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A Review on Biomarkers in Cancer Diagnosis

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A B S T R A C T

The field of cancer biomarkers has evolved significantly, enabling more precise detection and better patient outcomes. Advances in technology have opened new opportunities to identify and validate potential diagnostic and therapeutic biomarkers. These biomarkers, including proteins, nucleic acids, and metabolites, reflect the altered physiological state in cancer and hold promise for early detection, prognosis, and treatment monitoring. Despite numerous discoveries, only a few have gained clinical approval, indicating the need for further validation. This review explores the types, platforms, recent advances, limitations, and the future direction of biomarkers in cancer research.

Keywords: Biomarkers, Cancer Diagnosis, Cancer Therapy, Diagnostic Indicators, Treatment Effectiveness.

1. Introduction

The knowledge of cancer and its therapy has advanced significantly over the previous three decades. Molecular biomarkers are compounds that indicate the presence of cancer in the body and are used in cancer research. Variations in messenger RNA (mRNA) and/or protein expression, post-translational modifications of proteins, metabolite levels, and genes are examples of biomarkers. Genomic, proteomic, and metabolomic biomarkers have the potential to be used to diagnose cancer. Prostate tissue secretes PSA, which is authorized for use in the treatment of prostate cancer. Ovarian tissue secretes a protein known as CA-125, which is thought to be unique to ovarian cancer. Finding these biomarkers is very important since early cancer detection may improve available treatments, improving survival rates and enabling better disease management[1]. Less than 12 biomarkers for cancer response, surveillance, or recurrence have been authorized by the US Food and Drug Administration (FDA) in the last 20 years. This is unexpected given that thousands of biomarkers have been identified or recognized as possible indicators for the identification and diagnosis of cancer. None, though, have shown to be successful thus far the molecules known as biomarkers are those that change significantly during cancer and have significant therapeutic implications. Prognostic, predictive, and diagnostic biomarkers can be proteins, isoenzymes, nucleic acids, metabolites, or hormones. The current focus in clinical cancer diagnosis is on creating analytical techniques that can detect biomarkers in a sensitive and parallel manner, making point-of-care diagnostics useful[2]. The currently available clinically approved cancer biomarkers are most beneficial However, single biomarkers with satisfactory sensitivity (ability to detect individuals with the disease) and specificity (ability to distinguish individuals with the disease from those that are either normal or have some other condition) have not been identified for the most common cancer[3]. Global cancer statistics for 2018 predicted 18.1 million new cases and 9.6 million cancer-related deaths. Lung, breast, and prostate cancer are the three main types of cancer The primary reason for the development of new diagnostic methods for cancer detection is that the disease is curable if it is discovered early. A biomarker is a crucial tool for the identification and tracking of cancer. Examples of biomarkers include changes in gene transcription or translation, protein product modification, and/or gene mutations[4]. Currently, early illness detection and recurrent disease identification are the most prominent uses of tumors biomarkers. In the future, more advanced diagnostics that might anticipate the course of a tumors and forecast how each tumor would react to specific treatment medications might be created. Finding stable biomarkers that can be regularly assessed in readily accessible samples is one of the main issues in cancer research It has been demonstrated over many years that serum and other bodily fluids include cell-free DNA and RNA and that these circulating nucleic acids may serve as potential biomarkers. Clinical oncologists might benefit from quantifiable characteristics known as diagnostic and prognostic biomarkers when they initially contact with suspicious patients. These are especially helpful in determining who is at risk of making an early diagnosis and choosing the most effective treatment option Tracking therapy responses These biomarkers come in a variety of forms; conventional biomarkers are those that may be evaluated using radiological Methods[5].

