Academic Science Journal

Review Article: Tumor Markers, Types and Clinical Applications

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Received: 16 December 2024 **Accepted: 16 February 2025**

Published: 29 April 2025

DOI: https://dx.doi.org/10.24237/ASJ.03.02.941C

Abstract

Over the past ten years, tumor markers have played an increasingly important role in clinical oncology. This trend is expected to continue as technology advances and our knowledge of the human body and disease processes grows. In the treatment of cancer, tumor markers are widely used for a variety of purposes, including screening, selecting a management strategy, determining the prognosis, and post-therapy follow-up. A comprehensive of the fundamentals of pathophysiology and identification strategies for each specific malignancy is necessary for their prudent application in clinical practice. Oncology's use of cancer biomarkers has transformed the way that cancer is treated, and led to notable improvements in patient outcomes and cancer treatment.

Keywords: Tumor marker, Cancer, Cell growth, Biomarker.

Introduction

Tumor cells create biochemical substances called tumor markers as a result of the malignant process or its genesis. These indicators may be either the product of normally occurring endogenous products or the consequence of recently activated genes that were dormant in normal cells that are produced more frequently in cancer cells a marker for tumors that the

tumor produces and that, when found in large quantities, suggests the existence of cancer [1]. Tumor markers may be utilized in asymptomatic people to test for early cancer. In patients displaying symptoms, indicators could be beneficial in differentiation between benign and malignant diseases. Markers can be used to evaluate prognosis, forecast therapy, monitoring the response to systemic therapy, and measure postoperative surveillance after a tumor has been surgically removed [2]. A biomarker is any biological marker that may be detected in blood, body fluids, or tissues that indicates the existence of diseases, illnesses, or biological processes that are either normal or abnormal .When customized for the oncology domain, a cancer biomarker precisely detects cancerous traits, ideally with a high level of precision and dependability, as evidenced by its sensitivity and specificity [3].

Perfect marker for tumors.

While the classification and application of the marker influence its features to some extent, the general attributes of an ideal tumor marker consist of

- Expression in a manner specific to organ site
- Particular production early in the course of the disease by tissue that is cancerous or premalignant.
- Generated in every patient with a certain type of cancer at measurable levels..
- Proof of existence in physiological fluids obtained noninvasively or in tissue that is easily accessible.
- Quantitative levels associated with tumor size, biological activity, or the course of the illness.
- Comparatively low half-life, suggesting gradual changes in treatment responsiveness and tumor burden.
- • The availability of a quantitative, objective test that is validated, repeatable, and standardized [4].

The classification of tumor markers.

1. The antigens of oncofetal include AFP, CEA, fetal sulfoglycoprotein, pancreatic oncofetal antigen, and pancreatic oncofetal antigen.

P-ISSN: 2958-4612
E-ISSN: 2959-5568

2. Antigens linked to tumors and cancer, For example, CA125, CA19-9, CA15-3, CA72-4, CA50, and on.
3. Hormonal e.g. placental lactogen, calcitonin, and beta human chorionic gonadotropin, among others.
4. Hormone receptors, such as those for progesterone and estrogen.
5. Terminal deoxy nucleotidyl transferase (TDT), placental alkaline phosphatase (PALP), neuron specific enolase, lysozyme, alpha amylase, glycosyl transferases, PSA, PAP, and NSE, among other enzymes and isoenzymes.
6. Glial fibrillary acidic protein (GFAP), ferritin, and protein S-100 are examples of serum and tissue proteins beta-2 microglobulin, monoclonal immunoglobulin/para proteins, and fibrinogen degradation products.
7. Additional biomolecules such as polyamines [5].

Clinical uses of tumor markers.

Markers for pathological and clinical tumors serve numerous clinical purposes, such as assessing risk and prognosis, screening, selecting treatment methods, monitoring treatment response and progress during recovery, and detecting recurrence post-surgery. While tumor marker levels may show that cancer is present, they are not sufficient on their own, as shown in Table 1.

Table 1: Typical Clinical Applications of Various Tumor Markers [6].

Biomarkers	An increase in cancer cases	An Increase in non-cancerous conditions
AFP (alpha-fetoprotein)	HCCs, or cancers of the liver	Ataxia telangiectasia, cirrhosis, and hepatitis
Carcinogenic embryogenic antigen; CEA)	Breast cancer and colorectal cancer	Fibrocystic breast disease and smoking,
PSA(prostate-specific antigen)	Cancer of prostate	The prostatitis
Ca15-3	Breast cancer pancreatic cancer, lung cancer,	Endometriosis, pelvic inflammatory diseases, liver disease, pregnancy.

