Review Article

Tumor markers: Chemistry, diagnostic utility and prognostic significance: A review.

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General Introduction:
According to National Cancer Institute (NCI-NIH-USA), tumor markers are substances that are produced by cancer 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\(^1\). Most tumor markers are proteins. However, more recently, patterns of and changes to DNA have also begun to be used as tumor markers. Markers of the latter type are assessed in tumor tissue specifically.

A detailed information available on the website of NCI-NIH that so 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 (NCI-NIH-USA, accessed 3/13/2013).

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 (\(^1\), NCI-NIH-USA, accessed 3/13/2013). The present review details the chemistry, structure, diagnostic and prognostic utilities of 7 tumor makers including CA 27.29, CEA, CA 19.9, AFP, CA 125, PSA and CA 15-3 for current information and upgrading regarding its usefulness and significance in disease evaluation, progression and treatments. The information provided below gathered mainly through PubMed search engine of nearly 300 articles from year 2000 to 2013, wikepedia, cancer related sites and American Family Physician journal (2003/vol 68, , Perkins et al., 2003).

CA 27.29
CA 27.29 is a known mucus-containing protein which is produced by the MUC-1 gene (1). Breast cancer cells that developed due to malignancy will release replicates of the CA 27.29 protein in to the bloodstream. During regimens, the levels of CA 27.29 fall as per progression of wellness, indicating that the treatment is effectively reducing the cancer (2-4). If the CA 27.29 levels rise, it indicates that the cancer may be progressing and it may be necessary to re-adjust the treatments accordingly. It is also a monoclonal antibody to a glycoprotein (MUC1) which is present on the apical surface of normal epithelial cells. The information provided below gathered mainly through PubMed search, wikepedia, cancer related sites and American Family Physician journal (2003/vol 68, , Perkins et al., 2003) and detailed herewith.

Diagnostic utility:
CA 27.29 as stated highly associated with breast cancer, although it was observed and noted that levels may also be elevated in several other malignancies (1-7). CA 27.29 also can be found in patients with benign disorders of the breast, liver, and kidney, and in patients with ovarian cysts. However, if the levels are higher than 100% of the normal units, its rare that the condition is benign. Due to superior sensitivity and specificity, CA 27.29 has supplanted CA 15-3 as the preferred tumor marker in breast cancer. It was documented that CA 27.29 level is elevated in approximately one third of
women with early-stage breast cancer (stage I or II) and 
in two thirds of women with late-stage disease (stage 
III or IV). CA 27.29 however, be deficient in predictive 
capacity in the earliest stages of breast cancer and thus 
has no role in screening for or diagnosing the 
malignancy. Several trials (1-3) in patients showed that 
those who are at high risk for recurrence of breast 
cancer (stage II or III), CA 27.29 was highly specific 
and sensitive in detecting preclinical metastasis. The 
average time from initial elevation of CA 27.29 to onset 
of symptoms was reported to be five months. Since CA 
27.29 testing may lead to prompt imaging of probable 
sites of metastasis, it may be suggested that decrease 
morbidity through earlier institution of therapy is 
possible (7-11).

In general, Cancer antigen 27.29 (CA 27.29) is a that 
is given specifically for . The antigen CA 27.29 is 
found in the blood of women who have been diagnosed 
with breast cancer. If CA 27.29 levels rise, it may 
indicate that the cancer is progressing or spreading.

**CA 27.29 levels in Other malignancies and clinical conditions**

Other cancers have also have the ability to produce 
CA 27.29 such as that of colon, liver, lung, pancreatic, 
ovarian and prostate. However, some non 
life-threatening conditions may also cause CA 27.29 
to depict in the blood, notably, ovarian cysts and 
benign conditions of the breast, liver and kidneys. 
Having a rise in the levels of CA 27.29 is a cause for 
concern only if it is taken in to consideration with 
other test results that indicate a malignant condition 
such CT, MRI, Histopathology etc.

