ORIGINAL RESEARCH PAPER
Volume - 9 | Issue - 7 | July - 2020 | PRINT ISSN No. 2277 - 8179 | DOI : 10.36106/ijsr
INTERNATIONAL JOURNAL OF SCIENTIFIC RESEARCH

TUMOR MARKERS AND ROLE OF PSA IN DIAGNOSIS AND PROGNOSIS OF CARCINOMA PROSTATE, A REVIEW

Urology

Dr Chandra Mauli Upadhyay Associate professor, Surgery, JLNMCH, Bhagalpur

Dr Kumar Mehul * 2nd year PG, Surgery,JLNMCH, Bhagalpur.*Corresponding Author

ABSTRACT

Prostate cancer is the fourth most common male malignant neoplasm worldwide .Adenocarcinoma is most common malignancy of the prostate gland and one of the leading causes of cancer –related death in males. Prostate cancer is the most common cancer in men accounting for 33% of all malignant tumors in men & accounts for 9% of cancer deaths, the third highest in men after lung & colorectal cancers Among urologic malignancies, prostate cancer has greatly benefited from the discovery and application of tumor markers.

Since its discovery in 1979 to clinical application in the 1986, PSA has evolved into an invaluable tool for the detection, staging, and monitoring of men diagnosed with prostate cancer . Whereas the majority of prostate cancers in the 1980s and early 1990s commonly arose with an abnormal digital rectal examination (DRE) or elevated PSA, or both, today most prostate cancers arise as clinically non-palpable (stage T1c) disease with a PSA between 4 and 10 ng/mL. Prostate-specific antigen (PSA) is a protein produced by normal prostate cells. This enzyme participates in the dissolution of the seminal fluid coagulum and plays an important role in fertility. The highest amounts of PSA are found in the seminal fluid; some PSA escapes the prostate and can be found in the serum.

Rising levels of PSA in serum are associated with prostate cancer. The PSA level also tends to rise in men with benign prostatic hyperplasia (BPH) and is a good marker for prostate volume.PSA testing not only helps identify men in whom a prostate biopsy would be appropriate but also assists in assessing the response to therapy, determining tumor progression, and, in its most controversial role, screening for prostate cancer.

Aims and objective of study: To review the role of PSA in early diagnosis of Prostatic carcinoma for better outcome of treatment.

KEYWORDS

Introduction

PSA levels have been used in screening large populations of men for prostate cancer and have been shown to be useful . Before the PSA era, an abnormality in the prostate had to be palpably evident before a biopsy would be performed, and nearly 70% of men diagnosed with prostate cancer already had extraprostatic or metastatic disease. Since the advent of PSA evaluation, fewer than 3% of men have metastases at the time of diagnosis, and 75% of men have nonpalpable cancer. In this latter group, the cancer was detected on biopsy performed because of a rapidly rising or markedly elevated PSA level.

Despite the apparent survival advantage conferred by PSA screening, the US Preventive Services Task Force (USPSTF) recommends against screening for prostate cancer in men aged 75 years or older. The USPSTF also concludes that at present, the balance between the benefits and the drawbacks of prostate cancer screening in men younger than age 75 years cannot be assessed, because the available evidence is insufficient.

The 2010 update of the American Cancer Society (ACS) guideline for early detection of prostate cancer stresses the importance of involving men in the decision whether to test for prostate cancer. The ACS notes that PSA testing may reduce the likelihood of dying from prostate cancer but nevertheless poses serious risks, particularly those associated with the treatment of prostate cancer that would not have caused ill effects if left undetected.

The incidence of prostate cancer is higher in black men than in white men. Reports indicate that PSA levels are higher in black men, even when age, clinical stage, and Gleason grade are controlled for. Moul et al suggested that that these higher levels are related to the larger (ie, 1.3-2.5 times greater) tumor volumes found in these men. Morgan et al evaluated 411 black men who had prostate cancer and noted that 40% of cases would have been missed if the traditional age-specific reference ranges had been sued.

PSA levels tend to increase with age; this increase is related to prostate volume. Most PSA is made in the transition zone of the prostate, and this region of the prostate increases in volume in men with BPH.

The complete gene encoding PSA has been sequenced and localized to chromosome 19.

