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Review Article

Pro-Inflammatory Cytokines Predict the Response of Cancer Treatment

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ABSTRACT

The immune condition has an important effect on cancer growth and progression at both the systemic and neoplastic microenvironment levels. Immune modulation or activation has clinical significance for prognostic and diagnostic purposes. Cytokines are signalling proteins that allow communication between cells and are essential for a functioning immune system. Innate and adaptive immune cells, as well as non-immune cells and tissues, communicate via cytokines. Understanding the body's reaction to illness and therapies can be aided by keeping track of the levels of cytokines in the blood and other body fluids. According to reports, a few studies have shown the benefit of routinely checking cytokine levels in tumors. The main objective of the review is to understand the disease and treatment to help evolving immune environment. Along with blood observations, cytokines such as Interleukin-6, Interleukin-8, Interleukin-10, Interferon-Gamma, Tumor Necrosis Factor-Alpha and Transforming Growth Factor-Beta can be employed as predictive/prognostic biomarkers to assist comprehend the changing immunological milieu throughout illness progression and treatment. This study focuses on recent advances in cancer treatment like, proinflammatory cytokine-related processes, diagnostic markers and clinical applications.

Keywords: Cancer, Cytokines, Immune System, Tumor Markers.

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INTRODUCTION

Cancer is one of the non-communicable diseases that kill the most people worldwide. Deaths result from treatment failure or the lack of a suitable treatment for a certain kind of cancer. A serious health issue that can severely damage and adversely impact human lives is cancer. In the US, cancer is the 4th most common root of death.[1] Age, sex, ethnicity, local environmental conditions, diet and genetics are only a few of the many factors that affect the likelihood of developing cancer and the various types of cancer. The cancers most commonly diagnosed in men are those of the lung, throat and oral cavity, while women are more probable to be analyzed with cervical and breast cancer. It is estimated that in the United States in 2023, there will be 300,590 new cases of breast cancer, the most common form of cancer. The two cancers that follow in prevalence after breast cancer are prostate cancer and lung cancer. As the rectal and colon cancers are usually referred to as "colorectal cancers". It is estimated that in 2023, 106,970 people will be affected by rectal cancer and 46,050 by colon cancer resulting in a total of 153,020 new cases of colorectal cancer.[2] Every region of the human body is susceptible to developing cancer. Through the process of cell division, the body creates new cells. A set of illnesses, referred to as cancer, are characterized by abnormal cell growth and can potentially spread to other parts of the body. It is a broad category of disorders distinguished by uncontrolled or unchecked cell proliferation. Uncontrolled growth and propagation of cells are the characteristics of cancer and lead to the formation of tumors. That can invade or spread to neighbouring tissues of the body.[3]

Almost all tissues or cells undergo ordered, regulated cell division or proliferation, which maintains a careful balance between programmed cell death and proliferation to preserve the health of tissues and organs. But so far, for some reason this process is altered thus the cells will keep on dividing and form a mass known as a tumor. The beginning or development of cancer is the process of an abnormal rate of cell division due to damage to DNA which may be caused by external exposure to toxic chemicals, radiation and some microorganisms.[3] Over time, exposure to cancer-causing agents leads to a progressive transformation of normal cells, beginning with hyperplasia, followed by mild to moderate and severe dysplasia, then carcinoma *in situ* and eventually becoming an invasive malignant form of cancer.[1] Cancers are categorized into two classes Benign and Malignant tumors. A benign tumor is an abnormal growth that does not spread to other body parts from its origin. These tumors usually

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have slow growth rates and clear boundaries. Even though they may not be life-threatening, they can still grow large and cause pain or other health issues. Certain benign tumors should be monitored closely and may require surgical removal if they have the potential to become malignant tumors an example of this is colon polyps, which are an abnormal collection of cells that are often surgically removed because they may develop into cancer.

Malignant tumors are a type of cancer in which cells grow uncontrolled and spread to local and/or other tissues of the body. Malignant tumors are cancerous, meaning they can spread to other sites in the body via the lymphatic or blood systems, a process known as metastasis. This is especially dangerous as metastasis can affect entire tissues, such as the liver, lungs, brain and bone. Malignant tumors should be attended to without delay to stop them from advancing into other parts of the body. At an early stage of cancer, a typical treatment plan might involve surgery, along with either chemotherapy or radiotherapy. If the cancer has advanced to other organs, systemic treatments such as chemotherapy or immunotherapy may be employed. Depending on various risk factors, the likelihood of developing cancer may increase. Several dietary factors, including starchy foods, refined carbohydrates, including sugars and processed grains, heavy alcohol and cigarette use, red and processed meat, sugary drinks, salty snacks, lack of exercise, radiation exposure and exposure to air pollution, may contribute to the development of cancer, according to a 2017 assessment. The Epstein-Barr virus (EBS), which causes infectious mononucleosis, Helicobacter pylori, hepatitis B virus, the human papillomavirus, HIV and hepatitis C virus, are examples of specific viruses that can cause cancer. The likelihood of getting cancer increases with age.