**Carcinoembryonic Antigen**

Carcinoembryonic antigen (CEA), is an oncofetal 
glycoprotein and expressed in normal mucosal cells 
and overexpressed in adenocarcinoma, especially 
colorectal cancer (1, 12-14). Genetically, CEA and 
related make up the CEA family belonging to the 
superfamily. In humans, the carcinoembryonic antigen 
family consists of 29 genes, 18 of which are normally 
expresses. The information provided below gathered 
mainly through PubMed search, wikipedia, cancer 
related sites and American Family Physician journal 
(2003/vol 68, , Perkins et al., 2003). The following is a 
list of human genes which encode carcinoembryonic 
antigen-related cell adhesion proteins: CEACAM1, 
CEACAM3, CEACAM4, CEACAM5, CEACAM6, 
CEACAM7, CEACAM16, CEACAM18 
CEACAM19, CEACAM20, CEACAM21. Chemical 
structure is such that it is a involved in . It is normally 
produced during fetal development, but the production 
of CEA ceases before birth. Thus, it is not usually 
present in the blood of healthy adults, although levels 
are raised in heavy (13-15). CEA is a glycosyl 
phosphatidyl inositol (GPI)-cell surface anchored 
glycoprotein whose specialized sialofucosylated 
glycoforms serve as functional and ligands, which 
may be critical to the metastatic dissemination of cell.

**Diagnostic Utility:**

It is documented that non-neoplastic conditions 
associated with elevated CEA levels include cigarette 
smoking, peptic ulcer disease, inflammatory bowel 
disease, pancreatitis, hypothyroidism, biliary 
obstruction, and cirrhosis. Levels exceeding 10 ng per 
/mL are rarely due to benign disease.3 It was reported 
that fewer than 25 percent of patients with disease 
confined to the colon have an elevated CEA level. 
Thus sensitivity increases with advancing tumor stage; 
CEA values are elevated in approximately 50 percent 
of patients with tumor extension to lymph nodes and 
75 percent of patients with distant metastasis (12-16). 
It was well researched that the highest values (above 
100 ng per mL) occur with metastasis, although poorly 
differentiated tumors are less likely to produce CEA. 
Arguably, CEA is not useful in screening for colorectal 
cancer or in the diagnostic evaluation of an undefined 
ilness. A CEA level should be ordered only after 
malignancy has been confirmed. CEA levels typically 
return to normal within four to six weeks after 
successful surgical resection. The major role for CEA 
levels is in following patients for relapse after intended 
curative treatment of colorectal cancer. When patients 
with a normal preoperative CEA level have cance-
recurrence, CEA elevation is a sign in nearly one half of them (15-17). Notably, the American Society of Clinical Oncology recommends monitoring CEA levels every two to three months for at least two years in patients with stage II or III disease who are surgical candidates. When an abnormal level is found, the test should be repeated; if CEA elevation is confirmed, patients should undergo imaging of potential recurrence sites. Local recurrence or limited metastasis to liver or lung can be resected with curative intent. Clinical trials examined in one meta-analysis demonstrated a 9 percent (absolute value) improvement in survival after five years in patients who underwent CEA monitoring as part of post-treatment management (1, 16, 17-19).

The carcinoembryonic antigen (CEA) test measures the amount of this that may appear in the of some people who have certain kinds of cancers, especially large intestine (). It may also be present in people with cancer of the , breast, ovary, or lung.

**Prognostic significance:**

It was found that from individuals with colorectal carcinoma, gastric carcinoma, pancreatic carcinoma, lung carcinoma and breast carcinoma, as well as individuals with , had higher levels of CEA than healthy individuals (above 2.5 ng/ml). CEA measurement is mainly used as a to identify recurrences after surgical resection, or localize cancer spread through dosage of biological fluids. The CEA blood test is not reliable for diagnosing cancer or as a screening test for early detection of cancer. Most types of cancer do not produce a high CEA (19-22). Elevated CEA levels should return to normal after successful surgical resection, or within 6 weeks of starting treatment if cancer treatment is successful. As stated earlier, CEA levels may also be raised in some non-neoplastic conditions like ulcerative colitis, pancreatitis, cirrhosis, COPD, Crohn's disease as well as in .

**Cancer Antigen 19-9**

Elevated levels of CA 19-9, an intracellular adhesion molecule, occur primarily in patients with pancreatic and biliary tract cancers but also have been reported in patients with other malignancies. CA19-9 was discovered in patients with and in 1981. Following are the information available on wikipedia, med.portal and cancers related web sites and provided through PubMed search, and American Family Physician journal (2003/vol 68, , Perkins et al., 2003)

**Diagnostic utility:**

It is well documented that CA 19-9 has a sensitivity and specificity of 80 to 90 percent for pancreatic cancer and a sensitivity of 60 to 70 percent for biliary tract cancer. Benign conditions such as cirrhosis, cholestasis, cholangitis, and pancreatitis also result in CA 19-9 elevations, although values are usually less than 1,000 units per mL. The positive predictive value of levels over 1,000 units per mL is 97 percent when CA 19-9 testing is used in clinical situations that are consistent with pancreatic cancer (e.g., jaundice associated with a pancreatic mass) (1, 23-25). Furthermore, CA 19-9 levels above 1,000 units per mL predict the presence of metastatic disease. CA19-9 (carbohydrate antigen 19-9, also called cancer antigen 19-9, or sialylated Lewis (a) antigen) is a that is used primarily in the management of .

