Tumor Markers in the Blood

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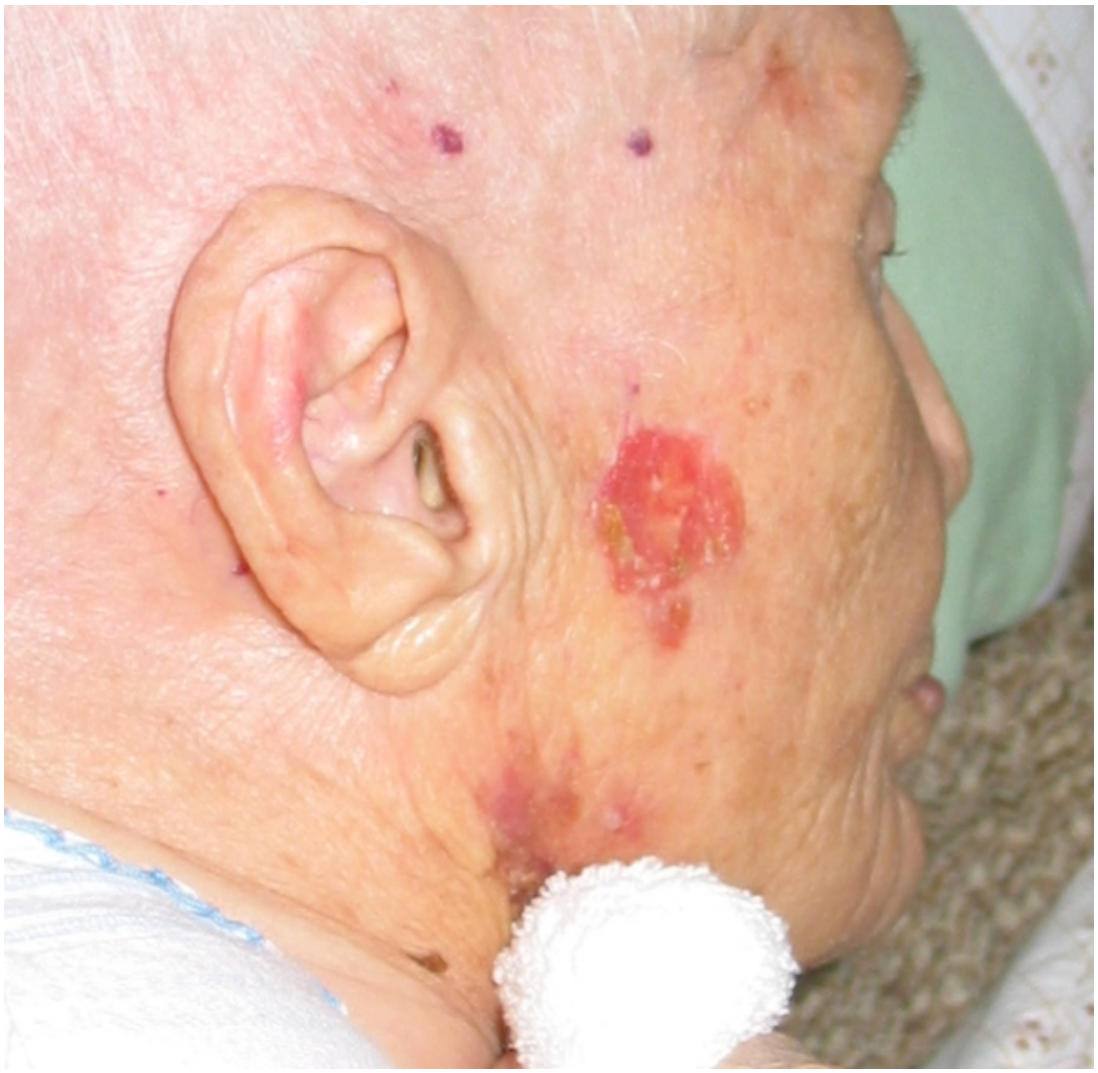
Cancer is one of the most widespread and dreaded diseases in the world. Its onset is often insidious and occurs initially without any noticeable symptoms. Successful treatment requires early detection. However, every year about 225,000 people worldwide lose this race against the clock. Tumor markers in the blood may represent an alarm system in the body. Are regular blood tests the optimal prophylaxis against cancer? Read more about this topic in the following article.



