Clinical Application of Serum Tumor Markers

Effective serum tumor marker tests would have the following characteristics:

- The marker is negative in health or benign disease.
- The marker is exclusively produced by specific tumor cells.
- The marker is present frequently in the targeted malignancy.
- The marker is detectable in occult disease.
- The marker's degree of expression reflects tumor burden and prognosis.
- The marker's degree of expression correlates with therapeutic results.

There are no currently available markers that have all six characteristics. However, many markers perform well by one or more characteristics and are clinically useful. No markers are currently useful as screening tools in asymptomatic persons.

Alpha-fetoprotein (AFP)

AFP has been used to screen for hepatocellular carcinoma in patients with liver disease, especially chronic type B hepatitis. Small asymptomatic tumors are associated with AFP values greater than normal but less than 215 ng/mL. AFP has also been used for determining the prognosis and monitoring therapy in non-seminomatous testicular cancer.

$Beta_2$-Microglobulin

$Beta_2$-Microglobulin has been used to predict response to treatment for lymphoma. Patients with $Beta_2$-Microglobulin levels less than 3.0 mg/L have a higher remission rate than those with elevated $Beta_2$-Microglobulin.

CA 15-3

CA 15-3 is used as a marker of breast cancer. However, it is present in the serum of healthy men and women and is increased in benign and malignant diseases including cancer of the stomach, pancreas, bile duct, colon, thyroid, lung, cervix, endometrium, ovary, and breast. Serum CA 15-3 increases during progression of disease and declines with successful treatment. Sensitivity varies with disease stage, 0-36% in stages I and II and 11-100% in stages III and IV. Specificity is between 85-100%

CA 19-9

CA 19-9 is infrequently elevated in colorectal cancer (20%), gastric cancer (42%) and hepato cellular cancer (22-51%) but is frequently elevated in patients with pancreatic cancer (70-100%). Elevations also occur in patients with pancreatitis and liver disease. Elevations following surgical resections predict recurrent cancer.

CA 27.29

CA 27.29 is a marker for breast cancer and has been shown to detect an antigen similar, if not identical to CA 15-3. As breast cancer progresses, the level of CA 27.29 antigen in the blood increases. The FDA approved this test in 1996 for breast cancer recurrence. When the test was applied to 166 women who had previously had breast cancer, it detected 15 or 26 women who had a recurrence (sensitivity of 58%) and in 8 of 140 women who did not (specificity of 94%).

CA-125 II

CA-125 II has been used as marker for ovarian cancer. It has a sensitivity of 80% and a specificity of 99% in the general population. In women with pelvic masses, the sensitivity is 87% and the specificity is 88%. Elevation correlates with tumor size and stage. A rising level during chemotherapy indicates progressive disease. However, normal values may be found in residual or recurrent disease.

Carcinoembryonic Antigen (CEA)

CEA has been widely accepted for colorectal carcinoma and for detecting recurrent cancer after surgery. CEA is also elevated in smokers.

A recent article has questioned the efficacy of CEA in detecting surgically curable recurrent colon cancer. [Moertel CE et al, An evaluation of the carcinoembryonic antigen (CEA) test for monitoring patients with resected colon cancer. JAMA 93; 270: 943-7]

Prostatic Acid Phosphatase (PAP)

Although PAP is elevated in 85 to 95% with patients with metastatic prostate cancer, only 12-30% of patients with early stage cancer have elevated levels. Elevated PAP may also occur in other cancers including multiple myeloma, osteogenic sarcoma, and bone metastases from other non-prostatic cancers. It may also be elevated in non-malignant diseases such as osteoporosis, hyperparathyroidism, and hyperthyroidism as well as in benign prostatic hypertrophy.

Prostate Specific Antigen (PSA)

PSA is localized to prostate tissue and is elevated in men with benign or malignant prostate disease, precluding its use as a sole screening test. Patients with stage A or B prostatic cancer can not be distinguished from patients with benign prostatic hypertrophy. After prostatectomy, PSA levels fall. Rising levels are associated with recurrent cancer in more than 90% of patients.

Free Prostate Specific Antigen (PSA II)

Men whose digital rectal examinations are not indicative of cancer but whose prostate-specific antigen (PSA) levels are in the range of 4 ng/mL to 10 ng/mL today find themselves in a diagnostic gray zone. About a quarter of them have prostatic carcinoma, usually in its earliest, most curable stage.

Determination of the free to total PSA ratio appears to show promise for increasing the specificity of a mildly elevated PSA result with minimal loss of sensitivity for prostate cancer. PSA in blood is predominantly (about 85 percent) bound to anti-chymotrypsin and other enzyme inhibitors with only a minority (about 15 percent) circulating in an unbound and probably enzymatically inactive form. For reasons not fully understood, patients with prostate cancer have a significantly lower percentage of free PSA than patients with benign prostatic hypertrophy.

Patients with free to total ratios of less than 7 percent have a high (greater than 90 percent) risk of prostate cancer which is altered little by their age or their exact level of total PSA. Conversely, patients with greater than 25 percent free PSA have a very low (less than 10 percent) risk of cancer, at least at PSA levels less than 10 ng/mL.