Guidelines from the discourage the use of CA19-9 as a screening test for cancer, particularly . The reason is that the test may be falsely normal () in many cases, or abnormally elevated in people who have no cancer at all (). The main use of CA19-9 is therefore to see whether a pancreatic tumor is secreting it; if that is the case, then the levels should fall when the tumor is treated, and they may rise again if the disease recurs (25-29).

**Benign conditions and other malignant states:**

Elevated levels of CA 19-9 can be seen in healthy individuals. Elevated levels can also be seen in benign conditions, such as the following, , , , , Thyroid disease. Elevated levels of CA 19-9 can be seen in the following malignant conditions of ovarian, and High CA 19-9 levels (ie, greater than 1000 U/mL) correlate
with unresectable or more advanced tumors, although this preoperative evaluation of CA 19-9 has not been widely used to establish inoperability (24-27). High marker levels may also be used to predict patient outcomes. A decrease or normalization of CA 19-9 levels postoperatively correlates with a longer duration of survival (27-30). Conversely, rising marker levels postoperatively have been correlated with shorter duration of survival and increased disease recurrence. Finally, CA 19-9 levels can be used to monitor tumor response to active treatment with surgery, with or without chemotherapy, radiation therapy, and/or other targeted or biological therapies. A decrease in CA 19-9 levels confirms the effectiveness of the therapeutic regimen, while a stable or rising level may indicate the need to change therapies (31-32).

**Alpha-Fetoprotein**

Alpha-fetoprotein (AFP) is the major protein of fetal serum but falls to an undetectable level after birth. The primary malignancies associated with AFP elevations are hepatocellular carcinoma and nonseminomatous germ cell tumors (1). Other gastrointestinal cancers occasionally cause elevations of AFP, but rarely to greater than 1,000 ng per mL. Patients with cirrhosis or viral hepatitis may have abnormal AFP values, although usually less than 500 ng per mL. Pregnancy also is associated with elevated AFP levels, particularly if the pregnancy is complicated by a spinal cord defect or other abnormality (1). The information provided in preceding paragraphs were procured from wikipedia, med.portal and cancers related web sites and including PubMed search, and American Family Physician journal (2003/vol 68, , Perkins et al., 2003)

**Diagnostic and Prognostic utility:**

AFP levels are abnormal in 80 percent of patients with hepatocellular carcinoma and exceed 1,000 ng per mL in 40 percent of patients with this cancer. Although randomized controlled trials have not shown mortality risk benefit, the use of AFP in hepatocellular carcinoma screening continues to be debated (33-35).

Retrospective studies in Asia showed improved survival with AFP screening, but the findings of this study have not been duplicated (1, 36-38). Some experts use annual AFP and ultrasound screening in patients with well-compensated nonalcohol-induced cirrhosis (39-41). In patients with a hepatic mass and risk factors for hepatocellular carcinoma, an AFP level above 500 ng per mL is often used in lieu of biopsy to diagnose hepatocellular carcinoma (42, 43).

**CA-125**

CA-125 (cancer 125 or carbohydrate antigen 125) also known as mucin 16 or MUC16 is a that in humans is encoded by the MUC16 . MUC16 is a member of the family . CA-125 has found application as a or that may be elevated in the blood of some patients with specific types of , or other benign conditions. Mucin 16 is a membrane associated mucin that possesses a single domain (1). The information provided in preceding and proceeding paragraphs were obtained from wikipedia, med.portal, cancers associations and their web sites, including PubMed search, and American Family Physician journal (2003/vol 68, , Perkins et al., 2003)

A unique property of MUC16 is its large size. MUC16 is more than twice as long as and contains about 22,000 , making it the largest membrane associated mucin. MUC16 is made of three different domains; an domain, a domain, and a The N-terminal domain and tandem repeat domain are both entirely and highly . All mucins contain a tandem repeat domain that has repeating sequences high in , and . The C terminal domain contains multiple extracellular SEA (sea urchin sperm protein, enterokinase, and agrin) modules, a transmembrane domain, and a tail. The extracellular region of MUC16 can be released from the cell surface by undergoing . MUC16 is thought to be cleaved at a site in the SEA modules. MUC16 is a component of the ocular surface (including the and) and the respiratory tract and female reproductive tract. Since MUC16 is highly it creates a environment that acts as a lubricating barrier against foreign particles and infectious agents on the of epithelial cells (1, 44-
46). The cytoplasmic tail of MUC16 has been shown to interact with by binding members of the . The expression of mucin 16 has been shown to be altered in dry eye, cystic fibrosis and several types of cancers.

