# TUMOR MARKERS: A REVIEW

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**ABSTRACT:** During the last decade, there has been increasing interest in the use of biomarkers in cancer epidemiology to enhance exposure assessment, to gain insight into disease mechanism, and to understand acquired or inherited susceptibility. To facilitate the use of biomarkers in health research, biomarkers have been divided into categories that depict the spectrum of cancer pathogenesis from exposure to disease. In this paper we are discussing the advantages, disadvantages, and logistical considerations in using biomarkers to answer research questions.
**KEYWORDS:** Tumor markers, Oncology, Cancer cells, Antibodies.

**INTRODUCTION**: Early tumor detection is among the most urgent problems of oncology, because early treatment is most efficient. It is known that the primary cause and driving force of carcinogenesis are defects of protooncogenes, suppressor genes, and several other functionally essential genes. The marker significance of a gene defect depends on its association with an oncological disorder.

Tumor markers are substances that can often be detected in higher-than-normal amounts in the blood, urine, or body tissues of some patients with certain types of cancer. Tumor markers are produced either by the tumor itself or by the body in response to the presence of cancer or certain benign (noncancerous) conditions.[1]

These tumor markers can be effectively made use of for early screening and detection of cancer. The prognostic evaluation and effectiveness of treatment can be noted. These tumor markers can facilitate early detection of recurrences. Tumor markers can be found in cells, tissues or body fluids. They can be measured quantitatively or qualitatively by chemical, Immunological or molecular biological methods to determine the presence of Neoplasia.[1]

**Table 1.** Acquired properties of the tumor cell [5]

| Property | Defect (an example) |
|---|---|
| 1. Self-sufficiency in growth signals | H-*RAS* activation |
| 2. Insensitivity to anti-growth signals | *RB* inactivation |
| 3. Evading apoptosis | *BCL-2* activation |
| 4. Sustained angiogenesis | *VEGF* induction |
| 5. Limitless replicative potential | Telomerase activation |
| 6. Tissue invasion and metastasis | *E-cadherin* inactivation |

**Definition:** "A tumor marker is a substance present in or produced by a tumor or by the tumor's host in response to the tumor's presence that can be used to differentiate a tumor from normal tissue or to determine the presence of a tumor based on measurement in the blood or secretions.'

Another group of investigators have defined tumor markers as "cellular products that are abnormally elaborated by malignancies that can be detected in various body fluids and on the surface of cancer cells.

Tumor markers can also be broadly defined as" biological or molecular attributes of tumor cells that distinguish them from normal cells.[2]

**History:** The enzymes were one of the first groups of tumor markers identified. Their elevated activities were used to indicate the presence of malignancy. The first tumor marker to be used came into light in 1845 and was named after its discoverers as "Bence-Jone's protein". If the history of the tumor markers is traced, different eras of development can be demarcated:

The first period of tumor markers was the era of Bence-Jone's protein.

The second era, from 1928 to 1963, included the discovery of hormones, enzymes, isoenzymes and proteins and their application in the diagnosis of cancer as well as the beginning of chromosomal analysis of tumors.

The discovery of a- fetoprotein (AFP) in 1963 and carcino embryogenic antigen (CEA).

In 1965 led to the use of the term' onco developmental markers' signifying the third era of marker development.[3]

The fourth ear started in 1975 with the development of monoclonal antibodies, Eg. Carbohydrate antigens such as CA125, CA 15-, etc.

**The milestones of tumor marker research can be brief outlined as follows:**

- 1845 Bence-Jone Bence-Jone's rotein.
- 1928 Brown WH Ecto ic hormone s ndrome.
- 1930 Zondek B Human chorionic gonadotro in (HCG).
- 1932 Cushin H Adrenocorticotro in 'ACTH.
- 1933 Gutmann and Gutmann Prostatic acid hos hatase (PAP).
- 1949 Oh-Uti K Blood group antigens.
- 1959 Markert C Isoenymes.
- 1960 Newell Phi/adel hia chromosome.
- 1963 Abelev GI Alpha fetoprotein (AFP).
- 1965 Gold P and Freeman Carcinoembry of {enic antif} en (CEA).
- 1969 Hubner R and Todaro G Oncogenes.
- 1985 Harris H, Sager Suppressor genes.

