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Tumor Markers

Key Points

- Tumor markers are substances found in the blood, urine, stool, other bodily fluids, or tissues of some patients with cancer.
- Tumor markers may be used to help diagnose cancer, predict a patient's response to certain cancer therapies, check a patient's response to treatment, or determine whether cancer has returned.
- More than 20 tumor markers are currently in use.

1. What are tumor markers?

Tumor markers are substances that are produced by cancer cells or by other cells of the body in response to cancer or certain benign (noncancerous) conditions. Most tumor markers are made by normal cells as well as by cancer cells; however, they are produced at much higher levels in cancerous conditions. These substances can be found in the blood, urine, stool, tumor tissue, or other tissues or bodily fluids of some patients with cancer. Most tumor markers are proteins. However, more recently, patterns of gene expression and changes to DNA have also begun to be used as tumor markers. Markers of the latter type are assessed in tumor tissue specifically.

Thus far, more than 20 different tumor markers have been characterized and are in clinical use. Some are associated with only one type of cancer, whereas others are associated with two or more cancer types. There is no "universal" tumor marker that can detect any type of cancer.

There are some limitations to the use of tumor markers. Sometimes, noncancerous conditions can cause the levels of certain tumor markers to increase. In addition, not everyone with a particular type of cancer will have a higher level of a tumor marker associated with that cancer. Moreover, tumor markers have not been identified for every type of cancer.

2. How are tumor markers used in cancer care?

Tumor markers are used to help detect, diagnose, and manage some types of cancer. Although an elevated level of a tumor marker may suggest the presence of cancer, this alone is not enough to diagnose cancer. Therefore, measurements of tumor markers are usually combined with other tests, such as biopsies, to diagnose cancer.

Tumor marker levels may be measured before treatment to help doctors plan the appropriate therapy. In some types of cancer, the level of a tumor marker reflects the stage (extent) of the disease and/or the patient's prognosis (likely outcome or course of disease). (More information about staging is available in the NCI fact sheet *Cancer Staging* at http://www.cancer.gov/cancertopics/factsheet/Detection/staging.)

Tumor markers may also be measured periodically during cancer therapy. A decrease in the level of a tumor marker or a return to the marker's normal level may indicate that the cancer is responding to treatment, whereas no change or an increase may indicate that the cancer is not responding.

Tumor markers may also be measured after treatment has ended to check for recurrence (the return of cancer).

3. How are tumor markers measured?

A doctor takes a sample of tumor tissue or bodily fluid and sends it to a laboratory, where various methods are used to measure the level of the tumor marker.

If the tumor marker is being used to determine whether treatment is working or whether there is a recurrence, the marker's level will be measured in multiple samples taken over time. Usually these "serial measurements," which show whether the level of a marker is increasing, staying the same, or decreasing, are more meaningful than a single measurement.

4. Does NCI have guidelines for the use of tumor markers?

NCI does not have such guidelines. However, some national and international organizations do have guidelines for the use of tumor markers for some types of cancer:

- The American Society of Clinical Oncology (ASCO) has published clinical practice guidelines on a variety of topics, including tumor markers for breast cancer, gastrointestinal cancers, and testicular cancer and extragonadal germ cell tumors in males. These guidelines, called What to Know: ASCO's Guidelines, are available on the ASCO website at http://www.cancer.net/patient/Publications+and+Resources/What+to+Know%3A+ASCO%27s+Guidelines.

- The National Academy of Clinical Biochemistry publishes laboratory medicine practice guidelines, including *Use of Tumor Markers in Clinical Practice: Quality Requirements*, which focuses on the appropriate use of tumor markers for specific cancers. More information can be found at http://www.aacc.org/members/nacb/LMPG/OnlineGuide/PublishedGuidelines/tumor/Documents/TumorMarkers_QualityRequirements09.pdf.