Diagnostic utility:
Elevated CA 125 values most often are associated with epithelial ovarian cancer, although levels also can be increased in other malignancies.9 CA 125 levels are elevated in about 85 percent of women with ovarian cancer, but in only 50 percent of those with stage I disease. Higher levels are associated with increasing bulk of disease and are highest in tumors with nonmucinous histology (44-47). Multiple benign disorders also are associated with CA 125 elevations, presumably by stimulation of the serosal surfaces (1, 44-46). Insensitivity in early-stage disease and low disease prevalence limit the usefulness of CA 125 in ovarian cancer screening. In the largest study to date, CA 125 levels were monitored in all patients annually for three years, and elevated values prompted ultrasound examinations. The positive predictive value was 20 percent, translating to five exploratory laparotomies for each ovarian cancer diagnosed. Survival was not improved in the women who were found through CA 125 screening to have ovarian cancer. Randomized trials are being conducted to assess the role of CA 125 in ovarian cancer screening. Annual ultrasound examination and CA 125 screening have been advocated for women with hereditary ovarian cancer syndromes (46-48). CA 125 has been used as an adjunct in the diagnosis of pelvic masses. In postmenopausal women with asymptomatic palpable pelvic masses, CA 125 levels higher than 65 units per mL have a positive predictive value of 98 percent for ovarian cancer. Because premenopausal women have more benign causes of elevated CA 125 levels, testing for the marker is less useful in this population (49-51), ovarian cancer is treated with maximal surgical reduction, which leaves minimal clinical or radiographic disease. Because studies have demonstrated concordance of CA 125 levels with disease activity, oncologists rely on CA 125 levels to guide therapeutic decisions (50, 51). After definitive treatment of ovarian cancer, CA 125 levels should be obtained every three months for two years, and with decreasing frequency thereafter. Elevated CA 125 levels during follow-up nearly always indicate ovarian cancer recurrence (47-51).

Prognostic utility, Specificity and sensitivity
CA-125 has limited for ovarian cancer because elevated CA-125 levels can be found in individuals without ovarian cancer. For example, while CA-125 is best known as a marker for ovarian cancer, it may also be elevated in other cancers, including endometrial cancer, fallopian tube cancer, lung cancer, breast cancer and gastrointestinal cancer. CA-125 may also be elevated in a number of relatively benign conditions, such as , several diseases of the ovary, menstruation and pregnancy (51-54). It also tends to be elevated in the presence of any inflammatory condition in the abdominal area, both cancerous and benign. Thus, CA-125 testing is not perfectly specific for ovarian cancer and often results in false positives. The specificity of CA-125 is particularly low in premenopausal women because many benign conditions that cause fluctuations in CA-125 levels, such as menstruation, pregnancy, and , are seen in this population. Elevations in CA-125 can also be seen in and diabetes mellitus.

Prostate-Specific Antigen:
Prostate-specific antigen (PSA) is a glycoprotein produced by prostatic epithelium. The PSA level can be elevated in prostate cancer, prostatitis, benign prostatic hypertrophy, and prostatic trauma (1, 55). In men with prostatitis, PSA levels return to normal within eight weeks of symptom resolution. Digital rectal examination does not elevate PSA levels above normal values (55, 56). In men who have been taking finasteride (Proscar) for more than six months, reported PSA levels should be doubled to accurately reflect true values, because the drug is an enzyme inhibitor that suppresses normal production of PSA by the prostate gland (56-58). The information, details and knowledge specified in preceding and proceeding
paragraphs were obtained through wikipedia, med.portal, cancers related web sites, including PubMed search, and American Family Physician journal (2003/vol 68, , Perkins et al., 2003)

Diagnostic utility:
In prostate cancer, the positive predictive value of PSA levels greater than 4 ng per mL is 20 to 30 percent and rises to 50 percent when PSA levels exceed 10 ng per mL. Nevertheless, 20 to 30 percent of men with prostate cancer have PSA levels within normal ranges (55-58). Modifications to improve the positive predictive value of PSA testing include revised limits of normal based on age, race, velocity, density, and percentage of unbound (free) antigen. To date, these modifications have not resulted in improved outcomes. However, in patients with PSA values between 4 and 10 ng per mL, the PSA velocity and percentage of free PSA have been helpful in making clinical decisions. A velocity of 0.75 ng per mL per year is predictive of cancer. When less than 10 percent of PSA is unbound, the positive predictive value for prostate cancer is 55 percent, compared with 8 percent when more than 25 percent of PSA is unbound (58-60). Prostate cancer screening remains controversial. Surrogate evidence of screening benefits include lower PSA levels33 and earlier stage of disease at the time of initial diagnosis (60).