**CLASSIFICATION: Johnson and Eibling (1994) classified the circulating markers of head and neck squamous cell carcinoma as:**

- **Onco fetal Protein:** CEA &, Alpha feto protein.
- **Proteins:** Ferritin, β- protein, Ceruloplasmin &Transforming growth factor- $\alpha$.
- **Glycoproteins:** $\alpha$- I-antitrypsin & $\alpha$- I-acid glycoprotein Albumin & Haptoglobin.
- **Enzyme:** Alkaline phosphatase Lactate dehydrogenase
- **Hormones:** Calcitonin Prostaglandins & Prostacyclins.
- **Metabolic byproducts:** Erythrocyte polyamines

- **Viral markers:** Epstein-Barr virus Herpes simplex virus
- **Tumor associated antigens:** Squamous cell carcinoma antigen. Tumor-associated trypsin inhibitor Others- CA-50, CA-125, CA 15-3, TAG-72.
- **Base elements:** Zinc & Copper.

**The latest classification by Schliephake in 2003[4]:**

**Enhancement of tumour growth;**

1. Epithelial Growth Factor (EGF) and Epithelial Growth Factor Receptor.
2. Cyclins (Cyclin A, B1, D1, E).
3. Proliferation Cell Nuclear Antigen (PCNA).
4. Ki67/MIB.
5. Argyrophylic nucleolar organizerregion associated proteins (AgNOR).
6. skp2.
7. Bcl2/BAG-1.
8. Heat shock proteins (HSP27 andHSP70).
9. Telomerase.

**Tumour suppression and anti-tumour response;**

1. Retinoblastoma protein (pRb).
2. Cyclin Dependent Kinase Inhibitors (CDKIs) (p15, p16, p21, p27).
3. p53.
4. Bax.
5. Fas/FasL.
6. ζ-chains.
7. Dendritic Cells S100/p55.

**Angiogenesis;**

1. VEGF/VEGF-R (Vascular endothelial growth factor/receptor).
2. NOS2 (Nitric oxide synthase type II).
3. Platelet-derived endothelial cell growth factor (PD-ECGF).

**Tumour invasion and metastatic potential;**

1. Matrix-Metallo-Proteases (MMPs).
2. Cathepsines.
3. Integrins.
4. Cadherins & catenins.
5. Desmoplakin/plakoglobin.
6. Ets-1.

**What Makes a Marker Useful?:** There is great interest in the development of new diagnostic markers that can aid cancer patients and their physicians in the process of clinical decision-making.

**There are two general categories of diagnostic markers[5,6]:**

- Prognostic markers.
- Predictive markers.

**Prognostic Markers:** Indicate the likelihood of outcome (tumor recurrence, patient survival) regardless of the specific treatment the patient receives.[7]

**Predictive Markers:** Indicate the likelihood of response to a specific therapy.

Some markers are an aid to the pathologist in confirming the tissue of origin of a tumor. Others can be used to monitor a patient's response to therapy or to detect the growth of metastases.[8]

Markers of precancerous conditions are also sought, in order to serve as the basis for screening strategies or to identify populations at high risk for cancer who might benefit from preventive measures. For example, treatment with the monoclonal antibody Herceptin is offered to patients whose tumors have amplified the Her2/neu gene or over-express the Her2/neu gene product.

A new diagnostic is obviously significant if it will have a clear impact on those decisions that provides information useful to physicians and patients in designing the course of cancer treatment.