Ca19-9 Ca 125 cancer Ca50	Bladder, colorectal, and pancreatic cancers Cancers of the breast, fallopian tube, and ovaries Cholangiocarcinoma, bile duct tumors, and pancreatic cancer	Pancreatitis, liver cirrhosis, diabetic nephropathy gallbladder obstruction Lupus, endometriosis, pregnancy, and congestive heart failure Cholangitis and pancreatitis
Ca 72-4	Ovarian and gastrointestinal cancers	cirrhosis, pulmonary conditions, rheumatoid disorders, gynecological conditions, pancreatitis, etc.
NSE	(Enolase specific to neurons) Melanoma, small cell lung cancer, thyroid medullary carcinoma, and neuroblastoma	Septic shock, pneumonia, nervous system trauma.
SCC-antigen	Carcinoma of the esophageal cancer as well as squamous cell carcinomas of the head, neck, and lungs.	Lung diseases, cirrhosis, pancreatitis, kidney failure, psoriasis, and inflammatory skin conditions including eczema
Beta 2-microglobulin	Multiple myeloma (MM), non-hodgkin lymphoma	Diabetic nephropathy.
Thyreoglobulin	Thyroid cancer, both follicular and papillary	Thyroiditis, rheumatoid arthritis, Graves' disease, and Hashimoto's disease

Therefore, Tumor indicators are always employed in conjunction with other techniques for investigation and diagnosis, such as endoscopy, ultrasonography, biopsies, PET (positron emission tomography) and CT (computerized tomography).

However, none of the tumor markers found have shown themselves to be entirely accurate or specific in identifying cancer. Thus have significantly superior qualities. It is not limited to a single cancer. Each tumor marker is unique to a class of cancers or an organ. It is recognized that some mechanisms can lead to cancer. A single organ might express multiple cancer markers depending on the type of malignant cells present. For example, ovarian adenocarcinoma may commonly express CA 125 and infrequently express carcinoembryonic antigen (CEA). Every time an ovary endodermal sinus tumor develops, AFP and hCG levels are always positive [7]. Evaluating tumor markers can significantly assist in tumor growth monitoring, staging, prognosis, and diagnosis. Once a patient tests positive for a specific marker before treatment

begins, its clinical utility becomes clear through ongoing measurement during the patient's care. Changes in marker concentration whether rising or falling often indicate disease, progression or remission in most cancers. Tumor marker diagnostic efficacy is dependent on multiple parameters, such as sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV). Sensitivity measures the likelihood that the presence of a tumor will cause a test to come up positive. Specificity, as a screening tool, indicates the percentage of healthy individuals who will be informed if the test is negative. PPV reflects the possibility that a medical condition exists when a test is positive, whereas NPV shows the possibility that a disease does not exist when a test is negative.

Uses of tumor markers in cancer screening.

Through screening people who don't show any symptoms or signs of a disease can have an early disease or preclinical stage identified. In contrast to disease diagnosis, screening is done on people who don't exhibit any symptoms at all. The application of cancer tumor markers screening may be anticipated to offer advantages over other well-established methods, such are the Mammograms for breast cancer, colonoscopies for colorectal cancer (CRC), and Papanicolaou tests for cervical cancer [8]. These advantages include:

• Markers are measurable in bodily fluids that can be acquired with the least amount of disturbance to the people being screened, such as blood and urine.

- There are automated assays available for several markers, which enable handling a lot of samples in a comparatively short amount of time.
- Marker tests generate quantifiable information with measurable goal.
- Marker tests are reasonably priced in comparison to radiography, histology, and endoscopic procedures. As cancer screening tests, markers have a few drawbacks despite these benefits. The lack of specificity for malignancy increased susceptibility to early invasive illness or precancerous lesions in existing markers limits their use in early malignancy screening of asymptomatic people. In addition to the low frequency of the majority of malignancies in the general population, the simultaneous issue of inadequate sensitivity and specificity makes markers having limited positive predictive values. when employed alone in screening asymptomatic individuals. Indeed, the majority of biomarkers cannot be used for cancer screening due to the low occurrence of cancer in the general population [9]. Nevertheless, some markers have either been assessed for cancer

screening or are currently doing so (table 2)[10]. Here is a discussion of some of the most extensively studied markers for cancer screening.[11]