Different Types of Cancers

Cancers can have more than 200 different forms, depending on their origin and the types of cells they are composed of. The name of the cancer is derived from where it first appears in the body, even when it spreads to other areas (Table 1).

Diagnosis of Cancer

One individual test cannot be used to identify cancer. So your doctor can ask you about your personal and family medical history after performing a physical check. They might suggest tests in the lab, imaging scans, or other procedures or examinations. A biopsy may also be performed because it is frequently the only method for identifying the cancer. Lab tests are used for the diagnosis of cancer (Table 2).

Tumor markers

Tumour markers are biochemicals that can be measured and are associated with cancer. The body either produces these indicators in reaction to tumor cell invasion or as a result of tumor cells (tumor-associated). Usually, these are compounds that are introduced into the bloodstream and then measured there. Although they can be used as laboratory tests to help in the diagnosis, tumor markers are not the primary methods for cancer diagnosis (Figure 1).[26]

Different treatment approaches for cancer

Cancer is a complicated collection of signs and symptoms that proceed slowly with an extended loss of growth control. For many years, patients had only a few alternatives for cancer treatment, which included surgery, radiation therapy and chemotherapy as individual treatments or in combination. When administered alone or along with radiotherapy, chemotherapy is thought to be the most efficient and popular form of cancer treatment. A new approach for treating neoplastic cancer or creating medication that targets specific cancers is dependent on understanding the pathways and characteristics of the tumor cells. The methods for the treatment of cancers can be divided into conventional and advanced or novel or modern methods (Table 3).

Cytokines as Predictive Factors for Cancer

There has been a growing focus on the role of the immune system about cancer in recent years. Treatments such as checkpoint inhibitors and cellular immunotherapies, including dendritic cells, T cells and NK cells, are now commonly used in clinical practice. It is now understood that the systemic and local aspects of the immune system both play a major role in the emergence and growth of cancer. Cytokines are known to be the communicative molecules that facilitate a variety of immune responses. A variety of cytokines with known roles in immune regulation are important in both predicting patient prognosis and aiding in diagnosis. Cytokine analysis has been most routinely done using plasma or serum samples. However, there is increasing evidence of the value of monitoring cytokines in other tissues and fluids such as saliva, urine and also tumor. Cytokines including IL6, IL8, IL10, IFN-G, TNF-A and TGF-B can be tracked during the progression of the illness and its treatment to gain more insight into the ever-shifting immune system. These cytokines, along with blood parameters and intra-tumoral immune microenvironments such as TILs, can be used as predictive and prognostic biomarkers.

Interlukin-6 (IL-6)

In a meta-analysis of over 11,500 patients with 23 different types of cancer, it was found that 85.6% had a strong relationship between elevated IL-6 blood levels and reduced survival. Moreover, 91% of reported cases indicated a definitive relationship between rising IL-6 and advanced stages of the tumor or metastases.[36] Elevated levels of IL-6 have been associated with worse outcomes for both overall and disease-free survival.[37] Serum Interlukein-6 levels were found to be an important indicator of recurrence in multivariate studies. The presence of elevated IL-6 in the bloodstream was determined to be a significant factor in predicting a poor outcome.[38] A 12% lower incidence of liver cancer was substantially related to a drop of 1 pg/mL in circulating IL-6.[39] The IL-6 level

Table 1: Different Types of Cancers.

