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CANCERS AND TUMOR MARKERS

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OBJECTIVES

After completing this chapter, the reader should be able to

- Define tumor markers, describe the characteristics of an ideal tumor marker, and discuss the usefulness of tumor markers in the diagnosis, staging, and treatment of malignant diseases
- List malignant and nonmalignant conditions that may increase carcinoembryonic antigen levels and define the role of carcinoembryonic antigen in the management of colon cancer
- Describe how CA-125 may be used to diagnose and monitor ovarian cancer
- Describe how human chorionic gonadotropin and α-fetoprotein are used to diagnose and monitor germ cell tumors
- Discuss the role of estrogen and progesterone receptors and human epidermal growth factor receptor 2 in determining treatment decisions for breast cancer
- Outline the role of the *BCR-ABL* gene in the diagnosis and as a target for treatment in patients with chronic myelogenous leukemia
- Describe how mutations in epidermal growth factor receptor, V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, v-Raf murine sarcoma viral oncogene homolog B1, or anaplastic lymphoma kinase are used in determining treatment decisions for melanoma, lung cancer, and colorectal cancer

For most types of cancer, treatment is likely to be most successful if the diagnosis is made while the tumor mass is relatively small. Unfortunately, many common types of cancer (e.g., carcinomas of the lung, breast, and colon) are frequently not diagnosed until the tumor burden is relatively large and the patient has developed symptoms related to the disease. As the search for more effective treatments for cancer has intensified, much effort and many resources also have been dedicated to elucidating new methods of detecting cancers earlier while the tumor burden is low and the patient is asymptomatic. These efforts have led to improved radiologic and other diagnostic imaging, and the identification of biologic substances, which occur in relation to the tumor and can be detected even at very low concentrations in the blood or other body fluids.

The term *tumor marker* is used to describe a wide range of proteins that are associated with various malignancies. Typically, these markers are either proteins that are produced by or in response to a specific type of tumor, or they may be other physiologic proteins that are produced by malignant cells in excess of the normal concentrations. In either case, the concentration of the marker usually correlates with the volume of tumor cells (e.g., as the tumor grows or the number of malignant cells increases, the concentration of the marker also increases). In other cases the presence of a biologic marker may be used to predict response to treatment (e.g., the estrogen receptor [ER] or progesterone receptor [PR] in breast cancer) or to monitor the effects of treatment. More recently, some tumor markers have been shown to be essential to the viability of tumor cells, and specific therapies have been developed that target these markers of disease. These tumor markers are often identified by genetic mutations, translocations, or amplification of genetic material.

This chapter describes tumor markers that are used clinically to detect cancers, monitor cancer burden, and help choose drug therapy as well as the laboratory methods used to measure them. In addition the sensitivity, specificity, and factors that may interfere with evaluation of these tests are briefly discussed. For tumor markers that are widely used to screen for cancers, to confirm a cancer diagnosis, or to assess response to treatment, the clinical applications are described.

TUMOR MARKERS

Tumor markers may be found in the blood or other body fluids or may be measured directly in tumor tissues or lymph nodes. They can be grouped into three broad categories: (1) tumor-specific proteins are markers that are produced only by tumor cells—these proteins usually occur as a result of translocation of an oncogene and may contribute to the proliferation of the tumor; (2) nonspecific proteins related to the malignant cells including proteins that are expressed only during embryonic development and by cancer cells; and (3) proteins that are normally found in the body but are expressed or secreted at a much higher rate by malignant cells than normal cells.[1] In addition to the laboratory tests that are described in this chapter, it also should be remembered that abnormalities in other commonly used laboratory tests may provide some evidence that a malignancy exists. However, they are not related to specific tumors. For example, suppression of blood counts may represent infiltration of the bone marrow by tumor cells. Increased uric acid

TABLE 20-1. Serum Tumor Markers in Clinical Use

TUMOR MARKER	MALIGNANT DISEASE	SCREENING	DIAGNOSIS	STAGING OR PROGNOSIS	MONITORING TREATMENT OUTCOME OR DISEASE RECURRENCE	COMMENTS
PSA	Prostate carcinoma	X		X	X	Usually combined with digital rectal examination of the prostate for screening
						Inflammatory disorders of the prostate, instrumentation of the genitourinary tract, and mechanical manipulation of the prostate by biopsy, transurethral resection of the prostate or prostatectomy may increase PSA
						Certain medications may decrease PSA including 5-α reductase inhibitors, NSAIDs, statins, and thiazide diuretics
						Herbal products (e.g., saw palmetto) may also decrease PSA
CEA	Colon and breast carcinoma			X (in colon)	X	Hepatic cirrhosis, hepatitis, pancreatitis, peptic ulcer disease, hypothyroidism, ulcerative colitis, or Crohn disease may elevate CEA
CA 15-3, CA 27.29	Breast carcinoma			X	X Metastatic disease only	Other cancers (e.g., gastric, colorectal, lung), benign breast disease, and liver disease may all elevate levels
CA-125	Ovarian carcinoma			X	X	Endometriosis, ovarian cysts, liver disease, or pregnancy may elevate CA-125; in certain high-risk groups (strong family history) CA-125 in combination with ultrasound technology may be used to screen asymptomatic patients
hCG	Germ cell tumors of ovaries and testes; hydatidiform mole		X	X	X	Pregnancy, other types of cancer, or marijuana use may elevate hCG
CA 19-9	Pancreatic carcinoma			X	X	Pancreatitis, cirrhosis, gastric, and colon cancer may elevate CA 19-9
AFP	Hepatocellular carcinoma Testicular (nonseminoma-tous germ cell tumors)	X (hepato-cellular carcinoma)	X	X	X	Pregnancy; hepatitis; cirrhosis; and pancreatic, gastric, lung, and colon cancers all can elevate AFP; some non-U.S. countries, which have a high incidence of hepatocellular cancer, use AFP to screen for hepatocellular cancer
B_2M	Multiple (plasma cell) myeloma			X	X	Lymphomas, chronic lymphocytic leukemia, and renal failure may elevate
	Chronic lymphocytic leukemia					

AFP = α-fetoprotein; B_2M = β-2 microglobulin; CEA = carcinoembryonic antigen; hCG = human chorionic gonadotropin; NSAIDs = nonsteroidal anti-inflammatory drugs; PSA = prostate specific antigen.

and lactate dehydrogenase are frequently associated with large tumor burdens. Alkaline phosphatase is frequently elevated in patients with tumors of the biliary tract or bone. Occasionally, tumors may also produce hormones in excessive amounts, such as calcitonin or adrenocorticotropin.

Clinical Uses

Tumor markers are used for several purposes including detection of occult cancers in asymptomatic individuals (e.g., cancer screening and early detection), determining the relative extent or volume of disease (staging), estimating prognosis, predicting and assessing responsiveness to treatment, and monitoring for disease recurrence or progression.[1] **Table 20-1** lists many of the commonly used tumor markers found in blood and their clinical applications. **Table 20-2** lists tumor markers found on tumor cells or genetic abnormalities found in tumor cells and their clinical applications. **Table 20-3** lists genetic mutations or translocations that help determine the best therapy. The characteristics of an ideal tumor marker are somewhat dependent on the specific application. Normal values are provided although laboratory reference ranges (normal values) may slightly differ, as will the interpretation of the laboratory value in an individual patient. For example, rising levels of a tumor marker that are still in the normal range may indicate early tumor recurrence.

Sensitivity and Specificity

For a tumor marker to be clinically useful, it must have a high degree of *sensitivity* and *specificity*. That is, the presence of the marker should correlate with the presence of the tumor, and