Table 2: Biomarkers that have been evaluated or are being evaluated for use in the cancer screening of asymptomatic subjects

Test or marker	Malignancy
FOBT	Colorectal
PSA	prostate
CA 125	ovarian
VMA/HVA	neuroblastoma
AFP	hepatocellular1
Pepsinogen	gastric1
HCG	trophoblastic2

Alpha Fetoprotein (Afp)

Alpha-fetoprotein (AFP) is a well-known and widely researched oncofetal glycoprotein, functioning as a significant globulin present has a molecular weight of about 69-70 kDa in fetal serum. This single-chain glycoprotein resembles albumin in amino acid sequence and has a carbohydrate content of roughly 3%.. AFP is produced during malignancies as well as during intrauterine or early postnatal development. The gene for AFP is nearly entirely repressed in fully developed fetuses, leading to a decline in protein levels shortly after birth. While AFP is abundant in fetal blood, normal adult levels are typically less than 15 ng/ml. An elevation AFP level in serum exceeding 500 ng/ml usually suggests a cancerous tumor underneath, unless it's a pregnancy. During pregnancy, AFP is produced Via the fetal liver and released into the fetal bloodstream. [12].

Human Chorionic Gonadotropin (Bhcg)

Between weeks 10 and 12 of pregnancy, the HCG concentration reaches its peak. The standard levels in serum are fewer than 5 IU/ml for healthy males and women who are not pregnant, and less than 10 IU/ml for women who have gone through menopause. When it comes to extragonadal and gonadal choriocarcinomas (testimonia and ovary), HCG is the preferred marker. In addition to hydatidiform moles, HCG exhibits 100% sensitivity for choriocarcinomas, regardless of their location. When it comes to testicular tumors, the histological findings and the identification of AFP and HCG correlate, making it essential for therapeutic procedures. Three months before the patient shows signs of metastases or a clinical

relapse, the biochemical recurrence is detected with repeated determination of βhCG. Additionally, the marker aids in the surveillance of high-risk individuals with testicular tumors, especially those who are the healthy monozygotic twin of a patient suffering from a testicular tumor or who have an undescended testicle. Elevations in βhCG signify a dismal prognosis, and regular testing throughout treatment is connected with the degree of clinical improvement. Seldom are serum HCG levels higher in nontrophoblastic malignancies such bladder, breast, pancreatic, and lung cancers [13].

Carcino Embryonic Antigen Cea

A glycosylated protein with a molecular weight of 180 kDa .Many human carcinomas, such as pancreatic, colorectal, stomach, and lung non-small cells, and breast malignancies, overexpress the carcinoembryonic antigen (CEA). Phil Gold and Freedman, Samuel O. discovered 12 CEA in extracts of human colon cancer tissue for the first time in 1965. The primary uses of CEA assessment are as a tumor marker to locate cancer spread by biological fluid dose or to detect recurrences following surgical excision. The CEA blood test is unreliable as a screening tool for early cancer detection or for cancer diagnosis. Most cancer forms don't have elevated CEA levels following a successful surgical resection, or in six weeks after the beginning of treatment if cancer is the cause, the high CEA levels need to go back to normal. In addition, smokers and people with certain non-neoplastic diseases CEA levels may be higher in conditions such Crohn's disease, ulcerative colitis, pancreatitis, cirrhosis, and COPD. [14].

Prostate Specific Antigen (Psa)

Previously called gammaseminoprotein, PSA, is the prostate specific antigen that is present in plasma that is seminal. PSA is a single-chain glycoprotein that is 34 KD in size. that is made up of 7% carbohydrates and 93% amino acids. It is a monomer consisting of 240 residues of amino acids. PSA belongs to the glandular kallikrein group family and is a neutral serine protease with activity similar to those of chymotrypsin and trypsin. The prostate epithelium effectively stops the protease from escaping into the bloodstream by synthesizing PSA. A small quantity of PSA does, however, enter the bloodstream. PSA is known to bind to distinct protease inhibitors in serum and seminal fluid, forming complexes. As a result, several molecular forms of PSA are known to circulate in blood [15].

Tumor Associated Antigens

Monoclonal antibodies that are highly specific raised against the primary tumor's cell lines or tumor tissue that have been histologically identified are used to identify CA 125, CA 19.9, CA 15.3, CA 72.4, and other tumor-associated antigens.