Definition of Tumor Markers

In medicine, the term tumor markers refers to substances or cellular changes, which provide information about the presence, development, and prognosis of malignant tumors, using qualitative and quantitative analytical methods. The tumor markers can be

proteins with carbohydrate or lipid portion, enzymes, antigens, or hormones.

Classification of tumor markers

Cellular tumor markers are **tumor antigens** located in the membranes, receptors for growth-promoting substances, and cell markers indicating increased expression of oncogenes and monoclonal cell growth. They are detected histologically in tumor cells and biopsies.

Humoral tumor markers are synthesized in the organism in response to a tumor. Such markers are detected in bodily fluids such as blood or urine in higher concentrations than under normal physiological conditions. Humoral tumor markers are synthesized and secreted by the tumor tissue itself or released when the tumor disintegrates. To serve as a laboratory diagnostic marker for tumor detection, an ideal humoral or cellular tumor marker should meet specific criteria:

- Total (100%) specificity to distinguish healthy individuals from patients carrying a tumor
- Early detection of tumor in all patients
- Organ specificity and localization of the tumor
- Correlation with tumor stages
- Indicating all treatment-related changes
- Prognostic validation

Epidemiology of Malignant Diseases

Annually, cancer is diagnosed in 1,800 children and adolescents under the age of 15 years. In men, **prostate cancer** is the most common type of cancer and the third most frequent cause of death.

Nearly 75,000 new cases of **breast cancer** are detected each year and is the most common type of cancer in women. In children under the age of 15, **leukemia** accounts for 60% of all cancerous conditions. After cardiovascular diseases, tumors are the second most common cause of death in industrialized countries. Statistically speaking, one in three persons in the Western world suffers from a tumorous condition at least once in his or her life. Tumors are the cause of death in one in four persons.