Sl. No.	Type of cancer	Description
1	Laryngeal and hypopharyngeal cancer.	Laryngeal and hypopharyngeal cancers are two of the most common cancers in the head and neck region. In the US, white men are less prone to develop laryngeal cancer than black men. The survival rate of patients diagnosed with laryngeal cancer ranges between 34-78%. In India, laryngeal cancer affects 1.26-8.18 out of every 100,000 people. Risk factors for laryngeal and hypopharyngeal cancers include the use of tobacco, alcohol, age, gender, race/ethnicity, poor nutrition, Plummer-Vinson syndrome and HPV.[4,5]
2	Nasal cavity and paranasal sinus cancer.	Malignancies of the paranasal sinuses and nasal cavity account for 3 to 5% of head and neck cancers in the US. White people are more likely to be diagnosed and men are twice as likely as women. 5-year survival percentage is 80%.[6] Risk factors include occupational exposures, smoking, age and heredity.
3	Oral and oropharyngeal cancer.	Oral and oropharyngeal carcinoma is the 8th most common malignancy in men, with 476,125 cases reported in 2020. In the US, there are 11,230 fatalities per year and the 5-year survival rate is 67%. Risk factors include tobacco use, extended sun exposure, HPV, gender, age, fair skin, poor oral hygiene and marijuana use. To prevent these cancers, it is important to stop using tobacco products, maintain a healthy lifestyle, get vaccinated against HPV and have a balanced diet.
4	Salivary gland cancer.	Salivary gland cancer has a low prevalence in the US, but the risk increases with age. Globally, 53,580 cases of salivary gland cancer were reported in 2020. In India, the incidence rate is estimated to be 2.77% with a prevalence of 0.003%.[7] In the US, the likelihood of surviving salivary gland cancer for a period of 5 years is estimated to be 75%. The precise causes of salivary gland cancer remain unknown, but age, environmental and/or occupational exposures, as well as radiation and radioactive substance exposure, may play a role in its development.
5	Nasopharyngeal cancer.	Nasopharyngeal Cancer (NPC) is more prevalent in certain regions of Asia, the Middle East and North Africa, particularly in certain regions of China. In 2020, the number of people diagnosed with NPC worldwide was 133,345 and it has been reported to have killed 80,008 people globally. In India, except the north-eastern hill states of Nagaland, Manipur and Mizoram, its prevalence covers the entire spectrum, from 0.5% to 20%.[8] Prevention factors involve stopping the use of all tobacco products, maintaining a healthy lifestyle, vaccination against HPV and having a balanced diet.
6	Stomach cancer.	Stomach cancer is the 4th leading cause of cancer-related deaths around the world and it is estimated that 11,090 people in the US will succumb to it in 2023. If the disease is identified and treated in its early stages, the 5-year survival rate is 70%. But if the cancer has metastasized to adjacent tissues or organs and/or the local lymph nodes, the 5-year survival rate decreases to 32%.[9] In India, the incidence rate of stomach cancer is lower than the global average, with an age-adjusted rate ranging from 3.0 to 13.2 compared to 4.1 to 95.5.[10] Factors responsible for stomach cancer include age, gender, bacteria, diet, tobacco and alcohol use, occupational exposure and family history genetics.
7	Liver cancer.	Liver cancer is the third foremost source of mortality globally, with Southeast Asia and sub-Saharan Africa having higher geographical prevalence rates than the United States. In 2023, it is projected that 41,210 individuals in the US, will be diagnosed with primary liver cancer, with male patients outnumbering female patients.[9] In India, liver cancer caused 14,000 cancer deaths in 2010, with a cancer mortality rate of 6.8 per 100,000 cases (age-standardized.[11] Liver cancer can be prevented by controlling cirrhosis and viral hepatitis.
8	Colorectal cancer.	In the United States, colorectal cancer is the second most fatal form of cancer; a majority of these deaths are attributed to unhealthy lifestyle habits.[12] In 2020, 1,880,725 persons were reported with colorectal cancer, including 732,210 cases of rectal cancer and 1,148,515 cases of colon cancer. According to projections, 151,030 adults will be diagnosed with colorectal cancer in 2023, of which 106,180 fresh cases of colon cancer and 44,850 fresh incidences of rectal cancer will occur.[9] In India, rectal and colon cancer are more common among men with the annual case rate being 4.4 and 4.1 per 100,000, respectively. Colorectal cancer can be attributed to a variety of genetic, environmental and lifestyle-related factors, such as hereditary CRC syndromes, age and gender, cigarette smoking, ulcerative colitis, obesity, acromegaly and history of cholecystectomy.[13]

