



DETECTION OF PROSTATE CANCER AND BENIGN PROSTATIC HYPERPLASIA USING PROSTATE-SPECIFIC ANTIGEN TESTING: A REVIEW OF CLINICAL RESEARCH STUDIES

Md. Azizul Islam^{1&2*}, Md. Jawadul Haque², Mokther Hossain³ and S. M. Shahinul Islam^{1*}

¹Institute of Biological Sciences, University of Rajshahi, Rajshahi-6205, Bangladesh

²Rajshahi Medical College, Rajshahi, Bangladesh

³Khulna Medical College, Khulna, Bangladesh

Abstract

The most often diagnosed diseases in males, prostate cancer (Ca-P) is now the third most common malignancy to cause mortality in different countries of the world. Data showed that serum PSA and prostate volume were demonstrated a substantial log-linear association with age. Numerous studies have demonstrated that the level of fPSA and the ratio of fPSA/total PSA can distinguish between benign and malignant prostatic diseases, with much lower levels in patients with prostate cancer. In a group of 681 LUTS patients, researcher assessed total PSA, fPSA, and prostate volume. The prostate volume significantly correlated with both total serum PSA and free PSA, with $r = 0.51$ ($p < 0.001$) and $r = 0.61$ ($p < 0.001$), respectively. In the range of 10% to 20% of the observed prostate volume, fPSA produced 67% of the anticipated values and 91.2% of the actual results. For intervals of between 10% and 20%, total serum PSA was predicted to increase at rates of 63.0% and 90.9%, respectively. It is known that early-stage prostate cancer tumours release PSA, which can be used as a biomarker to track treatment response and disease progression and to help doctors make treatment decisions. Data shows before surgery, PSA levels can be used to forecast how radical prostatectomy would turn out. Preoperative PSA levels were substantially correlated with advanced, high-grade illness and biochemical markers. The usefulness of PSA as a prognostic indicator declines with prostate cancer progression. As the disease progresses, prostate cancer tumours become significantly more heterogeneous, both between patients and, crucially, within the same patient. This causes variation in tumour PSA expression, which may cause false positive or false negative PSA test findings. In symptomatic patients, PSA has a high sensitivity and a low specificity for the detection of prostate cancer. There is an urgent need for research into the usefulness of PSA for the detection of clinically relevant prostate cancer in primary care.

Key words: Benign prostatic hyperplasia, Prostate cancer, Prostate specific antigen.

Introduction

Benign prostatic hyperplasia (BPH) is a condition in men in which the prostate gland is enlarged and not cancerous. It has been reported that about the BPH affects globally about 210 million males as of 2010 (6% of the population) (Vos et al. 2012). Benign prostatic hyperplasia is also called benign prostatic hypertrophy or benign prostatic obstruction. Benign prostatic hyperplasia is a severe illness affecting middle-aged and geriatric male patients has been reported by Sasidharan et al. (2022) and Islam et al. (2022a,b). This disease normally occurs at the age of 40 or above and is also associated with sexual dysfunction. A diagnosis of BPH

*Author for correspondence: shahinul68@gmail.com & drazizbd@gmail.com

should be based on clinical context, history, absence of any other cause and digital rectal examination. BPH is a benign enlargement of the prostate brought on by cellular hyperplasia in the transitional zone (Fig. 1, A-B). In the United States, 32% of new cases of male cancer are of the prostate, making it the most frequent cancer in males (Wingo et al. 1997). The prostate gland is the male secondary sexual organ that is most frequently affected by benign or malignant neoplasia. One of the most common malignancies in men is prostate cancer (Ca-P), which is currently the third highest cause of cancer-related death in Western nations (Buck and Berry 1987, Islam et al. 2023).