Structure of PSA

Prostate-specific antigen (PSA) is a 33-kd protein consisting of a single-chain glycoprotein of 237 amino acid residues, 4 carbohydrate side chains, and multiple disulfide bonds. It is homologous with the proteases of the kallikrein family. PSA may be referred to as human glandular kallikrein (hK)-3 to distinguish it from hK-2, another prostate cancer marker with which it shares 80% homology. A third kallikrein, hK-1, is found mainly in pancreatic and renal tissue but shows 73% and 84% homology with PSA. PSA is a neutral serine protease. PSA splits the seminal vesicle proteins seminogelin I and II, resulting in liquefaction of the seminal coagulum. PSA is found primarily in prostate epithelial cells and in the seminal fluid. The exact mechanism by which PSA gains access to the serum is unknown, but a possible mechanism has been suggested.

The lumen of the prostate gland contains the highest concentration of PSA in the body. A number of barriers exist between the glandular lumen and the capillaries, including the basement membrane of the glands, the prostatic stroma, and the capillary endothelial cell. Diseases such as infection, inflammation, and cancer may produce a breakdown in these barriers, allowing more PSA to enter the circulation.

PSA levels can rise dramatically with a prostate infection, but they return to the reference range after the infection has healed. A vigorous prostate massage also can produce a brief elevation of the PSA level.

Low concentrations of PSA have been identified in urethral glands, endometrium, normal breast tissue, breast milk, salivary gland tissue, and the urine of males and females. PSA also is found in the serum of women with breast, lung, or uterine cancer and in some patients with renal cancer.

Serine proteases are bound mostly to various serum proteins. A small percentage of serum PSA exists as free PSA (fPSA), but the majority exists as complexed PSA (cPSA) and is bound to either $alpha_2$ -macroglobulin (AMG) or $alpha_1$ -antichymotrypsin (ACT). These are the 2 major serine protease inhibitors in the blood, constituting 10% of total serum protein. The ejaculate primarily contains fPSA, in a concentration of 1 million ng/mL.

The half-life and metabolic clearance rate of PSA have been determined from studies of patients undergoing radical prostatectomy. Stamey et al found the half-life to be 2.2 ± 0.8 days, [7] whereas Oesterling et al determined it to be 3.2 ± 0.1 days. [14] Because of the relatively long half-life of PSA, a minimum of 2-3 weeks is required

for the serum PSA to reach its nadir after radical prostatectomy, at which point it should be undetectable.

Production in benign hyperplasia

The majority of PSA is produced by the glands in the transitional zone of the prostate. This portion of the prostate is associated with benign prostatic hyperplasia (BPH). The peripheral zone, where 80% of prostate cancers originate, produces very little PSA.

By measuring PSA before and after transurethral resection of the prostate, Stamey et al were able to calculate the amount of PSA produced per gram of benign prostatic tissue.[7] the PSA level was 0.31 ± 0.25 ng/mL per gram of hyperplastic tissue. The polyclonal Yang assay was used for this study.

The Hybritech monoclonal assay produced a measurement of 0.5 ± 0.4 ng/mL. Using the monoclonal assay, Lee et al calculated a serum PSA elevation of 0.12 ng/mL per gram of benign prostatic tissue.

Other Prostate Cancer Markers

Human glandular kallikrein–2

Human glandular kallikrein (hK)-2 is a serine protease that has approximately 80% structural homology with prostate-specific antigen (PSA; ie, hK-3). It is responsible for the conversion of the inactive pro-PSA zymogen to the enzymatically active PSA in vitro, which is a prerequisite for formation of PSA–alpha$_1$-antichymotrypsin (ACT) and other complexes. As prostate cancer cells become more anaplastic, hK-2 levels rise, whereas PSA levels tend to fall. Concentrations of PSA and hK-2 are high in prostatic and seminal fluid but low in the blood.

Prostate-specific membrane antigen

Prostate-specific membrane antigen (PSMA) is a selective antigenic marker of prostate epithelial cells that can be found in the serum. Bostwick et al found that this marker is expressed in 70% of benign epithelial cells, 78% of prostate intraepithelial neoplastic cells, and 80% of invasive cancer cells. PSMA is expressed to a greater extent than PSA in higher-grade cancers. The development of immunoassays and Western blot–based assays for PSMA has permitted an increasing number of studies. PSMA levels seem to correlate with stage and tumor volume. After radical prostatectomy, PSMA levels become undetectable, but they rise if the tumor recurs. Reverse transcriptase polymerase chain reaction (RT-PCR) testing with PSMA primers has been used to detect circulating prostate cancer cells. This method detects tumor cells at concentrations as low as 1 per 10 million lymphocytes. The use of this method for clinical decision-making has been limited. With this technology, cancer cells can be identified in the circulation and in the bone marrow of patients with all stages of prostate cancer.