Tumor Pathology

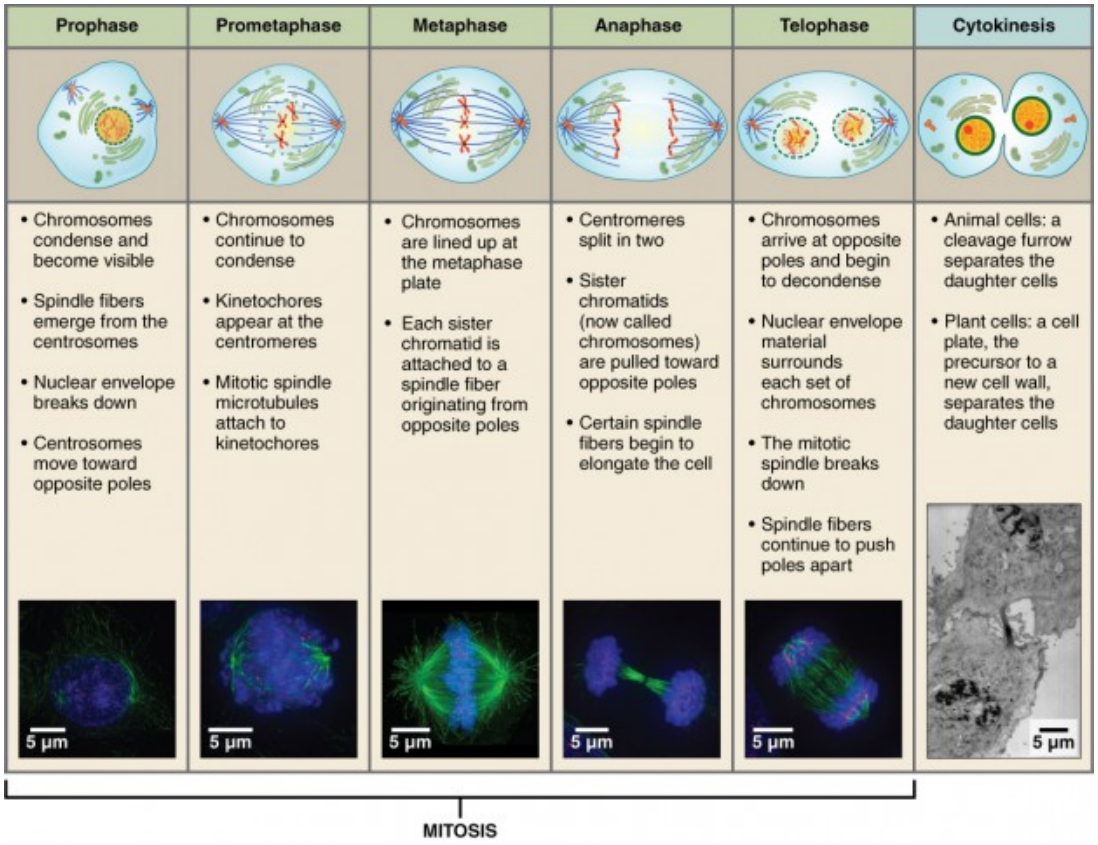


Image: 'Stages of Mitosis and Cytokinesis' by philschatz. License: CC BY 4.0

Every tumor begins as a localized lesion in a single cell (**monoclonality**). Chemical, viral, and physical noxae have **mutagenic effects** in humans and animals as well. Normal cells cease proliferation as soon as they contact each other (**contact inhibition**). Cell adhesion molecules facilitate intercellular attachment and communication to form healthy tissues.

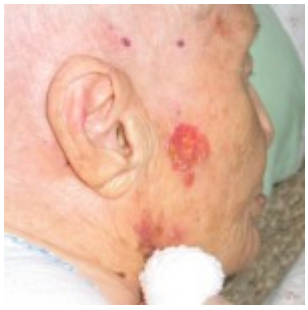


Image: "Basal Cell Carcinoma"
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Tumorous cells, however, develop a mutant genome, following exposure to noxious elements. Exposure to a harmful environment alters cellular differentiation and disrupts the communication between the cells, leading to uncontrolled growth and proliferation. As the cells are no longer held together, their proliferation is limited and they no longer remain in a cell group.

Tumor cells are characterized by a lack of a fixed location. The original cell group 'grows wild', changes its morphology, and spreads like a weed.

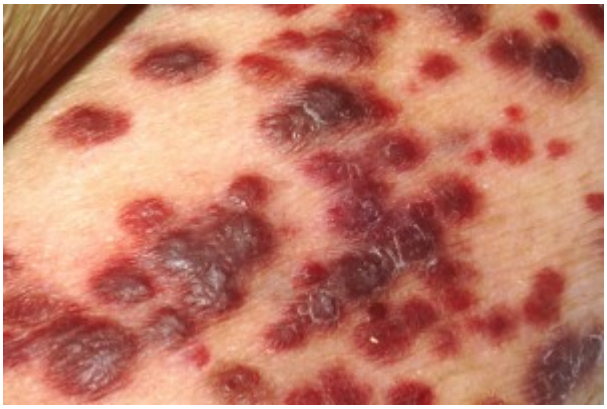
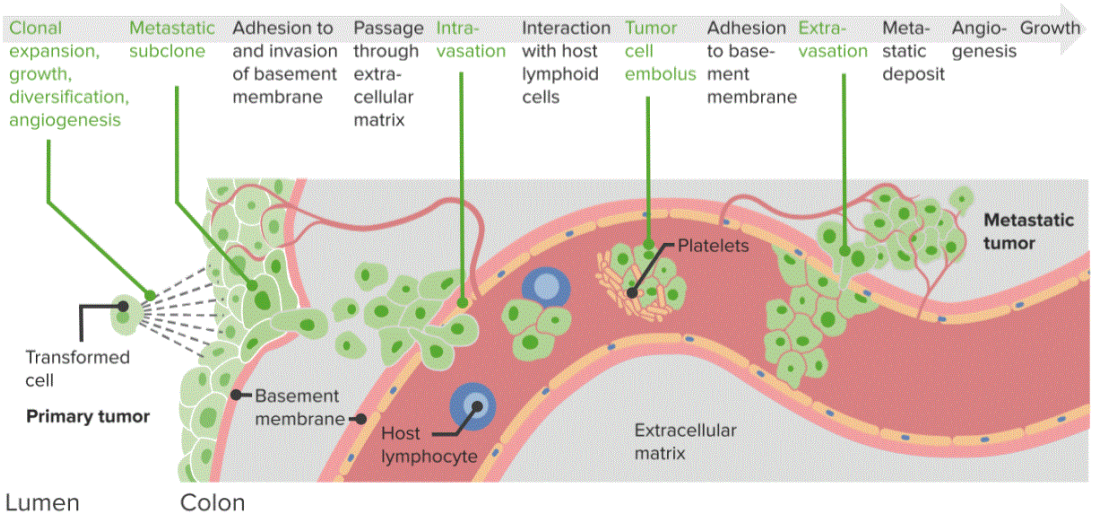