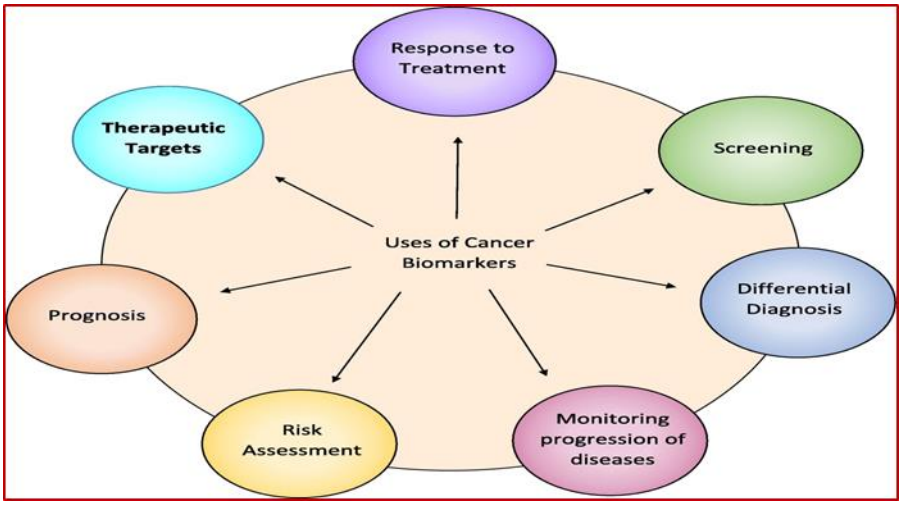

Figure 1: Uses of cancer biomarkers

2. PLATFORMS FOR THE ANALYSIS OF BIOMARKERS

2.1 GENOMIC TECHNOLOGIES

Genomic technologies make it possible to determine and keep track of genetic changes brought on by environmental agents and the genetic elements underlying carcinogenic transformation. Genomic technologies that are frequently utilized include fluorescence in situ hybridization (FISH), PCR-based tests, and DNA microarrays. These genomic approaches have several advantages, such as the availability of numerous robust high-throughput testing methods and the capacity to amplify particular DNAs and RNAs that may be present in very low concentrations in the specimens. Genetic mutations, loss of heterozygosity (LOH), microsatellite instability (MSA), and DNA methylation are examples of DNA-based biomarkers. The majority of mRNAs discovered in tissues and physiological fluids are used as RNA-based biomarkers. SAGE technology is a relatively new advancement that is sensitive, all-inclusive, and capable of analysing gene expression in species whose genomes are unknown. Microarray technology has been used by several scientists to monitor and modify gene expression. Following BRCA1-induced expression in MDA435 breast cancer cells, several genes were overexpressed, including the early growth response 1 (EGRI) gene and the DNA-damage inducible gene (GADD45). Ki67 and the pro thymosin A gene, which were predictive indicators of breast cancer in the past, were two of the repressed genes[6].

2.2 PROTEOMIC TECHNOLOGIES

Although it was first used to refer to large-scale, high-throughput protein separation and identification processes, the word proteomics has since been extended to cover protein structure and functional analysis. Information from proteomics differs from and complements information from genomes. By marking distinct protein populations with fluorescent dyes, the differential in-gel electrophoresis technique, which was developed recently, makes it easier to evaluate protein expression. Recently, this method has been applied to find proteins that are differently expressed in breast cancer and squamous cell carcinoma. The primary constraints of the 2D-PAGE technique are its incapacity to identify proteins with low abundance and the challenges associated with implementing it in high-throughput assays. Protein-based biomarkers include variations in the amounts and posttranslational modifications of proteins detected in tissues and body fluids. One benefit of proteomic approaches is the availability of well-established and quantitative testing techniques. The majority of cancer biomarkers that are currently employed in clinical settings are antibody-based assays for proteins in sera, such as cancer antigen-125 (CA-125) for ovarian cancer and prostate-specific antigen (PSA) for prostate cancer. Previously, the main proteomic technique for finding biomarkers was mass spectrometry in conjunction with two-dimensional polyacrylamide gel electrophoresis (2D- PAGE)[7].

2.3 METABOLOMIC TECHNOLOGIES

Metabolomic methodologies evaluate populations of low-molecular-weight metabolites using analytical techniques such as gas-liquid chromatography (GLC), high-performance liquid chromatography (HPLC), nuclear magnetic resonance spectroscopy (NMR), and mass spectrometry (MS). Metabolomics refers to the study of metabolites found in cells, organs, and biological fluids. Because the identities, concentrations, and fluxes of these molecules represent the results of interactions between gene expression, protein expression, and the cellular environment, metabolomics has the potential to be useful for both cancer detection and monitoring. Changes in cellular metabolites are frequently a part of carcinogenic transformation, and body fluids can contain metabolites of environmental poisons that are crucial to this process[8].