PSMA serves as the basis for the ProstaScint scan. This is an imaging study used to detect metastatic cancer. Its primary use has been to identify prostate cancer cells in lymph nodes and in the prostate base.
PSMA is being evaluated as a means of providing therapy. When PSMA is used as an immunotherapeutic agent, dendritic cells are primed with PSMA and infused into the patient. This is intended to produce a specific immune response to prostate cells. With PSMA used as a guide to identify and target prostate cells, radioactive isotopes and cytotoxic agents can be delivered to these cells.

Cell cycle inhibitor p27

The cell cycle inhibitor *p27* is a putative tumor suppressor gene. Loss of *p27* is associated with a poor prognosis in patients with breast, colorectal, and prostate carcinoma. In men treated with radical prostatectomy, loss of *p27* expression correlates with an increased probability of cancer recurrence and lower survival rates. Decreased *p27* expression also is associated with high-grade cancer cells, positive surgical margins, seminal vesicle invasion, and lymph node metastases.

Serum insulin like growth factor

Insulinlike growth factor (IGF)-1, its binding protein (IGF-binding protein [IGFBP]), and its receptor (IGF receptor [IGFR]) have been implicated in the development of prostate cancer. PSA cleaves IGF-1 from its binding protein, allowing this potent growth factor to act on prostate epithelial cells.

Plasma concentrations of IGF-1 have been associated with an increased risk of prostate cancer. The clinical usefulness of this assay has yet to be demonstrated, because alternative explanations for these findings may exist. Prostate size and a large overlap in actual values limit the utility of the test but do provide additional information regarding the biology of prostate cancer.

Factors Influencing PSA Levels

For clinical purposes, prostate-specific antigen (PSA) is considered specific for the prostate gland but not specific for prostate cancer. A major limitation of PSA as a prostate cancer marker is the overlap in values between benign prostatic hyperplasia (BPH) and prostate cancer. Normal, hyperplastic, and neoplastic epithelial cells all make PSA, but the amount of PSA produced by cancer cells is 10 times higher per gram of tissue than the amount produced by normal or hyperplastic tissue.

Hyperplastic tissue and epithelial-stromal ratio

The interpretation of PSA may vary according to the amount of BPH tissue and the epithelial-stromal ratio. Most PSA is produced in the hyperplastic transitional zone of the prostate. A relatively small amount of PSA is produced in the peripheral zone, where 80% of prostate cancers originate. Cancers developing in the transitional zone tend to produce large amounts of PSA.

High-grade cancer cells tend to lose their ability to produce PSA. A Gleason grade 5 prostate cancer produces less PSA than a grade 3 cancer does. Some patients with advanced prostate cancer may have low or undetectable PSA levels.

PSA Testing for Detection of Prostate Cancer

The introduction of prostate-specific antigen (PSA) testing into clinical practice has greatly increased the detection of localized prostate cancer and, by doing so, has decreased the diagnosis of regional and metastatic disease. PSA testing has had such a profound clinical effect that questions have arisen regarding the significance of the cancers that are being detected.

Stage, grade, tumor volume, and PSA testing are used to determine whether a prostate cancer is clinically significant or insignificant. However, there is no generally accepted precise definition for this distinction.

The goal of early detection of prostate cancer is to identify clinically significant cancers at a time when treatment is most likely to be effective. The risk of death from prostate cancer is significant in those with moderate- to high-grade tumors. This is especially true in younger men. Long-term survival is compromised when the cancer has spread beyond the confines of the prostate, into the regional lymph nodes, and to distant sites. Several studies have shown that with a PSA cutoff of 4.0 ng/mL, clinically insignificant cancers are detected in fewer than 20% of men, but nearly 50% of all the cancers detected because of an elevated PSA level are localized, and these patients are candidates for potentially curative therapy. Only a small proportion of prostate cancers detected by PSA testing and treated with radical prostatectomy are low-volume (< 0.2 cm^3) and low-grade (Gleason grade 1-2) tumors. Nearly one third of cancers identified because of PSA screening and treated with radical prostatectomy show evidence of capsular penetration, high Gleason grades (4-5) (see the image below), large tumor volumes, or distant metastases. These prognostic risk factors do not always correlate with survival, but they do increase the possibility of tumor recurrence and progression.