Prognostic utility and screening:
Limitations of screening include uncertainty about outcome benefit after treatment of localized prostate cancer, potential identification of clinically insignificant tumors, and attendant morbidity of treatment (58-60). Experts from the American Urological Association suggest that patients should be given sufficient information to allow them to make an informed decision about prostate cancer screening using PSA levels (60-62). If PSA testing is undertaken, an age of 40 years has been suggested for initiation of screening in black men and in all men with a family history of prostate cancer. In patients without established risk factors and a minimum life expectancy of 10 years, screening could begin at age 50. If elevated PSA values are confirmed, patients should be referred for biopsy. Randomized clinical trials are being conducted to assess the validity of these recommendations. PSA levels predict the presence of metastatic disease. Patients with newly diagnosed prostate cancer and PSA levels below 20 ng per mL rarely have osseous metastasis and do not need bone scanning, because the incidence of metastatic disease in these men is lower than 2 percent (60-62). In addition, computed tomographic scanning is unnecessary in men with PSA levels below 25 ng per mL. At our institution, if a prostate nodule is detected, the bone scan is widely positive, and the PSA level exceeds 100 ng per mL, treatment is often instituted without performance of biopsy. After treatment of prostate cancer, PSA levels should be obtained every six months for five years, and then annually. In men who have undergone radical prostatectomy any detectable PSA is significant. Salvage radiotherapy may be appropriate in these patients if recurrence is limited to the prostate bed as determined by ProstaScint scanning, a nuclear medicine test using a radio-labeled antibody that targets only prostate tissue. After radiotherapy, a PSA nadir is not reached for one to two years. Three consecutive elevations of the PSA level indicate biochemical relapse in previously irradiated patients. Metastases do not become clinically evident for an average of eight years, and death does not occur for an average of 13 years. Thus, management decisions must include consideration of a patient’s age and co-morbid conditions (1, 60-63).

CA-15.3
Cancer antigen 15-3 (CA 15-3) is used to monitor response to breast cancer treatment and disease recurrence. The reference range of serum CA 15-3 is less than 30 U/mL. The upper limit of the range varies depending on the laboratory and kit used for the test (1). Values obtained with different assay kits, methods, or laboratories cannot be used interchangeably. Adequate treatment can indicate that the tumor is not responding to treatment or that the tumor is recurring.
The information provided in proceeding paragraphs were procured from wikipedia, med.portal and cancers related web sites and including PubMed search, and American Family Physician journal (2003/vol 68, Perkins et al., 2003).

**Diagnostic utility:**
CA 15-3 measurement can also be used to survey disease recurrence after treatment of metastatic breast cancer. In the absence of measurable disease, an increase in CA 15-3 levels could indicate treatment failure. However, CA 15-3 levels can rise during the initial 4-6 weeks of starting therapy (63-65). This transient rise does not usually correlate with disease progression. Higher CA 15-3 levels have been correlated with more advanced stages of breast cancer or with larger tumor burden. If the tumor produces CA 15-3, marker levels will increase as the tumor grows. The highest levels may be seen in metastatic breast cancer, particularly when metastases to the liver or bones exist (65-67). However, CA 15-3 can be low or absent in all of these settings, since not all breast cancers produce CA 15-3 or early-stage breast cancers may not produce detectable CA 15-3 levels. Thus, normal levels do not ensure the absence of localized or metastatic breast cancer (65-69).

Elevation of CA 15-3 levels can also be seen in healthy individuals, in benign conditions, and in other malignant conditions. However, CA 15-3 levels tend to remain relatively stable over time in benign conditions; thus, elevated levels need to be interpreted within the context of the patient's history and physical examination, diagnostic imaging, and laboratory workup (65-70). Benign causes of elevated CA 15-3 levels are as follows, Chronic hepatitis, , , benign breast disease, , endometriosis, , Lactation and pregnancy (71-75). Malignant causes of elevated CA 15-3 levels are; , , , ovarian cancer, , (74-77).

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