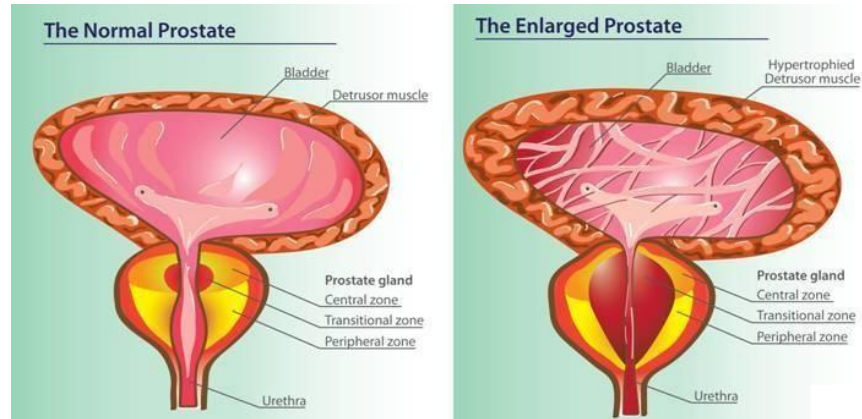
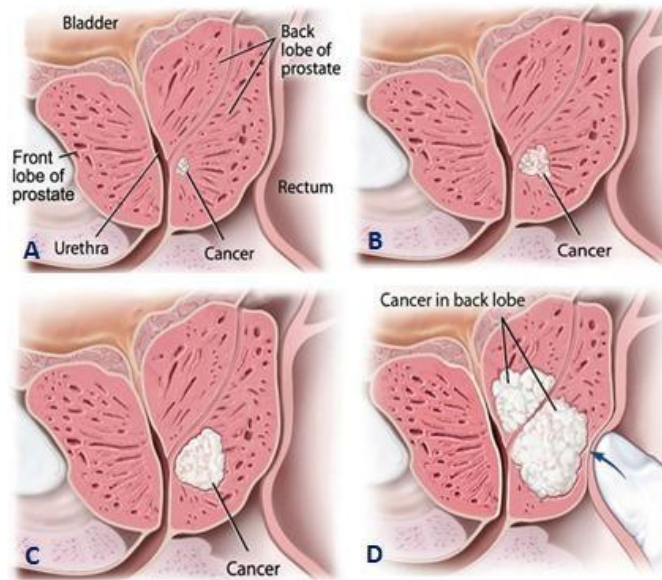


Fig. 1 (A-B): Diagrammatic representation of BPH with the enlarged prostate transition zone causing obstruction of the prostatic urethra and the secondary changes in the bladder leading to hypertrophy of the detrusor muscle (<https://www.ncbi.nlm.nih.gov/books/NBK279008/>).

Prostate cancer (PCa) can be detected using serum prostate-specific antigen (PSA), which enables doctors to monitor patients' responses to cancer treatment (Cooner et al. 1990). However, early PCa investigations typically combine a DRE (digital rectal examination) and PSA level assessment. Different stages of early prostate cancer are illustrated in Fig. 2. In this it Fig. A and B shows the cancer is so small it can't be felt during a DRE. Fig. C and D shows the cancer is most often found by accident (<https://www.dovemed.com/classification-disorders-and-tumors/benign-and-malignant-tumors-prostate>).



Figs. 2(A-D): Different stages (of early prostate cancer).

These measurements may be used to recommend a biopsy that is being guided by transrectal ultrasound (TRUS). Although PSA has greatly increased the number of people with PCa who have been diagnosed, one of the biggest challenges for doctors is to distinguish PCa from non-malignant diseases. Therefore, it is evident that more precise methods are required to risk stratify males who exhibit PCa symptoms in order to avoid over diagnosis and unnecessary treatment of patients with benign illnesses. If successfully adopted in primary care, this will lower patient over diagnosis rates and release strain on healthcare providers' budgets and management systems. Recent studies indicate that this categorization is probably based on the discovery of trustworthy biomarkers that can replace the existing method of diagnosing PCa with PSA measurement. Biomarkers could help distinguish between BPH and PCa are presented and evaluated. Around 50% of men in their fifties, 70% of men in their seventies, and 90% of men in their eighties have BPH (Skinder et al. 2016, McVary 2006). Lower urinary tract infections (LUTIs), urethral blockage, and prostate size growth are all consequences of prostatic cell proliferation. Age, diminished testicular function, metabolic syndrome, a familial history of BPH, and obesity are all risk factors for BPH (Skinder et al. 2016). Although the underlying pathophysiology linking BPH and PCa is yet unknown, some research has looked into this relationship (Chokkalingam et al. 2003, Schenk et al. 2011).