Free, complexed, and total PSA

Free PSA (fPSA) is a major indicator for the diagnosis and management of prostate cancer. However, within the range of 4-10 ng/mL, in which 75% of men do not have cancer, the fPSA level lacks specificity. Stenman et al reported that men with prostate cancer had more complexed prostate-specific antigen (cPSA) than fPSA, unlike men with benign prostatic hyperplasia (BPH). After the development of an immunoassay, the investigators demonstrated that the ratio of fPSA to total PSA (tPSA), or f/tPSA, was lower in men with prostate cancer. In the PSA range of 4-10 ng/mL, tPSA segregates adequately between men with or without cancer. The f/tPSA is a more discriminatory indicator.

For men whose prostates are smaller than 40 cm^3, an f/tPSA of 0.137 or lower is used to detect 90% of the cancers, and 76% of the negative

biopsy findings can be eliminated. For men with prostates larger than 40 cm^3, a cutoff of 0.205 allows detection of 90% of the cancers, and 38% of the negative biopsy findings can be eliminated. If the patient has a normal-sized prostate on digital rectal examination (DRE), a value of 0.234 is necessary to detect 90% of the cancers, sparing 31.3% of the patients an unnecessary biopsy. In a large population of men with PSA levels of 4-10 ng/mL and a cutoff point of 25% or less, 95% of the cancers would be detected, and 20% of the patients would be spared a biopsy.

The fPSA is most useful in men with persistently elevated PSA levels who previously underwent a biopsy with negative findings. As the percentage of fPSA declines, the probability that a cancer is present increases. Conversely, a higher percentage of fPSA indicates a lower probability of cancer. Even with this added information, the decision to perform a biopsy on any given patient ultimately depends on the physician's judgment.

The value of fPSA in the staging of prostate cancer has not been conclusively demonstrated, though several studies indicate that a correlation may exist. In the Baltimore Longitudinal Study of Aging, the f/tPSA significantly segregated those who developed cancer from those who did not up to 15 years before the diagnosis.

The specificity of PSA at levels higher than 4.0 ng/mL is 60-70%. Specificity can be improved by using age-adjusted values, PSA velocity (PSA-V), and the ratio of free PSA (fPSA) to total PSA (tPSA). Another method is to adjust the PSA according to the size of the prostate or volume determinations of the transitional zone, which produces most of the PSA, and the peripheral zone, which produces less PSA but a majority of prostate cancers.

The level of PSA correlates with the detection rate of prostate cancer. Men older than 50 years have a 20-30% possibility of having prostate cancer if their PSA level is higher than 4.0 ng/mL. If the PSA level is between 2.5 and 4.0 ng/mL, a biopsy is likely to detect cancer in 27% of men. For PSA levels greater than 10 ng/mL, the possibility of positive biopsy findings increases to 42-64%.

Even at PSA levels of 4-10 ng/mL, Partin et al found that one half of the patients treated with radical prostatectomy had extraprostatic extension. When the PSA level is higher than 10 ng/mL, the risk of extra prostatic cancer is increased greatly. In the same study, Partin et al noted that 80% of men with PSA levels higher than 20.0 ng/mL had extra prostatic disease.

Recommendations for PSA Testing

According to a 2019 position statement from the European Association of Urology, a baseline PSA test in men aged 45 years at risk of prostate cancer should be used in combination with family history, ethnicity, and other factors to establish individualized screening frequency.

The American Urological Association (AUA) and the American Cancer Society (ACS) offer divergent recommendations on prostate-specific antigen (PSA) screening. The AUA recommends baseline PSA testing, along with digital rectal examination (DRE), at age 40 for all men with a life expectancy of 10 years or more, with subsequent testing intervals determined on the basis of the PSA level and DRE results.

The ACS does not specify an age at which to pursue screening in asymptomatic men with a life expectancy of 10 years or more; rather, the ACS advises clinicians to provide men with information on the risks and benefits of screening so the patient can make an informed decision. In addition, the ACS recommends that men whose initial PSA level is below 2.5 ng/mL can be screened every 2 years, but men with higher PSA values should be tested annually.

In men with a strong family history of prostate cancer, testing should be performed at 6-month intervals. Serially observing PSA levels and performing biopsies on patients whose PSA levels rise by more than 20-25% or 0.75 ng/mL in a year represents typical practice. All patients with PSA levels consistently higher than 4.0 ng/mL should be referred to a urologist for evaluation and a determination of the need for a biopsy.