Sl. No.	Type of cancer	Description
9	Pancreatic cancer.	Pancreatic cancer is rare cancer in India, with only 1.03% of new cases and 18th in mortality. On a global scale, it is the 14th most frequent cancer and the 7th leading cause of death.[14] A given stage of pancreatic cancer has a 5-year survival rate of about 50%.[15] Risk factors for pancreatic cancer include smoking, being overweight (obese), type 2 DM, inherited genetic syndrome, diet, age, gender, physical inactivity, coffee, alcohol and infections. Certain hereditary conditions, such as HP, PJS, Lynch Syndrome, HBOC Syndrome, LFS and FAP, can considerably raise the likelihood of pancreatic cancer and other forms of cancer.
10	Kidney or renal cancers.	Kidney or renal cancer is a form of cancer that is usually diagnosed in people aged between 65 and 74, with the average age of diagnosis being 64. In the United States, it is the 6th most common cancer among men and the 7th most common cancer among women. In India, the estimated rate of kidney cancer is 2 per 100,000 men and 1 per 100,000 women.[16] Factors that may increase the risk of developing kidney cancer include being overweight, smoking, hypertension, acquired cystic kidney disease and occupational exposure to specific chemicals. Reducing blood pressure, refraining from smoking and using tobacco, sustaining a healthy weight and consuming a balanced diet full of vitamins and minerals and low in fat are all ways to stop or prevent kidney cancer.
11	Lung cancer.	Lung cancer is the most widespread type of cancer worldwide, with 8.1% of all cancer-related fatalities and 5.9% of all cancer cases in India.[17] In the USA only tobacco use causes 85-90% of lung cancer fatalities, yet every year over 15,000 people who have never smoked die away from lung cancer. In the US, lung cancer has been diagnosed in over 541,000 people throughout the course of their lifetimes and in 2018, it was anticipated that 234,030 new instances of lung cancer will be discovered.[18] The primary culprit behind this is smoking, which is responsible for around 90% of lung cancer cases. Radiation, toxic chemicals, air pollution and genes or family history are additional factors causing lung cancer.
12	Papilloma	A papilloma is a small, non-cancerous tumor that develops in the breast milk duct. It is most likely to affect women aged between 35-55 years of age but can occur in women of any age.[19] After the tumor has been completely removed, it has been discovered that 17-20% of intraductal papilloma's are malignant, but the majority are not carcinogenic. The most effective way to prevent the growth or progression of intraductal papilloma to DCIS or atypical ductal hyperplasia is to surgically remove it.[20]
13	Prostate cancer	Prostate cancer is the most frequent malignancy common in men, with 1,414,259 men diagnosed in 2020 and 268,490 men in the US in 2023.[21] It is the sixth most deadly disease among men globally, with an incidence rate of 29.8% from 1990 to 2016. Vasectomy, sexually transmitted infections, chemical exposure, smoking, obesity and diet are secondary factors. Primary causes of prostate cancer are age, race/ethnicity, geography, family history and genetic mutations.
14	Ovarian cancer	Ovarian cancer is a deadly disease, with India having the 2nd highest number of new incidences and fatalities.[22] In 2023, around 19,710 females will be diagnosed with ovarian cancer, with 13,270 of those cases being fatal in the US. Factors such as age, hormone therapy after menopause, family history of ovarian cancer, HBOCS and genetic mutations can increase an individual's risk. Preventive measures such as gynaecologic surgery and oral contraceptives are advised for females with hereditary ovarian cancer.
15	Sarcoma	Sarcomas are tumors that develop from mesenchymal or connective tissue and accounted for 0.8% of all cancer cases in the US in 2018.[23] In India, male incidence rates vary from 3.6% to 14.8% and female incidence rates range from 3.7% to 9.5%. In the US, it is estimated that between 3,500 and 4,000 individuals are lost to this type of cancer annually.[24]

before surgery determines the likelihood of Colorectal cancer recurrence.[40] Before surgery, blood levels of IL-6 and CRP may serve as indicators of tumor invasion, lymph node metastases and the extent of the Tumor (T), extent of spread to the lymph Nodes (N) and presence of Metastasis (M). High levels of preoperative interleukin-6 are a negative prognostic factor for recurrence and survival in patients with gastric cancer.[41] In the majority of patients with pancreatic cancer, the level of serum IL-6 and clinical status are significantly correlated.[42] Studies have shown that higher levels of interleukin-6 in the blood of those with breast cancer are associated with increased tumor growth. Breast cancer patients can employ IL-12 and IL-6 serum level assays as non-invasive prognostic testing for tumor progression. Patients with breast cancer and elevated serum IL-6 levels had drastically poorer survival rates than those with lower IL-6 levels. Additionally, those who did not respond to chemo-endocrine therapy had significantly elevated IL-6 serum levels than those who did. A study involving multiple variables has suggested that elevated levels of IL-6 might be a sign of aggressive metastatic breast cancer, as it is a distinct predictive factor for this form

of the disease.[43] Elevated levels of interleukin-6 in the serum have been linked to a poorer prognosis and diminished effect of chemo-endocrine therapy for individuals with metastatic breast cancer.[44] In pharyngeal cancer patients, IL-6 was found to be closely linked to decreased response to treatment, as well as shorter survival times.[45] Increased IL-6 expression in cancer tissue and higher levels in the blood both indicate a poor prognosis for the survival of the patient.[46] Statistical study showed a clear correlation between high IL-6 levels and an increased risk of cancer. All cancers studied were linked to this association, which held up over the entire research.[47] The tumor size and the concentration of IL-6 were found to be important predictors of the diagnosis of soft tissue sarcoma and IL-6 was seen to be an imperative indicator of both survival and event-free survival. As a result, monitoring Interlukein-6 levels may be a valid signal for locating people who are at a higher risk for developing soft tissue sarcoma and dying from tumor-related causes.[48] Research has shown that increased levels of interleukin-6 in the blood can indicate a higher risk of cancer relapse. Measuring IL-6 levels in the serum may be beneficial in determining which Oral squamous cell carcinoma patients have a greater chance of relapse.[49]

Interlukin-8 (IL-8)

An increase in IL-8 levels in the blood is related to an increased tumor load, a poorer prognosis and the occurrence of metastases to the liver or lymph nodes. A tumor microenvironment that is immunosuppressive and myeloid-enriched corresponds with interleukin-8, which is produced by intra-tumoral and circulating myeloid cells and has a poor prognosis for cancer.[50] There is an association between IL-8 and endometrial cancer development..[51] IL-8 has been utilized to identify colon cancer in its early stages as well as track the growth of colon tumors.[52] It was determined that the most reliable biomarker for diagnosing bladder cancer was urinary interleukin-8.[53] Elevated IL-8 and

Table 2: Diagnosis of Cancer.