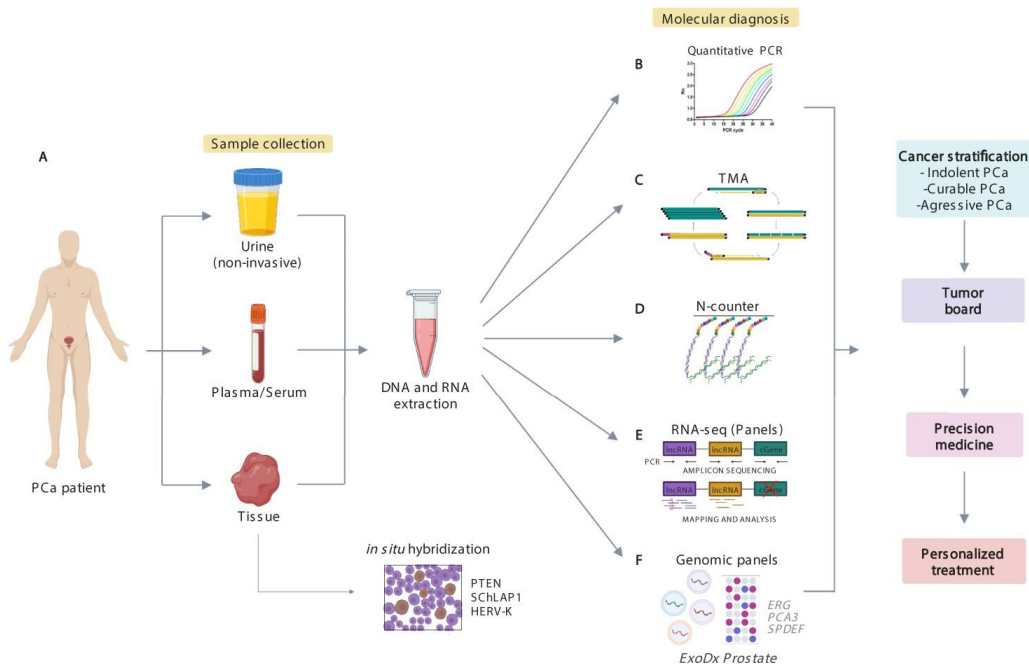


Fig. 3: A) Sample collection, B) Quantitative PCR (qPCR), C) Transcription Mediated Amplification (TMA), D) N-counter. E RNA Sequencing, F) There is also genomic panels used for the diagnostic of PCa focused on specific biomarkers, such as the commercial test ExoDx Prostate (<https://www.nature.com/articles/s41391-022-00537-2>).

BPH was linked to a higher risk of PCa, according to a meta-analysis of 19 studies involving 15,899 patients, risk ratio (RR) 2.93, (95% CI = 1.88-4.56), $p < 0.0000$. The scientists showed that, when compared to Caucasians, the connection between BPH and PCa was greater in Asian populations (RR 6.09 and 1.54, respectively). The authors also asserted that metabolic syndrome, inflammation, and hormones are likely to be involved in the pathophysiology of BPH (Dai et al. 2016). There is evidence that BPH patients frequently experience disruptions in the balance between prostate cell proliferation and cell death, which is maintained by dihydrotestosterone (DHT) and estrogen (Hendriksen et al. 2006). Additionally, those with aggressive BPH have a higher probability of getting PCa than people without the condition, and the cancer they get as a result may be high grade (Hammarsten and Högstedt 2004). The evidence does support the concept that BPH is a risk factor implicated in the pathogenesis of PCa, even though the majority of the findings are hypothesis-generating rather than hypothesis-confirming (Ørsted and Bojesen 2013, Alcaraz et al. 2009). Nevertheless, despite this evidence, it is not always the case that BPH will develop into PCa in a particular person. Therefore, it's critical to be able to identify BPH sufferers early on to spare these people from future invasive and pointless procedures. New biomarkers are needed to improve patient risk classification at this point because PSA testing alone cannot make this distinction.

