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Tumor markers in prostate cancer

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ABSTRACT

Tumor markers are substances produced by body during cancer. Their levels are elevated during cancerous conditions. They are used by doctors as a confirmatory test. They are also used to detect cancer recurrence, prognosis and diagnosis. In this article, the tumor markers and their usefulness is explained. This is then followed by a brief explanation of prostate cancer and then by the various tumor markers present for the detection of prostate cancer. These include- PSA, kallikrein markers and sarcosine among others. The latest research and advancement in this field is listed. Although tumor markers have been a part of many controversies, they have now started to being accepted widely.

Keywords: *Prostate cancer, PSA, EPCA 2, Sarcosine, KLK.*

INTRODUCTION

A tumor marker is a biomarker that is produced by the body during cancer as a response or it is produced by the cancer itself. Some of these markers are specific to one type of cancer while some are seen in many cancers. These markers are generally used to evaluate the patient's response to treatment or to monitor for recurrence. Tumor markers can be used together with other tests (scans, biopsies, etc.) to help detect a patient who has symptoms suspicious for cancer. Some markers can help physicians to determine prognosis and treatment.

Tumor markers have various uses like screening of cancer- detection of cancer at early age, before it has grown and spread ,disease staging for diagnosis etc. It was not easy for tumor markers to gain acceptance by people. One of the first tumor markers to be accepted (after a lot of controversy) was prostate specific antigen. The reason why tumor markers have not widely been accepted is the fact that there may be false positives, i.e. , their levels may seem elevated seen when there is no cancer present, or their levels may rise at a very later stage of cancer. The presence of tumor marker is seen as indication when no other indicator of disease is not available.

Tumor markers are not useful in all patients as they are not elevated in all types of cancers. For instance, carcinoembryonic antigen (CEA) is a tumor marker used to detect colon cancer recurrence, but it is only seen in 70-80% of the cases. Tumor markers can be useful in early detection but cannot compete with physical examination in the detection of cancer.

Examples of tumor markers and their associated tumors:

1. ***CA 2.29:*** breast cancer
2. ***CEA:*** colorectal cancer
3. ***CA 19-9:*** pancreatic and biliary tract cancer
4. ***AFP:*** hepatocellular carcinoma, nonseminomatus germ cell tumors
5. ***Beta Hcg:*** nonseminomatus germ cell tumors, gestational trophoblastic disease
6. ***CA-125:*** ovarian cancer
7. ***PSA:*** prostate cancer

In certain situations, the use of a combination of tumor markers may be appropriate example (1)measurement of both human chorionic gonadotrophin (hCG) and alpha-fetoprotein (AFP) is mandatory in patients in whom testicular or other germ cell cancers are strongly suspected (these markers are not raised in all such patients).

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Prostate cancer:

Prostate cancer is the development of cancer in the prostate gland which is a male reproductive organ. Mostly, prostate cancers grow slowly but in some cases they grow quickly and spread to lymph nodes and bones. There are many causes of prostate cancer like age, genetics etc. There have been recent studies stating that obesity might lead to prostate cancer. Also, statins may increase the risk of prostate cancer in people. Initially, there are no symptoms but in the later stages it leads to pain while urinating, pain in the back, or blood in urine.

There are around 10 types of prostate cancer, 9 out of which are acinar adenocarcenoma which starts from gland cells. Other types are ductal adenocarcinoma, trasitional cell cancer, squamous cell cancer, small cell cancer among others.

Tumor markers in prostate cancer:

The following tumor markers in prostate cancer have been detected:

I. PSA:

Prostate specific antigen (PSA) marker is very useful for the diagnostic purpose of prostate cancer. It is a glycoprotein having the molecular mass of 33 kDa. It has chymotrypsin like serine protease activity. Prostatic epithelial cells produce PSA and further it is secreted into seminal plasma. Its function includes proteolysis of seminal coagulum immediately after ejaculation. PSA test measures the PSA protein concentration in the blood and its higher level may be the indication of prostate cancer

PSA has different molecular forms. 70%-90% of total PSA is bound to protease inhibitor like alpha 1 antichymotrypsin and alpha 2 macroglobulin. Remaining 10-30% of total PSA is free. Free PSA consists of differentheterogeneous molecular forms including mature active and inactive PSA, various forms of nicked and inactivated PSA [30, 31]. The measurement of different molecular forms of PSA is a very potential diagnostic tool of prostatic disease [32]. ProPSA, BPH associated PSA and cleaved PSA which are different forms of isoforms,are very useful for diagnostic purpose. 2DE profile of PSA is even more helpful which increases the specificity and sensitivity of the prostate cancer diagnosis.

The efficiency of PSA can be increased through PSA kinetics. PSAV i.e. PSA velocity is such type of tool used for this purpose. PSAV basically is the serial evaluation of serum PSA level over time. It was found to be independent predictor of high grade prostate cancer.