Image: ‘Kaposis Sacroma Lesions’ by philschatz. License: CC BY 4.0

Thereby, the tumor cells practically suffocate adjacent healthy cells and may even threaten their own existence. Therefore, cancer cells are considered **destructive and antisocial**. Abnormal tissue growth occurs as a result of autonomous, progressive, and excessive cell proliferation, which in turn is caused by activated growth-inducing genes (**oncogenes**) and defective growth-inhibiting genes (**tumor suppressor genes**).

In addition, the apoptosis reveals genetic defects. Damage to the genome abrogates the expression of regulatory genes that control cell growth. The uncontrolled cell division is also referred to as **immortalization** of cells. The participating genes include the master control genes (**Hox genes**), **growth factor genes** (continuous proliferation), in addition to the oncogenes and suppressor genes mentioned above.

In most cases, the changed tissue patterns and mutant tumor cells are not recognized by the immune system as ‘strange” and are therefore not attacked and eliminated. Abnormal gene differentiation leads to poor recognition of the tumor cells by the immune system resulting in immune evasion.



‘Malignant Neoplasms’ Image created by Lecturio

If the tumor cells find other tissues congenial to growth and proliferation, tumor cell invasion or spread to other organs occurs. This process, called **metastasis**, is probably the most feared aspect of any tumor disease as it is impossible to confine the disease to a single cell area, resulting in multiple tumor foci in the body warranting immediate and concurrent treatment. Cells metastasize via lymph and blood circulation. The activation of

mobility factors facilitates metastasis.

Note: Tumor disease is characterized by uncontrolled growth, immortalization, absence of fixed localization, immune evasion, and metastasis.

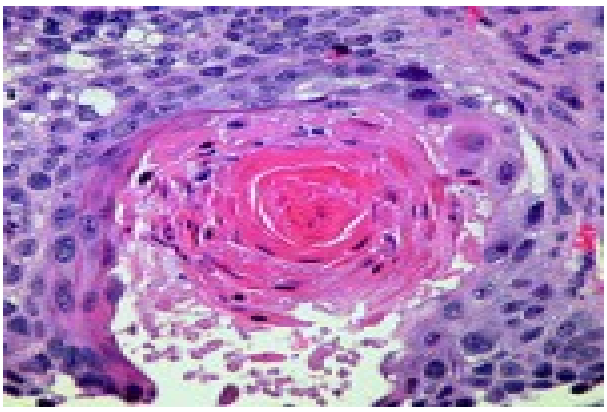


Image: 'Squamous Cell Carcinoma' by philschatz. License: CC BY 4.0

Note: The term 'tumor' refers to any new, uncontrolled growth of tissue. Depending on their behavior, they are classified as benign or malignant. Tumor morphology can be histologically examined to determine its origin and biological behavior.