PSA density

In 1992, in an effort to correlate prostate-specific antigen (PSA) levels with prostate volume, Benson et al introduced the concept of PSA density (PSAD). This concept was based on the knowledge that most PSA is produced in the transitional zone of the prostate; cancer cells produce more PSA per unit volume than benign cells do. PSAD is defined as total PSA (tPSA) divided by prostate volume, as determined by means of transrectal ultrasonography (TRUS).

PSA velocity

In 1992, Carter et al introduced the concept of PSA velocity (PSA-V) in an effort to improve the ability of PSA to detect prostate cancer. PSA-V is used to monitor the change in PSA over time using longitudinal measurements. Greater changes in PSA-V were detected in men with cancer than in those without cancer 5 years before the diagnosis was made. Additional studies have shown that this difference can be detected up to 9 years before prostate cancer diagnosis.

A PSA-V of 0.75 ng/mL or greater per year was suggestive of cancer (72% sensitivity, 95% specificity). A PSA-V of 0.75 ng/mL or greater correlated with the diagnosis of cancer in 72% of the patients, and only 5% had no cancer.

Nevertheless, in some situations, a PSA-V greater than 0.75 ng/mL per year is useful in helping to determine the need for initial or repeat biopsy.

Age-Specific PSA Reference Ranges

An overall specificity of 95% with the following reference ranges:

- Age 40-49 years – 0-2.5 ng/mL
- Age 50-59 years – 0-3.5 ng/mL
- Age 60-69 years – 0-4.5 ng/mL
- Age 70-79 years – 0-6.5 ng/mL

PSA Testing to Monitor Therapy

A pattern of increasing prostate-specific antigen (PSA) levels after local therapy distinguishes between local and distant recurrence. Distant disease can be predicted if the PSA level does not become undetectable after radical prostatectomy, begins to rise within 12 months, or has a doubling time of 6 months. The same characteristics apply to radiation therapy and cryotherapy, although the time to nadir is prolonged.

Patients whose PSA level becomes detectable 24 months or more after radical prostatectomy likely have local recurrence. Patients with PSA doubling times of 12 months or more after surgery, radiation therapy, or cryotherapy are likely to have local recurrence.

The ultrasensitive PSA assays have increased the lead time for identifying biochemical recurrence after definitive local therapy. These assays can measure PSA levels as low as 0.001 ng/mL. Ellis et al reported a 10-fold increased sensitivity in 24 patients who underwent radical prostatectomy. [ ] The patients' PSA levels were previously undetectable on the conventional assays.

Using multivariate analysis, Yu et al demonstrated that ultrasensitive PSA measurement possessed significant advantages over tumor volume and positive surgical margins with respect to the ability to detect early relapse.[4]

After radical prostatectomy

Serial PSA measurements provide the most effective means of detecting early recurrence after radical prostatectomy. Postoperatively, most men have a rapid decline in their PSA levels, which are expected to become undetectable within 1 month.

A PSA level that is elevated after a period during which it was undetectable connotes the presence of prostate cells somewhere in the body. These cells may be from residual normal glandular elements remaining in the bladder wall or at the apex of the prostate, but generally, a detectable and rising PSA level indicates the presence of residual cancer cells. The preoperative PSA level and the interval between surgery and the detection of PSA with standard assays can be used to predict disease-free survival and the pattern of recurrence. Pound et al analyzed data from 1623 men who had a radical prostatectomy and found that the 5-year actuarial recurrence-free rate was 54% for men whose initial PSA levels were greater than 20 ng/mL, 72% for those whose PSA levels were 10.1-20 ng/mL, and 82% for those whose PSA levels were 4.1-10 ng/mL.

After radiation therapy

A consensus has not been reached on what constitutes an acceptable PSA level after radiation therapy. PSA levels decline slowly, and a nadir may not be reached for a median of 17 months. In some patients, a transient rise in the PSA level may occur at 12 months after completion of therapy; the level usually decreases during the subsequent year.

Discussion

Among urologic malignancies, prostate cancer has greatly benefited from the discovery and application of tumor markers. Since its discovery in 1979 to clinical application in the late 1980s, PSA has evolved into an invaluable tool for the detection, staging, and monitoring of men diagnosed with prostate cancer [1,2]. Whereas the majority of prostate cancers in the 1980s and early 1990s commonly arose with an abnormal digital rectal examination (DRE) or elevated PSA, or both, today most prostate cancers arise as clinically non-palpable (stage T1c) disease with a PSA between 4 and 10 ng/mL.