Sl. No.	Diagnostic method	Description
1	Complete blood count.	The CBC is used to calculate the RBC, WBC and platelet counts. Some malignancies, including leukemias, can be diagnosed with CBC.
2	Cytogenetic analysis.	This test identifies chromosomal abnormalities in tissues, blood, bone marrow, or aromatic fluids. Chromosome alterations might involve additional, ruptured, altered, or missing chromosomes. This could be employed for cancer diagnosis and therapy planning.
3	Immunophenotyping.	Immunophenotyping makes use of antibodies to discriminate between various antigens or cell-surface markers. Blood or bone marrow samples are utilized for it most frequently. Other bodily fluids or tissue samples might also be used. With the help of immunophenotyping, blood disorders such as leukemia, lymphomas, myelodysplastic syndromes and myeloproliferative disorders can be found, graded and subsequently followed.
4	Liquid biopsy.	It is an examination of DNA from cancer cells or a blood sample to check for cancer. Liquid biopsy is useful for cancer early-stage detection.
5	Sputum cytology	Lung cancer is identified by sputum cytology, which examines the mucus and other material expelled from the lungs after coughing.
6	CT scan	Computed Tomography (CT) is an imaging technology that uses specialized X-ray equipment to create detailed scans of different regions of the body, the CT in the therapy of neoplasia includes screening for the disease, aiding in the diagnosis of tumor presence, providing information about the cancer stage, precisely locating (detecting) the location of the biopsy procedure, directing some local procedures like cryotherapy, radiofrequency ablation and the implantation of radioactive seeds, facilitating the planning of surgery or external radiation therapy, evaluating the efficacy of treatment for malignancy and more. By using this technique, colorectal and lung cancers are screened.
7	MRI	Magnetic Resonance Imaging is used to locate the tumors in the body by using powerful magnetic and radio waves to take pictures of your body.
8	PET scan	A PET scan is a nuclear scan that produces accurate 3D images of organs that show which areas absorb glucose more effectively. These images can be used to detect cancer by identifying areas that absorb glucose at a faster rate than normal. Before scanning, radioactive glucose is injected. A patient sits on a table or bed that is being scanned back and forth.
9	Biopsy	A biopsy is a diagnostic procedure often performed by a surgeon, radiologist, or interventional cardiologist. A sample of tissues or cells is taken to be tested to investigate if a disease is present or to determine its severity. The tissue is then mounted after being fixed, dehydrated, embedded, sectioned and dyed.[25] The biopsy of the sample can be done with a needle, with endoscopy, or with surgery.

its associated receptors have been linked to the advancement of Melanoma. It was observed that an elevation of serum IL-8 was the only predictor for clinically recognizable lung cancer. Incorporating IL-8 measurement into diagnostic practice increases prediction of lung cancer occurrence.[54] Individuals with elevated serum Interlukin-8 levels had a poorer prognosis than those with lower serum Interlukin-8 levels.[55] In breast cancer patients, the presence of IL-8 can predict post-relapse survival. In breast cancer patients, 52 out of 77 showed higher serum IL-8 levels than healthy individuals. This could indicate a faster disease progression, larger tumor sizes and the presence of liver and lymph node metastases.[56] The expression of IL-8 in the primary tumor tissue is a predictor of better survival outcomes in patients with nasopharyngeal cancer, including increased chances of survival without distant metastases, disease-free survival and overall survival.[57] Myeloid-Derived Suppressor Cells have been demonstrated to be augmented by both Interlukin-6 and Interlukin-8 and this correlation has been shown to result in unfavourable struggling with melanoma.[58] It was observed that in responding patients who had melanoma and NSCLC, there was a significant decrease ($p<0.001$) in serum IL-8 levels from baseline to best response and a significant increase ($p<0.004$) with progression when they were given anti-PD-1 therapy.[59]

Tumor Necrosis Factor and Interlukein-6

TNF- alpha may function as an endogenous cancer promoter when it is generated in the tumor microenvironment.[60] TNF-conc. in prostate cancer individuals correspond with the level of severity of the disease and can be tracked with other disease markers like IL-6. Studies have suggested that IL-6, IL-8 and TNF-alpha levels are correlated with the stage of clinical disease, lymph node metastasis and the expression of the ER and HER2

Table 3: Different Treatment Approaches for Cancer.