5. What tumor markers are currently being used, and for which cancer types?

A number of tumor markers are currently being used for a wide range of cancer types. Although most of these can be tested in laboratories that meet standards set by the Clinical Laboratory Improvement Amendments, some cannot be and may therefore be considered experimental. Tumor markers that are currently in common use include the following:

Tumor Marker	Cancer Type	Tissue Analyzed	How Used
ALK gene rearrangements	Non-small cell lung cancer; anaplastic large cell lymphoma	Tumor tissue	To help determine treatment and prognosis
Alpha-fetoprotein (AFP)	Liver cancer; germ cell tumors	Blood	To help diagnose liver cancer and follow response to treatment; to assess stage, prognosis, and response to treatment of germ cell tumors
Beta-2-microglobulin (B2M)	Multiple myeloma; chronic lymphocytic leukemia; some lymphomas	Blood, urine, or cerebrospinal fluid	To determine prognosis and to follow response to treatment
Beta-human chorionic gonadotropin (Beta-hCG)	Choriocarcinoma; testicular cancer	Urine or blood	To assess stage, prognosis, and response to treatment of testicular cancer

BCR-ABL	Chronic myeloid leukemia	Blood and/or bone marrow	To confirm diagnosis and monitor disease status
BRAF mutation V600E	Cutaneous melanoma; colorectal cancer	Tumor tissue	To predict response to targeted therapies
CA15-3/CA27.29	Breast cancer	Blood	To assess whether treatment is working or disease has recurred
CA19-9	Pancreatic cancer; gallbladder cancer; bile duct cancer; gastric cancer	Blood	To assess whether treatment is working
CA-125	Ovarian cancer	Blood	To help in diagnosis, assessment of response to treatment, and evaluation of recurrence
Calcitonin	Medullary thyroid cancer	Blood	To aid in diagnosis, to check whether treatment is working, and to assess recurrence
Carcinoembryonic antigen (CEA)	Colorectal cancer; breast cancer	Blood	To check whether colorectal cancer has spread; to look for breast cancer recurrence and assess response to treatment
CD20	Non-Hodgkin lymphoma	Blood	To determine whether treatment with a targeted therapy is appropriate
Chromogranin A (CgA)	Neuroendocrine tumors	Blood	To help in diagnosis, assessment of treatment response, and evaluation of recurrence
Chromosomes 3, 7, 17, and 9p21	Bladder cancer	Urine	To help in monitoring for tumor recurrence
Cytokeratin fragments 21-1	Lung cancer	Blood	To help in monitoring for recurrence
EGFR mutation analysis	Non-small cell lung cancer	Tumor tissue	To help determine treatment and prognosis
Estrogen receptor (ER)/progesterone receptor (PR)	Breast cancer	Tumor tissue	To determine whether treatment with hormonal therapy (such as tamoxifen) is appropriate
Fibrin/fibrinogen	Bladder cancer	Urine	To monitor progression and response to treatment

HE4	Ovarian cancer	Blood	To assess disease progression and monitor for recurrence
HER2/neu	Breast cancer; gastric cancer; esophageal cancer	Tumor tissue	To determine whether treatment with trastuzumab is appropriate
Immunoglobulins	Multiple myeloma; Waldenstrom macroglobulinemia	Blood and urine	To help diagnose disease, assess response to treatment, and look for recurrence
KIT	Gastrointestinal stromal tumor; mucosal melanoma	Tumor tissue	To help in diagnosis and determining treatment
KRAS mutation analysis	Colorectal cancer; non-small cell lung cancer	Tumor tissue	To determine whether treatment with a particular type of targeted therapy is appropriate
Lactate dehydrogenase	Germ cell tumors	Blood	To assess stage, prognosis, and response to treatment
Nuclear matrix protein 22	Bladder cancer	Urine	To monitor response to treatment
Prostate-specific antigen (PSA)	Prostate cancer	Blood	To help in diagnosis, assess response to treatment, and look for recurrence
Thyroglobulin	Thyroid cancer	Tumor tissue	To evaluate response to treatment and to look for recurrence
Urokinase plasminogen activator (uPA) and plasminogen activator inhibitor (PAI-1)	Breast cancer	Tumor tissue	To determine aggressiveness of cancer (and guide treatment)
70-Gene signature (Mammaprint)	Breast cancer	Tumor tissue	To evaluate risk of recurrence
21-Gene signature (Oncotype DX)	Breast cancer	Tumor tissue	To evaluate risk of recurrence
5-Protein signature (Ova1)	Ovarian cancer	Blood	To pre-operatively assess pelvic mass for suspected ovarian cancer

6. Can tumor markers be used in cancer screening?

Because tumor markers can be used to assess the response of a tumor to treatment and for prognosis, researchers have hoped that they might also be useful in screening tests that aim to detect cancer early, before there are any symptoms. For a screening test to be useful, it should have very high sensitivity (ability

to correctly identify people who have the disease) and specificity (ability to correctly identify people who do *not* have the disease). If a test is highly sensitive, it will identify most people with the disease—that is, it will result in very few false-negative results. If a test is highly specific, only a small number of people will test positive for the disease who do not have it—in other words, it will result in very few false-positive results.