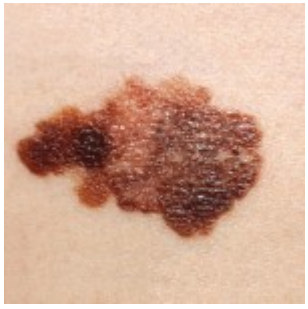


Image: 'Melanoma' by philschatz. License: CC BY 4.0

Clinical Significance

However, tumor markers are not appropriate for the screening of malignant diseases. For example, the prostate gland is activated by cycling or palpation. As a result, the prostate gland and the periurethral glands increase their production and secretion of **prostate-specific antigen** (**PSA)**. Therefore, an increase in PSA level in the blood can be caused by many different processes occurring in the prostate:

- Increased size of the prostate (**hyperplasia**)
- Inflammatory changes (**prostatitis**)
- Neoplastic change.

Indeed, any cellular signal that increases the synthesis of PSA can lead to elevated PSA levels. The PSA levels are not necessarily increased by tumor or malignant disease alone, and thus tumor markers cannot—with only a few exceptions—be used as a primary diagnostic tool for the detection of a malign tumor. Benign tumors containing actively dividing cells may secrete these markers without posing a dangerous health risk. However, tests may reveal normal marker levels despite serious health conditions.

In summary, tumor markers do not provide specific information related to tumor malignancy. The diagnosis of tumor localization remains imprecise. Elevated concentrations in the blood may also be attributed to other processes occurring in the body and do not represent a primary diagnostic tool.

Note: Test results within the **reference range** do not rule out a tumor since the blood concentration of a tumor marker does not necessarily rise despite the tumor growth, especially in the early stages (**lack of sensitivity**). Benign tumors also raise the marker levels in the blood, without being considered dangerous (**lack of specificity**).

Tumor diseases with their corresponding tumor markers and reference ranges

CEA	Carcinoembryonic antigen	Liver, colon, rectum, breasts, stomach, and bronchial tract	3.4 µg/L
AFP	Alpha-fetoprotein	Pregnancy, liver, and germ cell tumors	9 IU/mL
CA 19-9	Carbohydrate antigen 19/9 or cancer antigen 19/9	Gall bladder, pancreas, stomach, and liver diseases	≤ 37 IU/mL
CA 72-4	Cancer antigen 72-4	Gastric cancer	≤ 4 IU/mL
CA 125	Cancer antigen 125	Ovarian cancer	≤ 35 IU/mL
CA 15-3	Cancer antigen 15-3	Breast and pancreatic cancers	≤ 25 IU/mL
NSE	Neuron-specific enolase	Small-cell bronchial tumor, neuroblastoma, and cerebral diseases	serum: ≤ 18.3 g/L; liquor: 3–20 g/L
SCC	Squamous cell carcinoma antigen	Cervix, esophagus, lung, head, oral, and throat cancers	≤ 1.5 µg/L
CYFRA 21-1	Cytokeratin 19 fragment	Non-small-cell bronchial tumor	2 µg/L
hCG	Human chorionic gonadotropin	Pregnancy, germ cell tumor, chorionic carcinoma, testicular carcinoma with chorionic involvement	men under the age of 45: ≤ 2 U/L; women under the age of 45: ≤ 3 U/L; both from the age of 45: ≤ 7 U/L
PSA	Prostate-specific antigen	Prostatic hyperplasia, prostate tumor, inflammatory diseases, after rectal palpation	men under the age of 40: 1.4 µg/L; 40–60 years: 3.1 µg/L; 60–70 years: 4.1 µg/L; 70–120 years: 4.4 µg/L
HTG	Thyroglobulin	Thyroid, follicular and papillary diseases	
HCT	Human calcitonin	Thyroid and medullary disease	
Calcitonin		C-cell tumor, medullary thyroid carcinoma	men: ≤ 18.2 ng/L; women: ≤ 11.5 ng/L