3. DIAGNOSTIC & PROGNOSTIC BIOMARKERS

Recent discoveries in genomes and proteomics have yielded candidate markers that may be useful for cancer screening, even though few such markers have made it to the clinic. One of the novel tumours indicators that could aid in the early detection of cancer is calcitonin. A patient with thyroid medullary carcinoma has higher serum levels of calcitonin, which may be helpful in screening for this cancer after additional clinical assessments. It has been discovered that a number of identified cancer biomarkers have limited sensitivity since they are only present in a tiny fraction of individuals with a certain kind of cancer. These markers can help identify recurring diseases in patients whose tumours generate that specific marker, even though they are not effective for broad screening. CA- 125 is one such biomarker that is found in a subset of ovarian tumours. It is not advised to use CA-125 for general screening because it is also increased in endometriosis and a few other benign disorders, and it is unable to detect over 50% of early malignancies. One marker for colon cancer is CEA. It is helpful for follow-up but has inadequate specificity and insufficient sensitivity to be utilized as a screening marker[9].

4. ADVANCES IN BIOMARKER DISCOVERY

Finding and confirming novel biomarkers can be accomplished through the use of differential expression of proteins for many years, 2D-PAGE and mass spectrometry have been the main methods utilized in conventional proteomics investigation to find novel biomarkers. Many new biomarkers have been found thanks to recent developments in biomarker research that use gene arrays in addition to proteomic technologies like mass spectrometry and two-dimensional electrophoresis (2-DE). Nuclear matrix protein-22 and bladder tumours antigen (BTA) are two recent urine-based biomarkers that the FDA approved as diagnostic indicators for bladder cancer. Calreticulin (CRT), another potential diagnostic biomarker for bladder cancer, was recently discovered. Using nanoLC-MS/MS, Sokolowska et al. found receptors for the tumour differentiation factor (TDF), which is expressed in human breast and prostate cancer cells. Notably, the receptors in question were members of the heat shock 70-kDa protein family (HSP70), indicating a connection between the presence of cancer and this protein family.[10]

5. PREDICTIVE BIOMARKERS

Increasingly, markers that seek to predict cancer outcomes instead of early detection have been found in recent years. This advancement results from the ability of novel genomics and proteomics techniques to identify genes and proteins linked to certain cancer stages. Furthermore, these markers are frequently seen in the bloodstream at detectable concentrations, maybe as a result of tumours that are larger and necessitate a prognosis test. These biomarkers can differentiate between tumours that are invasive and non-invasive, metastatic and nonmetastatic, and benign and life-threatening[11].

