positron emission tomography with 18F-fluorodeoxyglucose (18F-FDG PET / CT), which is used routinely in oncologic imaging, however, this technique cannot discriminate between individuals with early stage disease to healthy individuals, including the reports of false positives, which harms the healthy subjects

treated with chemotherapy or surgery, which may not need and can bring physical and psychological complications in patients and families.

The growth of a tumor is accompanied by genetic and protein changes, which may find methylation or point mutations of DNA, RNA and proteins expressed in an aberrant or mutated way. We may also find carbohydrates, cytokines and chemokines altered, volatile organic compounds from peroxidation in the cell membrane. All of these changes can be used to detect with months or years in advance of clinical signs that may lead a diagnosis (Table 2) [33].

There are reports that suggest that detecting antibodies related to a tumor associated with a NSCLC can be foreseen five years before an autoradiography could identify it [33].

In order to design strategies that may lead to early detection of lung cancer, various techniques have been used for detection of antigens derived from the presence of cancer in the serum, these antigens may be found through ELISA and the detection method by hybridization of miRNA, however, these are very complicated, expensive and consume a lot of time and do not have sufficient sensitivity for low concentrations of these markers in early stages of cancer [2]. Mutations in proto-oncogenes feature a large proportion of abnormalities that are being targeted by many therapeutic treatments in lung cancer. For example, the EGFR mutation in non-small cell lung cancer (NSCLC) is present from 10% to 15% of caucasian patients with an advanced rate of disease [42].

It's also been reported that using random populations of people, where the compared their tyrosine-kinase inhibitors with conventional chemotherapy EGDR on clinically appropriate populations, and demonstrate that inhibitors have a superior effectiveness compared to conventional chemotherapy in terms of response, a progression-free

Cancer type	Molecular markers	Conventional detection studies	Molecular detection studies	Ref.
Ovarian	CA125, HE4, mesothelin, M-CSF, osteopontin, kallikrein(s) and soluble EGF receptor, (CA 125, CA 19.9, TATI, CASA, CEA, TPA, TPS and CYFRA21-1)	Transvaginal sonography (TVS), pelvic exam, ca-125 test	RT-PCR, microarray, this for gene expression, flow cytometry	[34]
Breast	Significantly up-regulated in DCIS: DEPDC1, NUSAP1, EXO1, RRM2, FOXM1, MUC1 and SPP1, other markers: anti-CK7, anti-CK20, anti-pan-CK, anti-CK8/CK18, anti-CK8, and anti-CK18, Ki-67, hormone receptors, and the human epidermal growth factor receptor 2	Mammograms, breast magnetic resonance imaging, scintimammography, thermography, ductogram, nipple discharge exam, nipple aspiration, and ductal lavage	RT-PCR, microarray, this for gene expression, flow cytometer	[21,35,36]
Uterine cervix	Over-expression G30CC, erbB2 (HER2/neu)		RT-PCR, flow cytometry	[37,38]
Prostate	DD3, PSA, HPC1, CAPB, PCAP, ELAC2, HPC20, 8p 22-23, HPCX	Digital rectal examination, transrectal ultrasound	FISH, CGH, qRT-PCR this are for gene expression, flow cytometry	[39,40]
Lung	(Tenascin-C, [C-X-C motif] ligand 14, S100 calcium binding protein A9, and keratin 17) were found to be upregulated in ELF, CD24+/CD38-		Microarray, qRT-PCR, flow cytometry	[41]

Table 2: Molecular markers used for the detection of certain cancers, conventional and molecular methods that are currently used.

survival (PFS), tolerability and quality of life, resulting in approval of these agents for the treatment of lung cancer [43]. Besides EGFR, it has also been discovered other mutations to detect lung adenocarcinoma, these mutations include BRAF [43], KRAS [44,45], HER2 [46,47], PTEN, AKT, and PIK3CA mutations [48]. In squamous cell of lung cancer, it has been found a variety of abnormalities, including mutations of DDR2, PIK3CA, PTEN, AKT, KEAP1, and NFE2L2 [48]. Many of these blocks or groups of mutations are located around the tyrosine-kinase genes of interest in the catalytic domains. Recurrent gene rearrangements involving ALK, ROS1, RET and NTRK and have been listed as important drivers in tumor growth factor in lung cancer. ALK rearrangements occur in approximately 3% to 5% and adenocarcinomas are associated with the response ranges from 60% to 80% with ALK inhibitor crizotinib [49,50].

The fusion of genes that share structural features that determine its detection as is the fusion of ALK, ROS1 and RET, retain full domains of tyrosine-kinase that are merged. This merge provides tail-tail domains (coiled), resulting in a ligand-independent activation of constitutive signaling proteins. These chromosomal rearrangements may form paracentric and pericentric reversals, or translocations between non-homologous chromosomes [50].

Conclusion

With the existing molecular techniques, there are a variety of reported and studied molecular markers that may be excellent candidates to be detected by using biosensors. However, these same yet need to continue to be investigated in detail, as not all are overexpressed in the same conditions in all patients, which could cause false positives and these limitations in the homogeneous behavior of molecular markers is primarily due to genetic diversity of samples, the conditions for taking a tissue, the lifestyle of the patient, the different treatments that the patients have been exposed, and among other things.

Furthermore, the use of biosensors for early detection of cancer and even monitoring the progress of the disease will be in the future the key factor for reducing the mortality rate of this disease. Therefore, it has to be studied in detail each molecular marker that has been registered and study each type of cancer, in order to find those that can be detected only in early stages, and thus, make biosensors essential tools for the preventive combat of cancer and save lives.

Finally, we can identify from this research, when comparing the five types of cancer in terms of knowledge in molecular markers, it can be suggested that lung and breast cancer are between the among the more studied tumors, due to their incidence. The National Cancer Institute reported that the most common type of cancer is breast cancer, with more than 234,000 new cases projected just in United States in 2015. The next most common cancers are prostate cancer and lung cancer. In regards, the more studied biosensor, it can be determined that electrochemical sensor are the most used for the study of cancer because of its transportability, friendly used and small size. Such biosensors can be used everywhere from home or in the doctor's office; hence, these kind of devices can be commercialized to patients, and become popular like insulin biosensors.

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