Sl. No.	Methods		Descriptions
1	Conventional treatment methods.		The conventional methods for the treatment of cancer include Surgery, Chemotherapy, Cyberknife and Radiotherapy.
2	Advanced or novel treatment methods.		Examples of novel treatment methods include Stem cell therapy, Gene therapy, immunotherapy and Targeted drug therapy.
	a	Stem cell therapy	Pluripotent stem cells Embryonic stem cells, which are homogenous inner mass cells of the embryo, can become any cell type in the body, apart from those in the placenta. In 2006, Yamanaka factors enabled scientists to make an important breakthrough in cell biology-the creation of iPSCs in culture from somatic cells. These iPSCs, which mimicked ESCs, provided a way to bypass the ethical issues connected to embryo destruction. Furthermore, both iPSCs and hESCs are being used to produce effector NK, T-cells and anti-cancer vaccines.[28] Adult stem cells In cancer treatment, adult stem cells, e.g. mesenchymal, neural and Hematopoietic, are regularly employed. Bone marrow contains hematopoietic stem cells, which can generate all the blood cells typically seen in an adult organism. The use of hematopoietic stem cells from cord blood to treat leukaemia and multiple myeloma has been approved by the FDA.[29] Cancer stem cells are a small segment of malignant cells that can replicate and differentiate and, when transplanted, can result in the emergence of tumors in a living organism. Identification and extraction of Cancer Stem Cells can be accomplished by the use of cell surface markers such as CD133, CD44 and CD24. A network of signalling pathways, such as Hedgehog, Notch, Wnt/β-catenin and microRNAs, control the characteristics of cancer stem cells.[30]
	b	Gene therapy	Cancer suppressor gene therapy involves incorporating genes that control cell growth and differentiation, thereby preventing the occurrence of cancer caused by uncontrolled cell proliferation. Examples are P53, P16 and others.[31,32] Gene silencing Specific genes in living organisms can be intentionally and selectively silenced by the process of gene silencing. The most widely employed method for treating cancer is RNA interference (RNAi), which is being used clinically.[32] Suicide gene therapy is the standard technique for treating solid tumors. It works by introducing genes into tumor cells that can cause them to self-destruct, thereby eliminating the cancerous cells.[33-35] Immune gene therapy is a therapeutic approach that seeks to combat cancer by introducing genetic materials, such as costimulatory molecules cytokines, antigens and receptors into cells to boost the body's immune system and eradicate the majority of tumor cells.[32]

antigens, which could make them useful biomarkers for cancer prediction.[61] Higher levels of IL-10 compared to TNF-alpha in HPV-infected lesions may indicate a possible downregulation of tumor-specific immune responses, offering a setting that encourages tumor development.[62] Expression of cytokines (IL-6 and TNF-alpha) was significantly higher in serum and tissue compared with controls. TNF-alpha and IL-6 may initiate the epithelial-mesenchymal transition, which could, in turn, lead to Lung cancer's growth and advancement.[63] Renal cancer patients have been detected with serum IL-6 and TNF-alpha and it has

Terminal transferase (TdT)	Tumor, Blood	Diagnosis	Leukemia, lymphoma.
JAK2 gene mutation	Bone Marrow and Blood	To help diagnose disease.	Certain types of leukemia.
DH1 and IDH2 gene mutations	Bone Marrow and Blood	To help determine treatment.	Acute myeloid leukemia.
Chromosome 17p deletion	Blood	To help determine treatment.	Chronic lymphocytic leukemia.
Cyclin D1 (CCND1) gene rearrangement or expression	Tumor	diagnosis	Lymphoma, myeloma.
Myeloperoxidase (MPO)	Blood	diagnosis	Leukemia
Immunoglobulins	Blood and Urine	To help diagnose disease, assess response to treatment and look for recurrence.	Multiple myeloma and Waldenström macroglobulinemia.
Lactate dehydrogenase	Blood	To assess stage, prognosis and response to treatment.	Germ cell tumors, lymphoma, leukemia, melanoma and neuroblastoma.
Urine catecholamines: VMA and HVA	Urine	diagnosis	Neuroblastoma
Chromogranin A (CgA)	Blood	Diagnosis, assessment of treatment response and evaluation of recurrence.	Neuroendocrine tumors.
Cytokeratin fragment 21-1	Blood	To help in monitoring for tumor recurrence	Lung cancer
ALK gene overexpression and rearrangement	Tumor	Determines treatment and prognosis.	Lung cancer, lymphoma, histiocytosis.
Des-gamma-carboxy prothrombin (DCP)	Blood	to monitor the effectiveness of treatment and to detect recurrence.	Hepatocellular carcinoma.
EGFR gene mutation	Tumor	To help determine treatment and prognosis.	Non-small cell lung cancer.
KRAS gene mutation	Tumor	To help determine treatment.	Colorectal cancer and non-small cell lung cancer.
DPD gene mutation	Blood	To predict the risk of a toxic reaction to 5-fluorouracil therapy	Breast, colorectal, gastric and pancreatic cancers
Estrogen receptor (ER)/progesterone receptor (PR)	Tumor	To help determine treatment.	Breast cancer
CA15-3/CA27.29	Blood	treatment	Breast cancer

