

Analysis of Different Types of Cancer Biomarkers

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Abstract. Malignant tumor is still the most important disease threatening people's lives and health, and people often have the fear of 'talking about cancer'. Cancer biomarkers are essential for reaching better clinical effectiveness and long-term outcomes, as well as for reducing the pain and decreasing disease-related social costs. The high burden of malignancies worldwide highlights the underutilization of biomarkers for cancer diagnosis, prognosis, treatment effect, and drug potency prediction. Novel strategies are urgently needed to discover cancer biomarkers and translate molecular diagnostics from experimental research to clinical practice. Nowadays, significant advancements have been achieved in the study of cancer biomarkers, such as Diagnostic, Prognostic, Predictive, Pharmacodynamic, and so on. The accurate detection of molecular markers can provide more valuable medical information for clinical practice and help to realize personalized medicine. This article summarizes some biomarkers in cancer patients and looks forward to more studies on the specificity and mechanism of the biomarkers.

Keywords: Cancer; Biomarker; Diagnostic; Prognostic; Predictive; Pharmacodynamic.

1. Introduction

Cancer continues to be one of the most urgent health issues facing the globe, and its complex etiology and heterogeneity pose significant barriers to effective diagnosis and treatment. According to statistics from the World Health Organization, in 2023, there were 9.7 million cancer deaths worldwide and close to 20 million freshly diagnosed instances of the disease [1]. In recent decades, efforts have been made to elucidate the molecular mechanisms underlying cancer development and progression. Researchers have delved into the intricate interplay between genetic mutations, environmental factors, and lifestyle choices that contribute to the growth and spread of cancer. In addition to advancing people's knowledge of cancer biology, these initiatives hope to open the door for the creation of cutting-edge diagnostic techniques and focused therapy approaches that will ultimately enhance patient outcomes.

With the development of medical technology, mankind has gradually discovered that while it is important to invent drugs and technology to treat cancer, it is also crucial to have technology that can detect the status of the cancer and the effectiveness of the drugs at the same time. Biomarkers, as measurable indicators of biological processes, have become invaluable tools for cancer research, diagnosis, prognosis, and treatment monitoring. Understanding the diversity of cancer biomarkers is critical to advancing personalized medicine and improving patient prognosis. Genetic biomarkers, including mutations in oncogenes, play a fundamental role in driving tumorigenesis and shaping cancer phenotypes. Technological developments in next-generation sequencing have aided the identification of recurrent mutations in various cancer types, providing opportunities for targeted therapies and precision medicine approaches. In addition, gene expression signatures derived from transcriptome analyses provide valuable predictive and prognostic information that facilitates risk stratification and treatment selection [2].

A biological substance that is detected in bodily fluids such as blood or tissues and indicates the presence of cancer is known as a cancer biomarker [3]. It can be proteins, nucleic acids, antibodies, peptides, etc. This paper will comprehensively analyze the different types of cancer biomarkers to elucidate their utility, limitations, and potential applications in clinical practice.

2. Diagnostic Biomarkers

Diagnostic cancer biomarkers are molecular indicators that determine the presence or risk of cancer. They include gene mutations, protein expression patterns, or circulating tumor cells. They identify disease presence or risk, facilitate early intervention and treatment planning, and enhance patient. Furthermore, in order to guarantee that patients receive the most suitable and efficient treatment for their particular cancer subtype, diagnostic cancer biomarkers aid in the improvement of personalized treatment plans. Ultimately, the integration of diagnostic biomarkers into clinical practice not only supports the detection of disease but also significantly improves the overall care and management of patients, thereby enhancing their quality of life [4].

2.1. Cancer Antigen 125 (CA-125)

Antigenic tumor marker CA-125 is typically expressed by epithelial ovarian tumors as well as other organs, which is a weight mucin glycoprotein on the ovarian cancer cells' surface. When serum samples from ovarian cancer patients are taken, this antigen is excreted and measured. In 50% of early-stage tumors (mostly type I ovarian cancer) and 92% of advanced-stage tumors (primarily type II ovarian cancer), serum CA125 levels are raised. Nevertheless, screening women at average risk with CA125 results in a significant percentage of false-positive results due to the low incidence of ovarian cancer [5]. To determine CA-125 levels, there are two assays available. 1. A monoclonal antibody to OC 125, which identifies the antigenic determinants on the CA-125 glycoprotein, was used in the initial test, a radioimmunoassay. 2. Two antibodies are used in the second generation of CA-125 assays: M 11 and OC 125. Typically, CA125 levels are fewer than 35 units per milliliter (u/ml). On the other hand, some women's blood levels of CA125 are naturally elevated. About 20% of ovarian cancers do not express CA125. As a result, screening should have a sensitivity of roughly 80%. With fewer false-positive outcomes, this test demonstrated increased sensitivity and precision [6].