Cancer Antigen 125 (Ca 125)

Researchers found that the monoclonal antibody produced by mice CA 125, which they generated through vaccination against a distinct cell line of ovarian adenocarcinoma, has a tumor-associated glycoprotein of over 200 KD. The high molecular weight glycoprotein on which the CA 125 monoclonal antibody is directed detects several repetitive antigenic features. In addition to typical the epithelium of the trachea, bronchi, bronchiolar, and terminal bronchiolar in adults and fetuses, similar epitopes are also detected in amnion and amniotic fluid, as well as vestiges of the mullerian duct. Although they are linked to epithelial ovarian cancer, CA 125 antigenic markers are absent from adult normal ovarian tissues. Pregnant women's serum, milk, and cervical secretions all had elevated CA 125 concentrations. The maximum of the normal range, or 35 u/ml, was selected as the cut off number regarding serum CA 125 levels in women who appear to be in good health who do not have any ovarian masses, whether benign or malignant. It has been established that CA 125 is the preferred marker for adenocarcinoma, ovarian epithelial cancer. According to published research, the marker is more sensitive compared to ovarian cancer with mucinous epithelial cells in nonmucinous epithelial cells. Depending on the ovarian cancer's stage, the sensitivity of serum CA 125 varied from 43% to 97% for ovarian cancer identified before therapy [16].

CA 19-9 (CANCER ANTIGEN 19-9)

The first-choice tumor marker for pancreatic and gallbladder cancers is CA 19-9. Tumor associated glycoprotein antigen (210 KD), which is present on glycolipid and glycoprotein as a carbohydrate determinant, serves as the marker. To characterize CA 19-9, BALB/c mice are immunized with a human colorectal cancer line. Monoclonal antibody 1116 - NS 19-9 is then employed. It has been determined that the carbohydrate antigenic determinant (CA 19-9) to which this antibody reacts is sialylated lacto-Nfucopentaose II, an oligosaccharide with structural similarities to molecules in the Lewis blood group. The antigen was found in either

it is extremely or modest concentrations on the liver, pancreas, small intestine, colon, and stomach epithelia in fetuses as well as on adult gastrointestinal tract and lung tissue, according to immunohistological examination. Additionally, Mucin-rich saliva, seminal fluid, gastric juice, amniotic fluid, urine, ovarian cyst fluid, pancreatic, gall bladder, and intestinal secretions all contain detectable levels of CA 19-9. Serum CA 19-9 levels are less than 37 u/ml in 99.6% of healthy persons. Less than 100 u/ml is regarded as the gray zone, where benign and malignant illnesses may coexist. It is possible to find levels more than 100,000 U/L in malignant tumors. Neither tumors nor organs are specific to CA-19-9[17].

CA 15-3

Researchers identified the 300 kD heterogeneous glycoprotein antigen CA 15-3 using two monoclonal antibodies, 115D8 and DF3, which they developed in response to breast cancer cells. Since elevated levels of CA 15-3 can also be found in benign breast illnesses, liver cirrhosis, and both acute and chronic hepatitis, its diagnostic sensitivity for breast cancer is limited. Furthermore, there is an increase in marker concentrations in pancreatic, ovarian, colon, lung, stomach, and uterine metastatic tumors. A recent Indian study on breast cancer patients receiving pretherapy, however, found that CA 15-3 and CEA had a stronger connection [18].

Uses of Tumor Markers

1. **Early detection and screening:** Searching for cancer in individuals without any indications of the illness is known as screening. Early detection of cancer refers to its discovery when it is still treatable and less likely to have spread. While most markers are not appropriate for routine screening, their usage can aid in identifying occult disease at an early stage, when a successful course of treatment is probably going to be beneficial due to the majority of biological indicators' lack of specificity and the inadequate assessment of their actual utility to patients. Only two indicators have been shown to be helpful in screening high-risk groups for tumors: Alpha-fetoprotein and calcitonin are indicators of hepatocellular carcinomas and medullary thyroid carcinomas, respectively.
2. **Differential diagnosis:** Most tumor indicators are usually ambiguous and present in benign, malignant, and normal tissue. They can still be utilized, nevertheless, to differentiate

between worrisome lesions. The test CA-125 aids in distinguishing ovarian cancer from other diseases.