HER2/neu gene amplification or protein overexpression	Tumor	To help determine treatment.	Breast, ovarian, bladder, pancreatic and stomach cancers.
21-Gene signature (Oncotype DX)	Tumor	To evaluate risk of recurrence.	Breast cancer
70-Gene signature (Mammaprint)	Tumor	To evaluate risk of recurrence.	Breast cancer
CA 27.29	Blood	To detect metastasis or recurrence.	Breast cancer
BRCA1 and BRCA2 gene mutation	Blood or Tumor	To determine treatment.	Breast and ovarian cancer.
HER2/neu gene amplification or protein overexpression	Tumor	to help determine treatment.	Breast, ovarian, bladder, pancreatic and stomach cancers.
HE4	Blood	To plan cancer treatment, assess disease progression and monitor for recurrence.	Ovarian cancer
5-Protein signature (OVA1)	Blood	To pre-operatively assess pelvic mass for suspected ovarian cancer.	Ovarian cancer
CA-125	Blood	diagnosis, assessment of response to treatment and evaluation of recurrence.	Ovarian cancer
Chromosomes 3, 7, 17 and 9p21	Urine	To help in monitoring for tumor recurrence.	Bladder cancer
FGFR2 and FGFR3 gene mutations	Tumor	To help determine treatment.	Bladder cancer
Fibrin/fibrinogen	Urine	To monitor progression and response to treatment.	Bladder cancer
Bladder tumor antigen (BTA)	Urine	Surveillance of patients with bladder cancer.	Bladder cancer, uterine and kidney cancer.
Prostate-specific antigen (PSA)	Blood	To help in diagnosis, to assess response to treatment and to look for recurrence.	Prostate cancer
Prostatic Acid Phosphatase (PAP)	Blood	To help in diagnosing poorly differentiated carcinomas.	Metastatic prostate cancer.
PCA3 mRNA	Urine (Collected After Digital Rectal Exam)	To determine need for repeat biopsy after negative biopsy.	Prostate cancer

17-Gene signature (Oncotype DX GPS test)	Tumor	To predict the aggressiveness of prostate cancer and to help manage treatment.	Prostate cancer
46-Gene signature (Prolaris)	Tumor	To predict the aggressiveness of prostate cancer and to help manage treatment.	Prostate cancer
Thyroglobulin	Blood	To evaluate response to treatment and to look for recurrence.	Thyroid cancer
Calcitonin	Blood	To aid in diagnosis.	Medullary thyroid cancer
5-HIAA	Urine	To help in diagnosis and to monitor disease.	Carcinoid tumors
CA19-9	Blood	Treatment	Pancreatic, gallbladder, bile duct and gastric cancers
C-kit/CD117	Tumor, Blood, Or Bone Marrow	Diagnosis and to help determine treatment.	Gastrointestinal stromal tumor, mucosal melanoma, acute myeloid leukemia and mast cell disease.
Carcinoembryonic antigen (CEA)	Blood	Treatment tracking.	Colorectal cancer and some other cancers.

Figure 1: Tumor markers commonly used for Diagnosis, Treatment, Prognosis and Recurrences.[27]

been proposed that high serum TNF-alpha may help in the early identification of the disease.[64] In patients with sophisticated, cachectic prostate cancer, levels of TNF-alpha will be elevated.[65] Plasma and chronic lymphocytic leukaemia both produce TNF-alpha. Patients who had elevated TNF-alpha levels were more likely to have serious symptoms including chromosomal abnormalities or low platelets or haemoglobin. TNF-alpha was higher in chronic lymphocytic leukaemia patients compared to healthy controls. Poorer survival was predicted by higher TNF-alpha concentrations.[66] High concentrations of serum TNF-alpha have been correlated with an increase in pancreatic cancer symptoms as well as a deterioration of nutritional status.[67]

Tumor Growth Factor-beta (TGF-β)

Studies on animals indicate an increase of both TGF-1 mRNA in tumor cells and TGF-1 in the blood plasma of individuals suffering from various types of cancer, which is accompanied by elevated levels of TGF-β1 in many metastatic cases. TGF-β1 is crucial to the altered collagen metabolism in hepatocellular cancer.[68] Patients with lung cancer usually have higher TGF-β1 levels. Monitoring plasma TGF-β1 patients who had increased levels at the diagnostic stage may help identify disease persistence and reappearance following treatment.[69] Increased serum levels of TGF-β1 are helpful for the detection of bladder cancer.[70] Through examining TGF- biomarkers, prognostic information can be obtained by patients with stage I-III breast cancer.[71] Patients with metastatic breast cancer whose plasma TGF-β1 levels were elevated had a lower chance of survival compared to those whose levels were close to normal.[72] Breast cancer occurrences, as well as malignant neoplasms, gliomas, ovarian malignancies and cervical cancers, have all been associated with increased TGF expression.[73] Patients with hepatocellular carcinoma and other cancers, like cancer of the lungs, breasts and pancreas, have worse prognoses when the blood has high amounts of TGF-β.[74] Systemic TGF-1 levels have been utilized as a proxy for tumor burden and/or therapeutic response.[75] TGF-beta possesses tumor-promoting qualities in breast cancer, notably in cells that avoid the TGF-β1 regulating properties throughout the metastatic phase.[76] Patients with operable breast cancer had considerably greater preoperative plasma TGF-β1 levels than healthy people (median 15293 and 3983 pg/mL, p 0.0001 and p 0.0001, respectively).[77] A clinically relevant tumor marker for assessing the extent and prognosis of the disease, serum TGF-β1 has an impact on both lymph node metastasis and tumor malignancy. Additionally, they offer clinical proof of a strong correlation between serum TGF-I(2)1 and the HER-2 Ile655Val SNP, which leads to a more aggressive tumor phenotype and an unfavourable prognosis.[78] TGF-1 levels are associated with mild to severe radiation-induced fibrosis. TGF-1 levels can be utilized as a biomarker to identify the starting point for moderate to severe radiation-induced fibrosis.[79]