2.2. Prostate Specific Antigen (PSA)

PSA is a very sensitive screening method that is nevertheless somewhat imprecise and non-specific because serum markers are elevated by both benign and malignant processes. Despite the associated dangers, serum PSA screening remains the gold standard for early prostate cancer detection. PSA has been shown to be far superior to rectal examination in detecting early prostate cancer. When serum PSA screening is performed using a method greater than 4.5 mm in diameter, it is useful in identifying prostate cancer cases. When values larger than 4 ng/mL are used, the specificity of serum PSA detection for prostate cancer approaches 91%. Rectal examination has a much lower specificity of 59% [7].

2.3. Carcinoembryonic Antigen (CEA)

Non-specific serum biomarker CEA is raised in several cancers-mucinous ovarian cancer, breast cancer, colorectal cancer, and medullary thyroid cancer. In healthy, non-smoking adults, CEA levels $\leq 3.0 \mu\text{g/L}$ are considered to be within the normal range. CEA may be elevated in smokers, so levels below $5 \mu\text{g/L}$ are considered within the normal range. The CEA threshold of $2.5 \mu\text{g/L}$ has an 82% sensitivity and 80% specificity for colorectal cancer, whereas the threshold of $10 \mu\text{g/L}$ has a 68% sensitivity and a 97% specificity. One benefit of using CEA is that serum-based CEA testing is included in many national and international surveillance recommendations and is an affordable means of surveillance for a variety of malignancies. However, it cannot be used as the gold standard of screening tests for the detection of malignant tumors due to its low sensitivity [8].

3. Prognostic Biomarkers

Prognostic cancer biomarkers are essential in order to forecast how a patient's condition will progress and how likely they are to survive. By providing insights into the prognosis of the disease, these

biomarkers inform healthcare professionals about the most appropriate treatments and enable them to tailor interventions to the different needs of patients. In addition, prognostic cancer biomarkers can help physicians develop long-term management strategies, facilitating ongoing monitoring and adjusting treatment plans as necessary. By utilizing these biomarkers, clinicians can optimize treatment outcomes and enhance patient care by delivering personalized targeted therapies that maximize efficacy while reducing adverse effects [9].

3.1. Ki-67

Ki-67 is an antigen found in the nuclei of tumor cells. In G0 cells that are at rest, it is significantly down-regulated, while it is robustly expressed in circulating cells. Because of this characteristic, Ki-67 is a proliferation marker that is clinically significant for the grading of many malignancies and has a strong prognostic value in large studies [10]. In Papillary Thyroid Cancer (PTC), in particular, Ki-67 exhibits excellent prognostic value and outlook. In a trial of 327 patients with PTC diagnosed at Karolinska University Hospital in Stockholm, Sweden, Ki-67 not only showed diagnostic value but also great prognostic value. Patients in the experiment with primary tumors had a mean Ki-67 index of 3%. The maximum Area under the ROC Curve (AUC) for Ki-67 > 2.45% in the main tumor was 0.64, and this result accompanied a sensitivity of 68% and a specificity of 56% ($P = 0.003$), according to Receiver Operating Characteristic (ROC) analysis and connection with cancer recurrence. A labeling index $\geq 2.85\%$ for the Ki-67 index of lymph node metastasis predicted tumor recurrence with 76% sensitivity, 52% specificity, and an AUC of 0.66 ($p = 0.01$).

The researchers also found that Ki-67 could be combined with other indicators, such as Thyroglobulin expression (Tg), to provide a completer and more accurate prognosis. There was a negative correlation found between Tg expression and the Ki-67 index in the main tumor and its accompanying lymph node metastases. Primary tumors with 0-25% Tg expression had a mean Ki-67 index of 5.3%, which was substantially larger than cases that have 51-75% ($p = 0.01$) and 76-100% ($p < 0.001$) Tg expression [11].

3.2. The Epidermal Growth Factor Receptor (EGFR)

EGFR works by helping cells grow and divide. When strongly expressed, the transmembrane tyrosine kinase receptor EGFR is involved in the development of tumors. In addition, the epidermal growth factor receptor controls basal intracellular glucose levels via the sodium/glucose cotransporter 1, thus shielding tumor cells from apoptosis. Still, this mechanism is usually inhibited when the epidermal growth factor receptor is greatly expressed due to cancer [12].