**Requirements of potentially useful marker[4]:**

1. Is there a biological rationale for this marker? If the marker was identified serendipitously, or the biological rationale is weak, then more preliminary data will be required to support the suggestion that the marker may have some interest or be worth further investigation,
2. Is there an assay system available that is working in at least one lab with reasonable reproducibility? Is there a reasonable scoring system?
3. Has the marker been examined in normal as well as abnormal or diseased tissue? Has it been examined in different organ sites? This is not so much to establish the exact distribution of the marker but to help determine the setting where the marker might have greatest value.
4. Can patient populations be defined for which this marker might have utility? What is an expected range for the prevalence of this marker in any populations of potential interest? Very rare (<5%) or very prevalent (>95%) markers are likely to be useful in more circumscribed settings.
5. Can the marker be measured in the types of specimens that will generally be available?

**Uses of tumor markers:**

- Measurements of tumor marker levels can be useful when used along with x-rays or other tests in the detection and diagnosis of some types of cancer.[9] However, measurements of tumor marker levels alone are not sufficient to diagnose cancer for the following reasons:
    - Tumor marker levels can be elevated in people with benign conditions.
    - Tumor marker levels are not elevated in every person with cancer especially in the early stages of the disease.

    - Many tumor markers are not specific to a particular type of cancer; the level of a tumor marker can be raised by more than one type of cancer.
- Screening in general population;
    - Screening; Presence of occult disease.

**Detect disease at early stage,**

- Diagnosis; for definitive diagnosis.
- Differential diagnosis;
- Clinical staging of cancer;
- Nuclear scanning of injected radioactive antibodies;
- Prognostic indicators for disease progression.
- Evaluating the success of treatment in monitoring the response to therapy.
- Detecting the recurrence of cancer.
- Monitoring responses to therapy.

**Limitations of tumor marker use;**

- Difficulty in identify minute quantities of particular substances in serum.
- Existence of proliferation related rather than tumor associated antigen.
- Cross reactive antigens, for instance common domains in different proteins,
- Cross reaction with degradation products of normal proteins taken up by tumor cells.
- Malignant tumors with extensive necrosis have increased hydrolytic enzymes. Antigenic degradation products may then form which would normally be absent from non-necrotic control tissue.
- Thus the financial and psychological cost to the society of routine screening for early cancers using currently available tumor marker would be prohibitive.

**REFERENCES:**

1. Schliephake Prognostic relevance of molecular markers of oral cancer- A review; Int. J. Oral Maxillofac. Surg. 2003; 32: 233–245.
2. G. T. Thomas M. P. Lewis and P. M. Speight Matrix metalloproteinases and oral cancer Review Oral Oncology 1999, 35 (3) 227-233.
3. Qianming Chen L. P. Samaranayake[a], Xin Zhen[b], Gang Luo[b], Minhai Nie[b] and Bingqi LiUp-regulation of Fas ligand and down-regulation of Fas expression in oral carcinogenesis Oral Oncology 1999 35(6) 548-553.
4. G.J. Thomas, M.P. Lewis and P.M. Speight, Regulation of matrix metalloproteinase (MMP) production by αv integrins in oral carcinoma cell lines. Journal of Dental Research 1998 79, 641.
5. Milena Gascoa, Tim Crookb The p53 network in head and neck cancer Review Oral Oncology 39 (2003) 222–231.
6. Eric M. Gendena, Alfio Ferlitob,, Patrick J. Bradleyc Alessandra Rinaldob, Crispian Scully Neck disease and distant metastases Review Oral Oncology 39 (2003) 207-212.

7. Golub TR, Slonim DK, Tamayo P, Huard C, Gaasenbeek M, Mesirov JP, Coller H, Loh ML, Downing JR, Caligiuri MA, Bloomfield CD, Lander ES. Molecular classification of cancer: Class discovery and class prediction by gene expression monitoring. Science 286: 531-36, 1999.
8. D.T.W. Wong1 R. Todd T.Tsuji1 R.B. Donoff MOLECULAR BIOLOGY OF HUMAN ORAL CANCER Crit Rev Oral Biol Med 7(4): 319-328 (1996).
9. Thomas, J. Jones and M. Speight Integrins and Oral Cancer Reviews Oral Oncology, Vol. 33, No. 6, 381-3813, 1997.

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