Interferon-gamma (IFN-γ)

IFN-gamma one of the most significant cytokines of the Type 1 T helper (Th1) pathway, was downregulated in situations with nodal involvement and this downregulation showed a linear association with regional development. When compared to

prognosis, IFN-gamma was the only serum cytokine to exhibit a protective impact. Patients with lung cancer had considerably lower plasma IFN-gamma levels.[80,81] PD-1 inhibition therapy in NSCLC and melanoma patients results in increased expression of IFN gamma protein and this is accompanied by considerably longer progression-free survival, suggesting that IFN gamma may be a biomarker for predicting response to immune checkpoint blocking.[82] After curative therapy, the amount of interferon-gamma in the blood can forecast whether or not a patient with hepatocellular carcinoma will have a relapse. Those patients with a lower starting level of IFN- are more likely to have a reappearance of their cancer.[83] Higher IFN-gamma, tumor necrosis factor, interleukin (1, 2, 4, 5, 6, 8, 10) and interleukin-12 levels may be an indication of the effectiveness of anti-PD-1 inhibitors in providing longer life and improved response to non-small cell lung cancer.[83] In metastatic melanoma patients, baseline IFN-gamma expression levels were considerably higher in those who responded to anti-programmed cell death-1 therapy than in those who did not.[84] The study demonstrated that, compared to controls, Head and Neck Squamous Cell Carcinomas (HNSCC) patients had significantly lower average serum IFN-gamma levels of 6.08 pg/mL in comparison to 26.20 pg/mL. Patients with HNSCC had significantly lower IFN-gamma concentrations in their serum regardless of the primary tumor site.[85] Individuals with prostate-specific antigen changes had greater concentrations of IFN-gamma. Serum IFN-gamma level measurements may be a novel marker that adds predictive data to an altered prostate-specific antigen in male serum and benefits men's health.[86]

Interlukin-10 (IL-10)

In most cancer types, high serous IL-10 expression has a detrimental effect on survival.[87] Peripheral T-cell lymphoma patients with increased IL-10 in their blood often have a shorter survival time and a higher risk of recurrence and measuring IL-10 levels in the blood can be used to predict prognosis and assist us in creating customized therapy strategies for each patient.[88] Numerous investigations have revealed a relationship between high Interlukein-10 levels and advanced disease stages or poor patient prognoses.[89] CD30, IL6 and detectable IL10 Serum Level Elevations Are Associated with Classic Hodgkin Lymphoma Diagnosis.[90] There is a clear relationship between high concentrations of IL-10 in the blood and ductal carcinoma, especially in terms of the stage of the tumor. High blood levels of Interlukien-10 were additionally linked to ductal carcinomas' negative ER and PR expression. By examining blood cytokine levels, we can single out individuals with a grim prognosis who could benefit from more aggressive care.[91] The previous results of these studies indicate that measuring serum IL-10 levels before treatment can be an effective predictor of the course of advanced gastrointestinal cancer and can assist in the identification of disease progression.[92]

CONCLUSION

The immune system plays a critical role in the proliferation and transmission of disease. Pro-inflammatory cytokines are connected to the progression of a disease and can be used to anticipate its prognosis. It is important to monitor their level of cancer. Elevated the levels in response to alterations in the environment and offer a dynamic depiction of the immunological environment. As a result, it can support cancer treatment at any stage of the disease.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

NK: Natural Killer; **TILs:** Tumor-Infiltrating Lymphocytes; **NSCLC:** Non-Small Cell Lung Cancer; **CRP:** C-Reactive Protein; **PD-1:** Programmed Death-1; **PD-L1:** Programmed Death-Ligand 1; **ER:** Estrogen Receptor; **HER2:** Human Epidermal Growth Factor Receptor 2; **ADCC:** Antibody-Dependent Cellular Cytotoxicity; **HL:** Hodgkin's Lymphoma; **HPV:** Human Papillomavirus; **HP:** Helicobacter pylori; **PJS:** Peutz-Jeghers Syndrome; **HBOC:** Hereditary Breast and Ovarian Cancer Syndrome; **LFS:** Li-Fraumeni Syndrome; **FAP:** Familial Adenomatous Polyposis; **iPSCs:** Induced Pluripotent Stem Cells; **hESCs:** Human Embryonic Stem Cells; **ESCs:** Embryonic Stem Cells; **CSF:** Cerebrospinal Fluid.

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