An EGFR "on" state is brought on by a genetic mutation or damage in EGFR-positive non-small cell lung cancer (NSCLC). This fuels the aberrant cell division that ultimately results in cancer. Mutations in EGFR and the level of expression can be detected by biopsy. Elevated levels are linearly associated with cancer recurrence [13]. Besides, epidermal growth factor is linked to prognosis and has an impact on how human head and neck tumors grow. By using EGFR as a biomarker for these two tumors' diagnosis and prognosis. This characteristic makes EGFR a viable therapeutic objective for the management of these two cancers.

4. Predictive Biomarkers

Predictive cancer biomarkers are indispensable tools for guiding cancer treatment decisions. By analyzing molecular signatures within patients' tumors, including gene mutations and protein expression patterns, predictive biomarkers enable healthcare providers to anticipate a patient's response to a specific treatment regimen (mainly including chemotherapy and radiotherapy). By utilizing this predictive information, physicians can tailor treatment regimens to the individual patient, thereby optimizing treatment outcomes while minimizing the risk of unnecessary interventions. Utilizing predictive cancer biomarkers in clinical practice is a critical step in advancing personalized medicine and ensuring that patients receive the most effective and appropriate treatment [14].

4.1. Breast Cancer Gene (BRCA)1/2

BRCA 1/2 mutations are used in BRCA-associated cancers such as breast and ovarian cancers. Mutations in the BRCA1/2 gene predict patient response to treatment with Poly (ADP-ribose) polymerase (PARP) inhibitors. With 23% of all cases occurring in women, the most common type in women is breast cancer. Roughly 10% women population are predicted to get the disease at some time in their lives. A small study of German Jews suggests that the predictive value of BRCA1 in preclinical models and the reaction to various chemotherapeutic medications can be translated into clinically useful prognostic and predictive tools. However, its predictive performance is more effective compared to its prognostic nature. In a clinical trial, ten out of eleven patients with BRCA mutations achieved clinical full remission, according to the findings of clinical research. This study suggests that anthracycline-based chemotherapy regimens are particularly effective in treating tumors with BRCA1 mutations. It doesn't seem like BRCA1's function is exclusive to breast cancer. A study exhibits that, following platinum-based treatment for breast cancer patients, 71 individuals with epithelial ovarian cancer (22 with BRCA1 and 12 with BRCA2) had a high incidence of remission [15].

4.2. Microsatellite Instability (MSI)

MSA is mainly used in colorectal cancer. Colorectal cancer (CRC) is one of the most common cancers and a leading cause of death in developed nations. MSI-high colorectal cancer contributes to 15% of all CRCs. Not only is the loss of function of the Mismatch repair (MMR) gene a major contributor to the pathophysiology of colorectal cancer (CRC), but it also causes the MSI-H condition, which is linked to a distinct response to traditional chemotherapy treatment techniques. The research findings indicate that adjuvant chemotherapy based on 5-FU is advantageous for patients diagnosed with stage II and stage III MSI-negative CRC (HR=0.72, p=0.04), yet it lacks efficacy in individuals with MSI-H status (HR=1.07, p=0.80). Additionally, preclinical studies suggest that tumor cells exhibiting MSI-H status tend to resist fluoropyrimidines but might respond to treatments involving mitomycin C and irinotecan [16]. At the same time, high microsatellite instability causes a variety of molecular and biological alterations in tumor cells by causing somatic mutations to accumulate. These changes are associated with increased sensitivity to checkpoint inhibitor drugs, such as patient feedback to treatment with immune checkpoint inhibitors, and anti-PD-1 antibodies [17].

5. Pharmacodynamic Biomarkers

Pharmacodynamic cancer biomarkers are important indicators for assessing the action and metabolism of drugs in the body during cancer treatment. These biomarkers provide valuable information about the effectiveness of drugs, potential side effects, and individual responses to treatment. By closely monitoring these markers, healthcare professionals can gain a comprehensive understanding of drug interactions with the body, allowing for timely adjustment and optimization of treatment regimens. This personalized approach not only improves efficacy but also minimizes the risk of adverse effects, thereby improving the overall quality of patient care and survival. By utilizing pharmacodynamic cancer biomarkers, clinicians can refine their treatment strategies, tailor interventions to the different needs of patients, and ultimately optimize the effectiveness of anticancer treatments [18].