Beta-2 microglobulin		Multiple myeloma, lymphoma, and leukemia	0.6–2.45 mg/L; elevated in case of limited renal function

Therapeutic monitoring

Tumor markers provide good indications of tumor activity. As a **prognostic marker of tumor progression following treatment**, tumor marker levels can serve only as benchmarks and are not 100% accurate. Still, they offer solid prognoses about the success of the treatment. If one of the examined marker concentrations declines below 50% of the biological half-life of the marker, it is considered a sign of **remission** (i.e., temporary or permanent subsidence of manifestations of a disease). This scenario occurs in the post-operative phase.

Tumor persistence or further increase by more than 25% suggests stable disease. An increase in the marker concentrations after treatment and after previous normalization of levels points to a **relapse**, indicating the need for further diagnostic measures.

Tumor marker levels must not be considered in isolation—instead, the patient's entire condition, including all diagnostic measures, should be evaluated. In 50% of all tumor cases, the increased tumor marker levels precede diagnostic imaging suggesting that a tumor can be detected first in the blood and then radiologically.

Note: The diagnostic accuracy of tumor marker tests is low. Nevertheless, they provide an opportunity to control disease progression and determine the treatment outcome without imposing any strain on the patient.

Westergren's erythrocyte sedimentation rate as a non-specific diagnostic tool

The erythrocyte sedimentation rate (ESR) is defined as the rate at which red blood cells settle out of the plasma under conditions of gravity in the blood that has been treated or is unable to coagulate. The standard method is known as Westergren's method, in which the height of the plasma layer above the settled red blood cells is measured in millimeters. The normal value for men is 3–8 mm within 1 hour and for women, it is 6–11 mm per hour.

The rate of sedimentation depends on the number of **erythrocytes (hematocrit)** and their form as well as aggregation. The more erythrocytes, the greater is the friction and interference between them and the slower they sink to the bottom.

Since women generally carry a lower hematocrit than men (42% vs. 47%), and their ESR is accordingly higher. The erythrocytes sink at a faster pace. Further, changes in plasma protein composition, temperature, or contamination affect ESR values.

An increased ESR is expected in the event of inflammation, immune response, and tumorigenesis. However, similar to tumor marker concentrations, the ESR can only serve as a non-specific exploratory parameter in inflammatory and malign diseases.

Note: In the presence of a tumor, the ESR in the **non-coagulating blood** is increased.

Tumor prophylaxis and diagnostic imaging

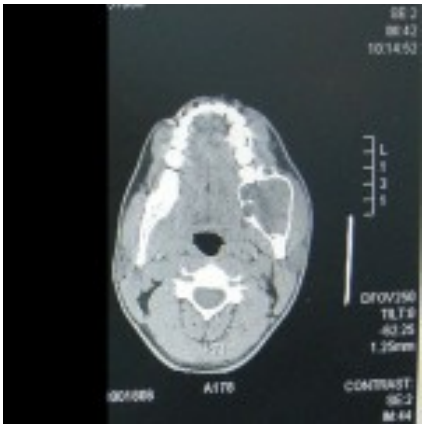


Image: “CT-Scan” by Berto1286. License: Public Domain.

In oncology, the field of cancer prevention is categorized into three stages. **Primary prevention** (preventing the development of the disease), **secondary prevention** (early detection or screening), and **tertiary prevention** (preventing recurrence). Imaging diagnostics are useful in all three stages. Nevertheless, they cannot replace histological confirmation of a malign tumor.

In any case, a holistic approach to treatment is based on changes in tumor marker levels, diagnostic images, and biopsy results.

Diagnostic imaging starts with non-invasive procedures. Only under reasonable grounds for suspicion, computed tomography (**CT**), magnetic resonance imaging (**MRI**), digital subtraction angiographies (**DSA**), and positron emission tomography (**PET**) are adopted for further investigation.

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