

Serum Tumor Markers in Oncology

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Tumor markers are serum proteins that may be elevated in the presence of cancer. Often tumor markers are present in low concentrations in the serum of normal persons; they may be associated both with specific cancer types and with response to therapy.

These characteristics provide the potential for these markers to be used in screening for, diagnosis of, and management of cancer. Table 1 enumerates the most common tumor markers, their upper limit of normal range, and the malignant disease with which they are most commonly associated.

Serum carbohydrate antigen 19-9 (CA 19-9), also known as sialylated

Lewis a-antigen, is an antigen defined by the monoclonal antibody 1116 NS 19-9 [1]. It is synthesized by normal human pancreatic and biliary ductal cells as well as by gastric, colonic, endometrial, salivary and bronchial epithelia [1,2]. People with Lewis (a-b) blood group do not synthesize Ca19-9. (This phenotype is seen in approximately 25–30% of American blacks compared to 5–10% of American Caucasians.) Ca 19-9 is considered the best serum tumor marker for pancreato-biliary cancer but like most tumor markers its sensitivity, specificity and predictive values limit its use as a reliable test [3-5] [Table 2].

An elevated CA 19-9 has a positive predictive value for pancreato-biliary malignancy of only 69%. This means that over 30% of those with an elevated CA19-9 may have another tumor originating in another organ, or they may have no tumor at all. False positive results have been associated with other pancreato-biliary disorders such as gallstones, pancreatitis, inflammatory bowel disease, other liver disorders, pulmonary diseases such as pneumonia, and hydronephrosis. In a study by Osswald et al. [6] there was no explanation for the elevated CA 19-9 in approximately 9% of above normal values. Heavy tea consumption has also been associated with an elevated CA 19-9 [7].

Thus, it is of no surprise that in the case reported by Rottenberg et al. [8] in this issue of *IMAJ* the tumor of origin was almost certainly not the pancreas. The truth is that a primary pancreatic tumor was not completely excluded since a small primary could have been missed, but the case does illustrate the low positive predictive value of this marker.

This is an opportunity to update oncologists and family physicians about

Table 2. CA 19.9*

Sensitivity	70–90%
Specificity	80–90%
Positive predictive value	69%
Negative predictive value	90%

Sensitivity = the proportion of patients who actually have pancreato-biliary cancer and present with CA 19.9 elevation

Specificity = the proportion of people without pancreato-biliary cancer who test negative

Positive predictive value = the proportion of people with a positive test who have the disease

Negative predictive value = the proportion of people with a negative test who do not have the disease

* See refs. 3-5

the limited role of tumor markers in the routine management of cancer patients. All tests performed on patients should only be done if they will lead to a change in the patient's management. The physician ordering a test should know what the next step will be if a tumor marker is either normal or elevated, and order the test only if concrete steps are planned in the case of marker elevation. Remember, just as a positive test does not always ensure a diagnosis of cancer, a negative test does not always guarantee no malignancy.

Elevated tumor markers are a source of marked frustration both to the patient and to those caring for him (family and physicians) and may lead to expensive and unnecessary follow-up procedures and increased anxiety levels. For example, a patient who exhausted treatment options for pancreatic cancer will not gain anything by measuring his or her CA 19-9 levels and it should be discouraged.

There are new guidelines regarding when and how often to use tumor markers depending on the type of cancer being treated/monitored. For example, the American Society of Clinical Oncology's 2007 guidelines for breast

Table 1. The common serum tumor markers

Name	Normal range *	Major associated cancers
CEA	< 5 µg/L (non-smokers) < 10 µg/L (smokers)	Colorectal cancer
CA 125	< 35 U/ml	Ovarian cancer
αFP	< 9 µg/L	Hepatocellular and germ cell cancer (non-seminoma)
βhCG	< 5 IU/L (males) < 10 IU/L (non-pregnant females)	Testicular cancer Trophoblastic tumors
LDH	< 260 IU/L	Testicular cancer (seminoma)
Thyroglobulin	< 55 µg/L	Thyroid cancer
PSA	< 4 µg/ml	Prostate cancer
CA 15.3	< 31.3 U/ml	Breast cancer
Calcitonin	< 10 pg/ml	Thyroid medullary carcinoma
Chromogranin A	< 76 ng/ml (males) < 51 ng/ml (females)	Neuro-endocrine tumors
Paraprotein		Myeloma
CA 19.9	< 37 U/ml	Pancreato-biliary and colorectal cancer

* Normal ranges can vary between laboratories.

cancer do not recommend any serum tumor markers in the diagnosis, staging or follow-up of breast cancer patients, except in the metastatic setting [9]. When used as supporting information in the diagnosis of a cancer of unknown primary origin, all markers might be helpful and should be ordered; however, as the current case report reveals [8], the results should be viewed with a grain of salt.

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