Review Article

Prostate Cancer and Prostate Specific Antigen

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Incidence of Prostate Cancer

Prostate cancer is a major cause of mortality and morbidity in men. It is the second leading cause of death due to cancer in men.[1] In the United States, benign and malignant diseases of the prostate are responsible for more surgery than any other organ disease in men over the age of fifty.[2] In Europe prostate cancer is the second leading cause of death in males[3]. In Netherlands the morbidity and mortality caused by this tumor are exceeded only by those of lung cancer[4] and in a retrospective study, 1.62 % incidence of prostate cancer is reported in Lahore, Pakistan.[5]

Prostate Specific Antigen

Prostate specific antigen (PSA) is a single chain polypeptide distinct from prostatic acid phosphatase. It is localized in prostatic epithelial lining cells of the acini and ducts in both primary and metastatic prostatic carcinoma cells.[6] It is shown that PSA is a more sensitive marker of low stage disease than prostatic acid phosphatase.[7] In 1980, PSA concentrations were first reported to be increased in prostate cancer patients and currently tests for PSA are widely used to monitor patients with prostate cancer.[8] PSA has better sensitivity than prostatic acid phophatase. However detection of cancer of prostate by PSA measurement alone is restricted by the fact that increased concentrations are also found in a significant number of patients with benign prostatic hyperplasia (BPH).[9]

Since the discovery of Prostate specific antigen (PSA) by Wang in 1979, it has been an important tool in the diagnosis of prostate carcinoma and is considered to be the best marker of disease progression and response to different treatments.[10] The tumor is adenocarcinoma in more than 90% of cases.[11]

Chemistry of Prostate Specific Antigen

Prostate specific antigen (PSA) is a 33,000 dalton neutral serine protease, composed of a single polypeptide chain of 33 amino acids.[12] It is a chymotryptic like serine protease that belongs to the human tissue kallikerine family.[13]The expression and secretion of PSA is under the androgen control. PSA usually is released into the blood at low conc. (<4ng/ml) in healthy individuals.[14] Recently using two site immunometric methods and gel permeation chromatography it has become possible to characterize the different forms of serum PSA. PSA complexed to ACT is the predominant immunoreactive form of PSA in serum whereas <30% of total PSA occurs in the noncomplexed free form. Thus PSA-ACT form and free PSA are two molecular forms that may be monitored using immunological methods such as immunoassay.[15] In serum the ratio free PSA : PSA-ACT is about 1:4.[16] Patients with prostate cancer have a lower proportion of f-PSA than patients with benign prostatic hyperplasia.[17]

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Role of Prostate Specific Antigen Levels in Prostate Cancer

Prostate specific antigen is the most useful marker in the early diagnosis of adenocarcinoma of the prostate.[18] PSA leaks into the systemic circulation due to the local breakdown of histological barriers

separating the prostatic duct acinar and the systemic circulation which is associated with the presence of malignancy.[19] Measurement of total serum PSA is routinely used for early detection and monitoring the progress of prostate cancer. However early detection is limited by the fact that increase concentration of PSA are found also in many patients with benign prostatic hyperplasia BPH.[20] In the past most prostate cancers were detected at an advanced stage by digital rectal examination. Now the majority of prostate cancers are detected early with PSA assay which increases the lead time for diagnosis.[21] PSA measurement is used in combination with other diagnostic procedures such as imaging methods and digital rectal examination for the detection of existing prostate disorder.[22] It has also been suggested that the use of PSA in monitoring the patients with prostate carcinoma can reduce repeated bone scan.[23] PSA concentrations are increased not only in patients with adenocarcinoma prostate but also in patients with benign prostate hyperplasia or inflammation and after manipulation of prostate .On the other hand not all the patients with prostate cancer have an elevated serum PSA concentration. 30-40% of men with organ confined prostate cancer have a normal serum PSA level.[24]

To eliminate the interference of factors that reduce diagnostic power of PSA, various concepts are being used such as age related reference values, PSA density, PSA velocity, and quantitative determinants of the different molecular forms.[25]

Age specific reference ranges are taken as opposed to the single reference range of 0.0-4ng/ml for men of all ages.[26] Use of age specific PSA reference ranges include age related changes in PSA production and secretion as well as prostate growth. In conjunction with PSA density, the age specific reference ranges identifies those patients who require biopsy.[27]

PSA density (PSAD) is the quotient of the serum PSA concentration divided by the volume of the prostate. It is useful in patients with PSA level between 4-10ng/ml.It is important to determine the PSAD in patients with PSA level of 4.1-10ng/ml who had no abnormal finding on TRUS and recommended that a biopsy should only be taken if the PSAD was >0.15. [28] PSA velocity is the longitudinal change in serum PSA level over time. Prostate cancer growth follows a simple exponential growth curve throughout its natural history. Since serum PSA is proportional to cancer volume, the rate of change of PSA with time in untreated patients should follow a similar course.[29] Determination of free PSA versus complexed serum PSA, which refers to the ratio of free PSA to PSA complexed to alpha -1 antichymotrypsin in the serum is important to improve the diagnostic potential and diagnostic specificity of PSA.[30] As f PSA is believed to be derived mostly from non malignant cells,[31] the measurement of ratio between total PSA and unbound or free PSA (percent free PSA) has been introduced as a useful clinical tool for early detection of clinically localized prostate cancer as prostate cancer is best cured by surgery when it is organ confined.[32] PSA has been recognized as a sensitive indicator of recurrent prostate cancer after radical prostatectomy. Numerous PSA assays with improved limits of detection have been developed. The rational behind the development of more sensitive PSA assays (lower limit of detection) is that the relapse of prostate cancer or the tumor doubling time, after radical prostatectomy can be detected much earlier if patients are monitored with more sensitive assays.[33] The measurement of the percentage of free PSA as a marker of cancer aggressiveness has been documented.[34] PSA appears to be the single most efficient primary tool in prostate cancer screening, in most screening programs PSA greater than 4ng/l or equivalent is considered abnormal and leads to further evaluation with digital rectal examination, transrectal ultrasound and biopsies according to various algorithms.[35] Although PSA screening has not been demonstrated to reduce prostate cancer mortality in clinical trials or population settings, the increase in its use during the early 1990 paralleled a dramatic increase in national prostate cancer rate. From 1990 to 1991, the incidence increased approximately 25%.[36]

Serial PSA determinations are especially useful in annual screening surveys and in following patients expectantly with potential clinically insignificant volumes of prostate cancer. [37] Although its role in monitoring the treatment of known prostate cancer is well established, its utility along with other tests in screening men from prostate cancer remains uncertain .This is largely due to the lack of convincing data showing reduction in disease specific mortality by earlier identification of cancer in asymptomatic population. Nevertheless PSA has been found to be more sensitive than other markers in identifying gland contained and presumably curable cancer and in detecting a preponderance of clinically significant tumors as opposed to latent indolent micro carcinomas.[38]

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