- The elevated serum PSA levels may reflect alterations within the prostate secondary to tissue architectural changes such as cancer, inflammation,or benign prostatic hyperplasia (BPH). Currently, serum PSA levels as low as 2.6 ng/mL are used as a threshold to perform transrectal ultrasound-guided biopsy in Western literature.

Although up to 30% of men presenting with an elevated PSA may be diagnosed following this invasive procedure, as many as 75 to 80% are not found to have cancer. To this end, the application of PSA derivatives such as PSA density, PSA velocity, age-adjusted values, and, more recently, molecular derivatives have attempted to improve the performance of PSA . The lifetime risk (from age 0 to 90 years) of death from prostate cancer is 3% and the lifetime risk of a diagnosis of prostate cancer is 17% (Surveillance, Epidemiology, and End Results [SEER] Program). The incidence of carcinoma prostate varies widely between countries and ethnic populations, and disease rates differ by more than 100-fold between populations.

The lowest yearly incidence rates occur in Asia (1.9 cases per 100,000 in Tianjin, China) and the highest in North America and Scandinavia, especially in African Americans (272 cases per 100,000) [9]. Mortality also varies widely among countries, the highest being in Sweden (23 per 100,000 per year) and the lowest in Asia (< 5 per 100,000 per year in Singapore, Japan, and China) .

conclusion

The positive predictive value of PSA testing for cancer detection increased from 12 to 32% for PSA levels of 4 to 10 ng/mL and as high as 60 to 80% for levels above 10 and 20 ng/mL . Thus, men with PSA levels greater than 10 ng/mL and benign DRE have up to a 60% likelihood of being diagnosed with cancer and are unlikely to benefit from further improvement of PSA sensitivity and specificity. Thus, men with PSA levels greater than 10 ng/mL are encouraged to undergo a biopsy regardless of PSA derivative values. For men with PSA levels between 4 and 10 ng/mL, the specificity of cancer detection has been more challenging. Cancers discovered within this range are often earlier in stage, and potentially curable, yet might represent “insignificant,” potentially non–life-threatening tumors. However, due to the considerable overlap in serum PSA concentrations in men with and without prostate cancer, this range has been described as the diagnostic “gray zone.” Efforts to improve the diagnostic accuracy of PSA within this diagnostic gray zone include PSA density, PSA velocity, and age-specific PSA.