Biomarker	Glycosylated	Cancer type	Specimen	Clinical use
Alpha-feto protein (AFP)	Yes	Testicular	Serum/plasma; Amniotic fluid[a]	Management of cancer
AFP-L3%	Yes	Hepatocellular	Serum	Risk assessment
Beta-2-microglobulin (B2M)	Yes	Blood cells	Serum, Urine, Cerebrospinal fluid	Monitoring progression and recurrence
Bladder tumor-associated antigen	Unknown	Bladder	Urine	Monitoring disease
CA 15–3	Yes	Breast	Serum/plasma	Monitoring disease; Response to therapy
CA 19–9	Yes[b]	Pancreatic	Serum/plasma	Monitoring disease
CA 27–29	Yes	Breast	Serum	Monitoring disease; Response to therapy
CA 125	Yes	Ovarian	Serum/plasma	Monitoring disease; Response to therapy
Carcinoembryonic antigen (CEA)	Yes	Colon	Serum/plasma	Monitoring disease; Response to therapy
c-Kit	Yes	Gastrointestinal stromal tumors	Tissue	Detection of tumor; Patient selection
EpCAM, CD45, cytokeratins 8, 18+, 19+	Yes	Breast	Whole blood	Monitoring progression and survival
Epidermal growth factor receptor (EGFR)	Yes	Colon	Tissue	Therapy selection
Estrogen receptor (ER)	Yes	Breast	Tissue	Prognosis; Response to therapy
HER2/NEU	Yes	Breast	Serum; Tissue	Monitoring progression; Therapy selection
Human chorionic gonadotropin	Yes	Testicular	Serum	Staging of cancer
Human epididymis protein 4 (HE4)	Yes	Ovarian	Serum	Monitoring progression and recurrence
Fecal occult blood (haemoglobin)	Yes	Colorectal	Feces	Detection of tumor
Fibrin/fibrinogen degradation product (DR-70)	Yes	Colorectal	Serum	Monitoring disease
Free prostate specific antigen	Yes	Prostate	Serum	Screening for disease
Nuclear mitotic apparatus protein (NuMA, NMP22)	Yes	Bladder	Urine	Diagnosis and monitoring disease
p63 protein	No	Prostate	Tissue	Differential diagnosis
Plasminogen activator inhibitor (PAI-1)	Yes	Breast	Tissue	Monitoring disease; Therapy selection
Progesterone receptor (PR)	Yes	Breast	Tissue	Therapy selection
Pro2PSA	Yes	Prostate	Serum	Discriminating cancer from benign disease
Thyroglobulin (Tg)	Yes	Thyroid	Serum/plasma	Monitoring disease
Total PSA	Yes	Prostate	Serum	Diagnosis and monitoring disease
Urokinase plasminogen activator (uPA)	Yes	Breast	Tissue	Monitoring disease; Therapy selection

Notes.
[a]Also used in prenatal diagnosis of birth defects, a non-cancer application.
[b]A tetrasaccharide carbohydrate that is usually attached to *O*-glycans on the surface of cells.

Figure 2: Biomarkers and their clinical use

6. LIMITATIONS OF BIOMARKER DEVELOPMENT

Proteomics limitations in the creation of biomarkers- By discovering toxicity biomarkers, proteomics has made it possible to better understand the underlying mechanisms of toxicity and clinical therapies. It has also been utilized to boost the sensitivity and speed of toxicological screening (Kennedy, 2002). Proteomics enhanced the predictability of early drug development, discovered non-invasive biomarkers of toxicity or efficacy, and shed light on the mechanisms of action of a wide range of chemicals, including metals and peroxisome proliferators (Kennedy, 2002).23 Low-detection limit clinical biosensors are very promising for the early identification of crippling illnesses. The ability to identify target molecules at the single molecule level have been demonstrated thanks to recent advancements in sensor development. For such sensors, measurement fidelity is a critical performance criterion that has not received enough attention. Since we anticipate that systems with higher sensitivity will also respond more strongly to interfering molecules, measurement fidelity is defined by the system's false positive rate[12].

7. FUTURE OF CANCER BIOMARKERS

The field of biomarker discovery has to be advanced by a significant and coordinated effort. The paucity of effective biomarkers for cancer detection, screening, and treatment is evident from recent developments. The majority of biomarkers do not meet the necessary standards for sensitivity and specificity to be used in clinical studies to measure the impact of drugs and for the identification of cancer. Prognostic and predictive cancer biomarkers hold the key to the future of clinical cancer management. The requirement for markers that indicate which treatment choices are most likely to be beneficial for a given patient with a given cancer and that predict outcomes has increased due to the development of new medicines. The need for a range of new biomarkers that are both sensitive and specific is expected to be met by the recent advancements in genomic and proteomic technologies, such as gene array technology, enhanced two- dimensional gel electrophoresis, and novel mass spectrometric techniques, in conjunction with advances in bioinformatic tools. Determining the cost- effectiveness of clinical cancer management will be significantly influenced by biomarkers that identify tumours, forecast cancer outcomes, and affect therapy selection. When combined, a limited panel of biomarkers will accurately predict the molecular staging of a disease. A key objective for the future of oncology is the development of straightforward diagnostic kits that may be used in the clinic or by prospective patients themselves, and that will reliably and precisely predict malignancy[13].