II. Serum Kallikreins:

Human kallikrein 2 (hK2: also known as human kallikrein-related peptidase 2), a secreted serine protease that

shares sequence homology with PSA of about 80%, is responsible for the cleavage of pPSA to active mature PSA . Both hK2 and PSA are primarily expressed in the prostate gland. Even though they have certain similarities, they differ in their enzymatic activities. hK2 is present in two forms in the blood: as bound to protease inhibitors and other as free form. Initially the level of hK2 showed no difference in tumor patients, but late it was found that the ratio of hK2 and Fpsa varied. Also ,it was later found that %Hk2 was different in cancer patients and non cancer patients. Others argued that this was not true. Meanwhile, it has been suggested that hK2 could also be useful for patients diagnosed with radical prostectomy in analyzing pathologic stage and biochemical outcome [4, 5]. Most studies have concluded that hK2 has an additive role in prostate cancer detection. Therefore, it is generally considered as a prognostic marker.Since it is difficult to detect the presence of cancer using a single marker, a combination of markers is used. A group of researchers led by Lilja and Vickers invented a statistical model for predicting prostate biopsy outcomes based on age, DRE (direct rectal examination), and a group of four KLK markers which were tPSA, fPSA, intact PSA, and hK2 [6]. Some have reported that higher kallikrein-related peptidase 4 (KLK4) mRNA levels of the prostate tissue obtained from biopsy are related to higher stage and score of gleason [7]. Kallikrein-related peptidase 5 (KLK5) is over expressed in normal as compared to cancerous prostatic tissue, and an opposite relation has been reported between KLK5 levels and pathologic tumor stage and grade [8, 9]. Also, some studies reported severe over expression of KLK5 gene transcription levels with treatment of the androgen-independent prostate cancer cell lines PC3 and DU145 with chemotherapeutic agents widely used in clinical setting [10, 11]. Meanwhile, elevated kallikrein-related peptidase 11 (KLK11) mRNA expressions have been found to be related with a less progressive stage, lesser Gleason score, and a favorable disease course for prostate cancer [7]. Expression of kallikrein-related peptidase 14 (KLK14), which is likely to have a major role in seminal clot liquefaction, points to a severe clinical outcome of prostate cancer patients as elevated KLK14 mRNA and protein levels have been associated with more aggressive tumors [7, 12]. The over expression of kallikrein-related peptidase 15 (KLK15) transcript varieties, alternatively spliced ones varieties included, has been observed to be associated with more aggressive prostate cancer [13, 14]. Overall, despite the promising findings reported, further research would be needed to come to a conclusion that kallikreins as biomarkers for prostate cancer are useful. Emerging and ongoing efforts on studying KLK-mediated pathways will further prove and support evaluations of KLKs as potential biomarkers for prostate cancer. Although KLKs may individually not be very selective and specific, groups of KLKs, possibly with other markers, may offer enhanced accuracy [6]. Despite the advances in technology and research, the role of KLK is beginning to be understood. With researches in genomics, proteomics, and other biotechnology, the actual roles of KLKs in prostate cancer will be discovered in the coming years.

III. EPCA 2:

Early Prostate Cancer Antigen is a nuclear matrix protein, originally described by Robert Getzenberg, reported to be a highly sensitive and specific test for prostate cancer. According to recent findings EPCA 2 is more useful in identifying presence of cancer than PSA. EPCA-2 is present in the structure of the nucleus of cancer cells. EPCA-2 is found specifically in prostate cancer cells, not healthy cells, and it can be measured in a blood sample from patients. It therefore offers an effective screening of prostate cancer. A recent research involved the use of 368 blood samples from people with benign prostate cancer, prostate cancer that may have spread or not, or with no cancer at all. Two types of EPCA- 2.22 and 2.19 were used and the results were compared to PSA results. The research concluded that EPCA proved more effective than PSA in detecting the cancer.

IV. Sarcosine:

Many complex events mark the beginning and progression of cancer. Uncoding the molecular networks that differentiate organ-confined disease from metastatic disease may lead to the discovery of useful biomarkers for cancer formation and disease severeness. Even though gene and protein expression have been extensively profiled in human tumors, little is known about the global metabolomic alterations that are a characteristic of neoplastic progression. Using a mixture of high-throughput liquid-and-gas-chromatography-based mass spectrometry, a group of researchers analysed more than 1,126 metabolites across 262 clinical samples related to prostate cancer (42 tissues and 110 each of urine and plasma). These metabolomic profiles were unbiased and were able to differentiate benign prostate, clinically localized prostate cancer and metastatic disease. Sarcosine, an N-methyl derivative of the amino acid glycine, was identified as a differential metabolite whose levels increase drastically during prostate cancer invasion and can be detected in the urine. Sarcosine levels were also increased in invasive prostate cancer cell lines relative to benign prostate epithelial cells. Here, by profiling the metabolomic alterations of prostate cancer progression, sarcosine was considered as a potentially important metabolic intermediary of cancer cell invasion and aggressivity [27].

CONCLUSION

PSA is a highly sensitive biomarker which helps in the early detection of prostate cancer. When PSA is used with DRE (direct rectal examination) the efficiency of detection increases. It involves simple blood test. PSA is the only biomarker that has been passed through all the five phases of testing. Also different forms of peptide show affinity for different forms of PSA and are either responsible for either PCa or BPH.Hence these peptides have the ability to recognize different forms of PSA and has the potential to act as therapeutic drug for treating cancer. Despite the fact that PSA screening has significant contribution in diagnosing the cancer it has some flaws like unnecessary detection, test and treatment. It is not able to differentiate between slow growing and advanced cancer. Regular use of PSA caused increased CaP incidence. In addition the large number of unnecessary biopsies due to false positive PSA results places a burden on the healthcare system and leads to patients discomfort [28].

Sarcosine is also one of the potential markers for the prostate cancer diagnosis. Its concentration in urine is sufficient which ultimately reduces the risk of false negative or false positive results. However concentration of sarcosine cannot be related to tumor growth. It cannot reliably predict the histological grade and behavior of tumor [29]. So combining serum sarcosine with other tumor markers like PCA3 and pro PSA is important to get the better results.

Kallekreins resemblance with PSA paved the way for its usage in prostate cancer diagnosis. Compared with PSA it is found that kalllekreins levels are less than 2 % in prostate serum and semen. %hk2 (human kallekreins) helps in distinguishing cancer patients from non-cancer patients. KLKs when used individually lack specificity and sensitivity while using it with other markers enhances its accuracy.

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