REFERENCES

1. Sensabaugh, G. F. (1978). "Isolation and characterization of a semen-specific protein from human seminal plasma: a potential new marker for semen identification." J Forensic Sci 23(1): 106-115. PubMed
2. Wang, M. C., L. D. Papsidero, et al. (1981). "Prostate antigen: a new potential marker for prostatic cancer." Prostate 2(1): 89-96. PubMed | CrossRef
3. Pound, C. R., P. C. Walsh, et al. (1997). "Radical prostatectomy as treatment for prostate-specific antigen-detected stage T1c prostate cancer." World J Urol 15(6): 373-377. PubMed | CrossRef
4. Pound, C. R., A. W. Partin, et al. (1999). "Natural history of progression after PSA elevation following radical prostatectomy." JAMA 281(17): 1591-1597. PubMed | CrossRef
5. Gretzer, M. B., J. I. Epstein, et al. (2002). "Substratification of stage T1C prostate cancer based on the probability of biochemical recurrence." Urology 60(6): 1034-1039. PubMed | CrossRef
6. Christensson, A., C. B. Laurell, et al. (1990). "Enzymatic activity of prostate-specific antigen and its reactions with extracellular serine proteinase inhibitors." Eur J Biochem 194(3): 755-763. PubMed | CrossRef
7. Christensson, A., T. Bjork, et al. (1993). "Serum prostate specific antigen complexed to alpha 1-antichymotrypsin as an indicator of prostate cancer." J Urol 150(1): 100-105. PubMed
8. Catalona, W. J., M. A. Hudson, et al. (1994). "Selection ofoptimal prostate specific antigen cutoffs for early detection of prostate cancer: receiver operating characteristic curves." J Urol 152(6 Pt 1): 2037-2042. PubMed
9. Quinn, M. and P. Babb (2002). "Patterns and trends in prostate cancer incidence, survival, prevalence and mortality. Part I: international comparisons." BJU Int 90(2): 162-173. PubMed | CrossRef
10. Muir, C. S., J. Nectoux, et al. (1991). "The epidemiology of prostatic cancer. Geographical distribution and timetrends." Acta Oncol 30(2): 133-140. PubMed | CrossRef
11. Landis, S. H., T. Murray, et al. (1999). "Cancer statistics, 1999." CA Cancer J Clin 49(1): 8-31, 31. PubMed
12. Bostwick, D. G., H. B. Burke, et al. (2004). "Human prostate cancer risk factors." Cancer 101(10 Suppl): 2371-2490. PubMed | CrossRef
13. Cooner, W. H., B. R. Mosley, et al. (1988). "Clinical application of transrectal ultrasonography and prostate specific antigen in the search for prostate cancer." J Urol 139(4): 758-761. PubMed
14. Hara M, Inorre T, Fukuyama T. Some physicochemical characteristics of gamma-seminoprotein, an antigenic component specific for human seminal plasma. Jpn J Legal Med. 1971. 25:322-324.
15. Papsidero LD, Wang MC, Valenzuela LA, Murphy GP, Chu TM. A prostate antigen in sera of prostatic cancer patients. Cancer Res. 1980 Jul. 40(7):2428-32. [Medline].
16. Stamey TA, Yang N, Hay AR, et al. Prostate-specific antigen as a serum marker for adenocarcinoma of the prostate. N Engl J Med. 1987 Oct 8. 317(15):909-16. [Medline]..
17 Allan GM, Chetner MP, Donnelly BJ, Hagen NA, Ross D, Ruether JD, et al. Furthering the prostate cancer screening debate (prostate cancer specific mortality and associated risks). Can Urol Assoc J. 2011 Dec. 5(6):416-21. [Medline].
18. THaythorn MR, Ablin RJ. Prostate-specific antigen testing across the spectrum of prostate cancer. Biomark Med. 2011 Aug. 5(4):515-26. [Medline].
19. U.S. Preventive Services Task Force. Screening for prostate cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med. 2008 Aug 5. 149(3):185-91. [Medline].
20. Wolf AM, Wender RC, Etzioni RB, Thompson IM, D'Amico AV, Volk RJ, et al. American Cancer Society guideline for the early detection of prostate cancer: update 2010. CA Cancer J Clin. 2010 Mar-Apr. 60(2):70-98. [Medline]. [Full Text].
21. Lovgren J, Piironen T, Overmo C. Production of recombinant PSA and HK2 and analysis of their immunologic cross-reactivity. Biochem Biophys Res Commun. 1995 Aug 24. 213(3):888-95. [Medline].
22. Oesterling JE, Rice DC, Glenski WJ. Effect of cystoscopy, prostate biopsy, and transurethral resection of prostate on serum prostate-specific antigen concentration. Urology. 1993 Sep. 42(3):276-82. [Medline].
23. Lee F, Littrup PJ. The role of digital rectal examination, transrectal ultrasound, and prostate specific antigen for the detection of confined and clinically relevant prostate cancer. J Cell Biochem Suppl. 1992. 16H:69-73. [Medline].
24. Fortier AH, Nelson BJ, Grella DK, Holaday JW. Antiangiogenic activity of prostate-specific antigen. J Natl Cancer Inst. 1999 Oct 6. 91(19):1635-40. [Medline].
25. Bostwick DG, Pacelli A, Blute M. Prostate specific membrane antigen expression in prostatic intraepithelial neoplasia and adenocarcinoma: a study of 184 cases. Cancer. 1998 Jun 1. 82(11):2256-61. [Medline].