3. **Cancer staging clinically:** Quantitation of the marker, or the measurement of the marker's serum level in relation to the amount of tumor present, helps with the clinical staging of the malignancy. Using radio immune detection, markers can also identify tiny metastases.
4. **Diagnosis:** One crucial role of any tumor marker is to identify the underlying illness. Tumor markers must have 100% sensitivity and specificity in order to identify any disease. Circulating tumor markers are employed in the great majority of diagnostic scenarios. As an illustration, urine containing Bence Jones proteins continue to be one of the most reliable diagnostic markers for multiple myeloma.
5. **Prognosis determination**: Tumor indicators aid in prognosis, treatment response, and survival time estimation according to proof of metastatic disease.
6. **Tumor localization using an antibody-specific radioactively tagged tumor marker:** Tumor-associated indicators were previously used for therapy monitoring and early tumor detection before metastasis. Recently, radiolabeled antibodies against certain markers linked to tumors have been developed, and external scintillation imaging has been utilized to locate the neoplasms using the radiolabeled antibodies. The combination of monoclonal antibodies against the neoplasm with radio therapeutic drugs presents a promising avenue for treating the neoplasm by injecting the patient with this mixture. Human chorionic gonadotropin β-subunit, carcinoembryonic antigen, and fetoprotein are the three tumor-associated indicators that are most frequently employed. Furthermore, prostatic acid phosphatase isoenzyme radioimmunoassay, creatine kinase BB, and galactosyl transferase isoenzyme II are among the newly created tumor-associated marker enzymes**.**
7. **Determining how well treatment is working:** Observing people during cancer treatment, particularly for advanced cancer, is among the most important uses of tumor markers.. Instead of taking additional tests like x-rays, CT scans, bone scans, or other procedures, the level of the tumor marker, if one is available for a particular type of cancer, may be able to be utilized to determine whether the treatment is effective. A decrease in the blood level of the tumor marker is nearly invariably indicative of a successful course of treatment.

However, if the amount of the marker increases, it means that the cancer is not responding to treatment and that it could be necessary to alter it. There is one exception: if a particular chemotherapy treatment is extremely sensitive to the malignancy. This situation can result in a temporary increase in the tumor marker level because the chemotherapy may kill a lot of the cancer cells and release a lot of the marker into the blood [19].

Applications of Artificial Intelligence in Cancer Detection.

AI has significantly advanced a number of sectors, including cancer research, biology, and medicine. AI uses mathematical techniques that support decision-making or action based on rational, independent thought and efficient adaptability to predict cancer behavior and prognosis. AI has the potential to greatly influence practically every aspect of cancer, from enhancing diagnosis to individualized care and the development of new anticancer medications. Reviewing the recent amazing developments in AI use and its potential in routine clinical practice is crucial, as is pointing out its drawbacks and potential hazards. Numerous studies have confirmed that AI-based methods have the ability to forecast diagnosis, prognosis, and response to therapy for a number of malignant tumors, such as lung, breast, skin, and colorectal cancer. It has been demonstrated that machine learning (ML), a subfield of artificial intelligence, reduces intercurrences in the classification of cancer and dysplasia, ensuring validity and uniformity and impacting treatment choices . In oncology and cancer research, developments in Deep Learning (DL) approaches have shown advancements in image-based diagnosis and illness detection. DL configurations consist of hierarchically connected non-linear layered artificial neural networks. Over the past few years, a variety of DL architectures based on input data types have been created. Concurrently, an evaluation of the model's performance revealed that the application of DL in cancer prediction outperforms the conventional methods used in ML[20]. AI is just one of many technologies being put into practice by the goal to increase the effectiveness and efficiency of healthcare care. Clinical process optimization and simplification are becoming more and more important due to the growing demand for medical treatment and the enormous volumes of data generated daily from multiple sources. Because AI is so good at spotting complex patterns in images, it has the potential to transform image interpretation from a wholly qualitative and subjective process to

one that is readily reproducible and quantifiable. Furthermore, AI could help clinical decision-making by quantifying information from photos that humans are unable to detect. AI can also make it possible to combine many data streams into strong integrated diagnostic systems that cover pathology, genetics, radiography, and electronic health [21]

Conclusion

In conclusion, tumor markers are important tools in the oncology field that aid in the early detection, monitoring, and prognostic assessment of cancers. While they offer valuable insights into treatment responses and disease progression, their limitations in specificity and sensitivity highlight the need for careful interpretation. As research continues to advance the understanding and application of tumor markers, they will play an increasingly vital role in personalized cancer treatment strategies. Ultimately, a multidisciplinary approach combining tumor markers with other diagnostic modalities is essential for effective cancer management.

Source of funding: Not available

Conflict of interest: The authors declared no conflicting interests.

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