5.1. Phosphorylation Status

The phosphorylation status of drug target proteins can be used as a very powerful pharmacodynamic cancer biomarker. Many anticancer drugs work by affecting the phosphorylation status of specific proteins in tumor cells. Phosphorylation of proteins is a reversible biochemical process wherein a phosphate group is added to the polar group R of various amino acids. This modification is facilitated by enzymes known as protein kinases. This addition allows proteins to alter their structure when interacting with other molecules, thereby affecting their effects. Therefore, the effect of a drug on the phosphorylation status of the target protein can be used as a biomarker of the therapeutic effect of the

drug. Phosphorylated proteomics has important relevance to many aspects of biology and is important for understanding molecular mechanisms, particularly those leading to tumorigenesis and growth. Comprehending the regulatory roles of kinases is a useful strategy for developing more potent cancer treatments, as the signaling networks via which protein kinases function are intricate [19].

5.2. Apoptosis Markers

Apoptosis markers can be an important factor in detecting drug efficacy. Given that certain anticancer medications are engineered to induce apoptosis or the deliberate death of cells, it becomes advantageous to track alterations in apoptotic markers (such as caspase-3 activity) in tumor tissues. An important measure of the effectiveness of pharmacological therapy on colon cancer is the rise or reduction in caspase-3 activity. One of the main mediators of apoptosis, caspase-3 is triggered when cells are exposed to immunotherapy, radiotherapy, or cytotoxic medicines. This phenomenon offers clinicians a useful way to evaluate efficacy while highlighting the complex interaction between medication mechanisms and biological responses. Healthcare practitioners can more precisely customize therapy regimens to optimize patient outcomes by using apoptotic indicators as biomarkers [20]. Thus, the use of apoptotic markers in clinical practice advances people's understanding of how medications function in biological systems and improves therapeutic monitoring. The importance of apoptosis markers as trustworthy indications of therapeutic response will continue to be crucial as research into the intricate dynamics of apoptosis and drug-drug interactions improves, advancing the field of personalized medicine and strengthening the battle against cancer and other disorders.

6. Future expectation

The top-tier biomarkers elucidate the relationships between exposure and disease, establish dose-response patterns, identify early disease indicators, explain how exposure induces disease, minimize misclassification of exposures, risk factors, and diseases, pinpoint variations and modifications in effects, and advance risk assessment for both individuals and populations. As outlined by the U.S. Food and Drug Administration (FDA), the ideal biomarker must exhibit specificity, sensitivity, predictability, durability, simplicity, precision, and cost-effectiveness. Conventional biological sources such as serum and urine should be used as the fundamental of the assay. Many of the cancer biomarkers will have broad applicability (and hence the need for collaborative, pre-competitive partnerships with industry. Public sharing of preliminary findings from collaborative biomarker discovery programs is a good idea, following in the footsteps of government-funded initiatives like the Human Genome Project and the Cancer Genome Atlas.

The study of the lacrimal gland and its secretion, tears, and the identification of additional proteins in tears has been considerably aided by advances in the field of proteomics. The discovery of new biomarkers in tears is an emerging field of study. Clinical oncologists may find new techniques to recognize novel biomarkers for early diagnosis and prognosis thanks to recent developments in proteomics technology.

It is valid to study each factor relative to the other, such as studying the effect of one factor on the other and on the process as a whole at the same time. Beyond all of these issues related to cancer early diagnosis, the most effective answer is the identification of biomarkers.

In the age of science and technology and many promising fields are increasingly developing, such as nanotechnology and medical inventions, the future of cancer detection, monitoring, and treatment is promising [2].

7. Conclusion

Cancers are an unprecedented group of diseases that afflict people often and hold a major influence on total mortality. Most of the conventional treatments in use today include surgery, radiotherapy,

and chemotherapy. Before treating cancer, doctors need to specifically detect its presence in any part of the body, and for this, they need an agent known as a biomarker.

Every disease has a latent phase, during which, if doctors can detect the disease, they can treat it before it becomes fatal. Biomarkers assist in identifying the disease early and aid in its therapy. For this reason, biomarkers are essential to the diagnosis and management of cancer in the early period.

In total, scientists have researched and summarized four different cancer biomarkers: diagnostic biomarkers, prognostic biomarkers, predictive biomarkers, and pharmacodynamic biomarkers. Molecules used in diagnostic cancer biomarkers ascertain the existence or likelihood of cancer. Cancer prognostic indicators are essential for forecasting how a patient's illness will progress and how likely they are to survive. Decisions about cancer treatment are greatly aided by predictive cancer biomarkers. Important signs for evaluating how medications function and are metabolized in the body during cancer treatment are pharmacodynamic cancer biomarkers.

Each type of biomarker provides unique insights into the underlying molecular mechanisms of cancer and is expected to guide therapeutic decisions and monitor treatment response. Incorporating a variety of cancer biomarkers into clinical practice can greatly increase the sensitivity and specificity of the test which has great potential to improve cancer detection, prognosis, and treatment outcomes.

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