26. Nadler RB, Humphrey PA, Smith DS, et al. Effect of inflammation and benign prostatic hyperplasia on elevated serum prostate specific antigen levels. J Urol. 1995 Aug. 154(2 Pt 1):407-13. [Medline].
27. Carter HB, Pearson JD, Metter EJ. Longitudinal evaluation of prostate-specific antigen levels in men with and without prostate disease. JAMA. 1992 Apr 22-29. 267(16):2215-20. [Medline].
28. Taksler GB, Keating NL, Cutler DM. Explaining racial differences in prostate cancer mortality. Cancer. 2012 Jan 13. [Medline].
29. Gorday W, Sadrzadeh H, de Koning L, Naugler C. Association of sociodemographic factors and prostate-specific antigen (PSA) testing. Clin Biochem. 2014 Aug 14. [Medline].
30. Moul JW, Connelly RR, Mooneyhan RM. Racial differences in tumor volume and prostate specific antigen among radical prostatectomy patients. J Urol. 1999 Aug. 162(2):394-7. [Medline].
31. Morgan TO, Jacobsen SJ, McCarthy WF. Age-specific reference ranges for prostate-specific antigen in black men. N Engl J Med. 1996 Aug 1. 335(5):304-10. [Medline].
32. Hu JC, Williams SB, Carter SC, Eggener SE, Prasad S, Chamie K, et al. Population-based assessment of prostate-specific antigen testing for prostate cancer in the elderly. Urol Oncol. 2014 Jul 10. [Medline].
33. Stenman UH, Leinonen J, Alfthan H. A complex between prostate-specific antigen and alpha 1- antichymotrypsin is the major form of prostate-specific antigen in serum of patients with prostatic cancer: assay of the complex improves clinical sensitivity for cancer. Cancer Res. 1991 Jan 1. 51(1):222-6. [Medline].
34. Brawer MK, Aramburu EA, Chen GL, et al. The inability of prostate specific antigen index to enhance the predictive the value of prostate specific antigen in the diagnosis of prostatic carcinoma. J Urol. 1993 Aug. 150(2 Pt 1):369-73. [Medline].
35. Schroder FH, Roobol-Bouts M, Vis AN. Prostate-specific antigen-based early detection of prostate cancer-- validation of screening without rectal examination. Urology. 2001 Jan. 57(1):83-90. [Medline].
36. Partin AW, Pearson JD, Landis PK, et al. Evaluation of serum prostate-specific antigen velocity after radical prostatectomy to distinguish local recurrence from distant metastases. Urology. 1994 May. 43(5):649-59. [Medline]
37. Gandaglia G, Albers P, Abrahamsson PA, et al. Structured Population-based Prostate-specific Antigen Screening for Prostate Cancer: The European Association of Urology Position in 2019. Eur Urol. 2019 Aug. 76 (2):142-50. [Medline].
38. American Urological Association. Prostate-Specific Antigen Best Practice Statement: 2009 Update. Accessed August 15, 2010. [Full Text].
39. Carter HB, Epstein JI, Chan DW. Recommended prostate-specific antigen testing intervals for the detection of curable prostate cancer. JAMA. 1997 May 14. 277(18):1456-60. [Medline].
40. Benson MC, Whang IS, Olsson CA, et al. The use of prostate specific antigen density to enhance the predictive value of intermediate levels of serum prostate specific antigen. J Urol. 1992 Mar. 147(3 Pt 2):817-21. [Medline].
41. Benson MC, Whang IS, Pantuck A, et al. Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. J Urol. 1992 Mar. 147(3 Pt 2):815-6. [Medline].
42. Seaman EK, Whang IS, Cooner W. Predictive value of prostate-specific antigen density for the presence of micrometastatic carcinoma of the prostate. Urology. 1994 May. 43(5):645-8. [Medline].
43. Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA. 1998 May 20. 279(19):1542-7. [Medline].
44. Zisman A, Leibovici D, Kleinmann J. Predicting CAP in patients with intermediate PSA using modified PSA indices. Can J Urol. 2000 Dec. 7(6):1144-8. [Medline].
45. Kovac E, Carlsson SV, Lilja H, et al. Association of Baseline Prostate-Specific Antigen

Level With Long-term Diagnosis of Clinically Significant Prostate Cancer Among Patients Aged 55 to 60 Years: A Secondary Analysis of a Cohort in the Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial. JAMA Netw Open. 2020 Jan 3. 3 (1):e1919284. [Medline]. [Full Text]..

46. Yu H, Diamandis EP, Wong PY. Detection of prostate cancer relapse with prostate specific antigen monitoring at levels of 0.001 to 0.1 microG./L. J Urol. 1997 Mar. 157(3):913-8. [Medline].
47. Pound CR, Partin AW, Eisenberger MA. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999 May 5. 281(17):1591-7. [Medline].
48. Patel A, Dorey F, Franklin J. Recurrence patterns after radical retropubic prostatectomy: clinical usefulness of prostate specific antigen doubling times and log slope prostate specific antigen. J Urol. 1997 Oct. 158(4):1441-5. [Medline].