Although tumor markers are extremely useful in determining whether a tumor is responding to treatment or assessing whether it has recurred, no tumor marker identified to date is sufficiently sensitive or specific to be used on its own to screen for cancer.

For example, the prostate-specific antigen (PSA) test, which measures the level of PSA in the blood, is often used to screen men for prostate cancer. However, an increased PSA level can be caused by benign prostate conditions as well as by prostate cancer, and most men with an elevated PSA level do not have prostate cancer. Initial results from two large randomized controlled trials, the NCI-conducted Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial, or PLCO, and the European Randomized Study of Screening for Prostate Cancer, showed that PSA testing at best leads to only a small reduction in the number of prostate cancer deaths. Moreover, it is not clear whether the benefits of PSA screening outweigh the harms of follow-up diagnostic tests and treatments for cancers that in many cases would never have threatened a man's life.

Similarly, results from the PLCO trial showed that CA-125, a tumor marker that is sometimes elevated in the blood of women with ovarian cancer but can also be elevated in women with benign conditions, is not sufficiently sensitive or specific to be used together with transvaginal ultrasound to screen for ovarian cancer in women at average risk of the disease. An analysis of 28 potential markers for ovarian cancer in blood from women who later went on to develop ovarian cancer found that none of these markers performed even as well as CA-125 at detecting the disease in women at average risk.

7. What kind of research is under way to develop more accurate tumor markers?

Cancer researchers are turning to proteomics (the study of protein structure, function, and patterns of expression) in hopes of developing new biomarkers that can be used to identify disease in its early stages, to predict the effectiveness of treatment, or to predict the chance of cancer recurrence after treatment has ended. More information about proteomics can be found in the NCI fact sheet *Proteomics and Cancer* at http://www.cancer.gov/cancertopics/factsheet/detection/proteomics.

Scientists are also evaluating patterns of gene expression for their ability to help determine a patient's prognosis or response to therapy. For example, the NCI-sponsored TAILORx trial (http://www.cancer.gov/clinicaltrials/noteworthy-trials/tailorx) assigned women with lymph node-negative, hormone receptor–positive breast cancer who have undergone surgery to different treatments based on their recurrence scores in the Oncotype DX test. One of the goals of the trial is to determine whether women whose score indicates that they have an intermediate risk of recurrence will benefit from the addition of chemotherapy to hormonal therapy or whether such women can safely avoid chemotherapy. The trial has accrued its required number of subjects and these subjects will be followed for several years before results are available.

NCI's Early Detection Research Network (http://edrn.nci.nih.gov/) is developing and testing a number of genomic- and proteomic-based biomarkers.

The Program for the Assessment of Clinical Cancer Tests (PACCT) (http://cdp.cancer.gov/scientificPrograms/pacct.htm), an initiative of the Cancer Diagnosis Program of NCI's Division of Cancer Diagnosis and Treatment, has been developed to ensure that development of the next generation of laboratory tests is efficient and effective. The PACCT strategy group, which includes scientists from academia, industry, and NCI, is developing criteria for assessing which markers are ready for further development. PACCT also aims to improve access to human specimens, make standardized reagents and control materials, and support validation studies. A new program, the Clinical Assay Development Program, allows NCI to assist in the development of promising assays that may predict which treatment may be better or that will help indicate a particular cancer's aggressiveness.

Selected References

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Related Resources

- *Cancer Staging* (http://www.cancer.gov/cancertopics/factsheet/Detection/staging)
- *Donating Tissue for Cancer Research: Biospecimens and Biorepositories* (http://www.cancer.gov/cancertopics/factsheet/information/donating-tissue-research)
- *Interpreting Laboratory Test Results* (http://www.cancer.gov/cancertopics/factsheet/Detection/laboratory-tests)
- *Prostate-Specific Antigen (PSA) Test* (http://www.cancer.gov/cancertopics/factsheet/Detection/PSA)
- *Understanding Prognosis and Cancer Statistics* (http://www.cancer.gov/cancertopics/factsheet/support/prognosis-stats)
- *What You Need To Know About™ Cancer* (http://www.cancer.gov/cancertopics/wyntk/cancer)

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- ***Chat*** using LiveHelp, NCI's instant messaging service, at http://www.cancer.gov/livehelp
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