8. CONCLUSION

Molecular markers are more likely to enhance diagnostic imaging throughout the screening process than to completely replace it shortly. When used in conjunction with diagnostic imaging, non-invasive molecular markers can help detect cancer sooner and streamline the screening process, giving physicians more tools in their arsenal. All of these, along with the entire genome, can be analyzed more quickly and affordably because of a variety of platforms and high throughput technological advancements. This is significantly influencing how medicine is currently practiced, resulting in the creation of precision medicine through a personalized approach. therapeutics grounded in pharmacogenomics. Three Recent developments in mass spectrometry, two-dimensional gel electrophoresis, gene array technology, and other proteomic and genomic technologies, along with improvements in bioinformatic tools, hold great promise for addressing the need for the identification of a wide range of novel biomarkers that are both specific and sensitive.18 Future and current genomic and proteomic technologies hold great promise for discovering new biomarkers. By enabling the customization of treatment to target the patient's unique molecular lesions and by offering instruments for anticipating and tracking therapeutic responses, these biomarkers can greatly improve the effectiveness of cancer care.

REFERENC*ES :*

[1] *Maruvada P., Wang W., Wagner P.D., Srivastava S., "Biomarkers in molecular medicine: cancer detection and diagnosis," Biotechniques, vol. 38(Supplmentry 4), pp. 9-15, 2018.*

[2] Manne U., Srivastava R.-G., Srivastava S., "Keynote review: Recent advances in biomarkers for cancer diagnosis and treatment," Science Direct, vol. 10(14), pp. 965-976, 2005.

[3] Seth S., Ali S., Philip P.A., Sarkar F.H., "Clinical advances in molecular biomarkers for cancer diagnosis and therapy," International Journal of Molecular Sciences, vol. 14(8), pp. 14771-14784, 2013.

[4] Mansoori B., Mohammadi A., Shirjang S., Baradaran B., "Micro-RNAs: The new potential biomarkers in cancer diagnosis, prognosis, and cancer therapy," Cellular Microbiology, vol. 61(5), pp. 1-10, 2015.

[5] Patel J., Patel P., "Biosensors and biomarkers: Promising tools for cancer diagnosis," International Journal of Biosensors & Bioelectronics, vol. 3(4), 2017.

[6] Kirwan A., Utratna M., O'Dwyer M.E., Joshi L., Kilcoyne M., "Glycosylation-based serum biomarkers for cancer diagnostics and prognostics," Biomedical Research International, vol. 2015, Article ID 490531, 2015.

[7] Badowski C., He B., Garmire L.X., "Blood-derived lncRNAs as biomarkers for cancer diagnosis: the Good, the Bad, and the Beauty," NPJ Precision Oncology, vol. 6, p. 40, 2022.

[8] Ramirez-Valles E.G., Rodríguez-Pulido A., Barraza-Salas M., Martínez-Velis I., Meneses-Morales I., Ayala-García V.M., Alba-Fierro C.A., "A quest for new cancer diagnosis, prognosis, and prediction biomarkers and their use in biosensors development," SAGE Journals, vol. 19, pp. 1-17, 2020.

[9] Chatterjee S.K., Zetter B.R., "Cancer biomarkers: knowing the present and predicting the future," Future Oncology, vol. 1(1), pp. 37-50, 2005.

[10] Brase J.C., Wuttig D., Kuner R., Sültmann H., "Serum microRNAs as non-invasive biomarkers for cancer," Springer Nature, vol. 9, p. 306, 2010.

[11] Bhatt A.N., Mathur R., Farooque A., Verma A., Dwarakanath B.S., "Cancer biomarkers - Current perspectives," Brigham Young University, Mar 1, 2016.

[12] Sinha A., Singh C., Parmar D., Singh M.P., "Proteomics in clinical interventions: Achievements and limitations in biomarker development," Proteomics, vol. 80(15), pp. 1345-1354, Mar 20, 2007.

[13] Chakraborty T., Murthy C.R., Varma M.M., "Fundamental limitations in biomarker-based early disease diagnosis," arX iv preprint, arXiv:1907.05199v1, Jul 11, 2019.