Methodology

The data mainly involve a critical review of various studies from sample groups of different ethnicities and age groups were evaluated.

Prostate specific antigen

One of the most frequently used biomarkers for the detection and treatment of PCa at the moment is PSA. Prior to PSA measurement, DRE was mostly used to predict PCa. However, DRE has limited sensitivity and specificity as a diagnostic tool, and clinician subjectivity when doing the examination (Gosselaar et al. 2008). In order to assess how well patients were responding to curative medication, PSA testing was launched in the United States in 1987. This was a definite diagnostic advancement. Soon after, PSA was introduced for PCa risk-assessing patients, which increased disease detection and decreased mortality (Alberts et al. 2015). To assist liquefy ejaculate and promote sperm motility, the prostate's epithelial cells release PSA, a serine protease that resembles kallikrein. The periurethral glands are the primary source of extra prostatic PSA generation, which results in detectable PSA levels in the serum. Following a study on healthy males, Hybritech Inc. of San Diego was the first business to suggest a serum PSA threshold of 4.0 ng/ml. After then, the industry norm for recommending a prostate biopsy was a PSA reading of >4.0 ng/ml. Since the implementation of this cutoff, studies have indicated that PSA testing has a sensitivity of 67-80% and has assisted in the diagnosis of a significant percentage of patients with PCa (Duskova and Vesely 2015). PSA is an organ-specific biomarker, however it is not a cancer-specific biomarker. Serum PSA levels can increase as a result of BPH and other disorders, such as prostatitis, an inflammation of the prostate. Contrarily, males with normal PSA levels who present have been shown to have PCa (Alberts 2015). As a result, the lack of specificity in PSA can result in over diagnosis of PCa and overtreatment. According to information compiled by the Surveillance, Epidemiological and End Results (SEER) registry, PSA-based PCa screening has led to an estimated 28% of over diagnosed cases in the USA (Etzioni et. al, 2013). Similarly, it was projected by the European Randomized Study of Screening for Prostate Cancer (ERSPC) experiment that utilizing PSA as a PCa screening tool resulted in over diagnosis in 50% of patients (Hsing et al. 2003). Actively diagnosing a clinically insignificant tumor may result in treatment that is not essential, like as radiation or a radical prostatectomy. Healthcare professionals are using the active surveillance approach to prevent this, which minimizes the risk of over diagnosis by combining routine PSA and DRE testing with biopsies over time. Regular exams and repeated prostate biopsies, however, are intrusive and may cause the patient great discomfort. Unsurprisingly, this can result in extreme anxiety and tension, which may deter the patient from seeking any kind of medical care (Alberts et al. 2015). Age-related increases in serum PSA levels are well-known. This is most likely a result of the larger prostate that comes with ageing, as well as the prostatic epithelium's diminished retention. Age-specific PSA has been proven to increase the frequency of biopsies conducted by 45% while also increasing the detection of PCa in younger men (50-59 years) by 15%. Numerous researches have looked into more precise measures of PSA expression to assist overcome these problems and enhance its value for PCa diagnosis. Significant study has shown that the ratios of free-to-total PSA in serum may increase the diagnostic specificity by 20% to 30% when compared to total PSA (tPSA) (De Angelis 2007).

ProPSA's [-2] isoform has become a promising biomarker since it can distinguish between PCa and BPH, where PCa's levels seem to be higher than those of BPH. In a significant prospective study of patients with PCa, the percentage of [-2] proPSA increased the specificity to 44.9% from total and free PSA, which were respectively 30.8% and 34.6%, while simultaneously reaching a sensitivity of 80% for PCa detection (Sokoll et al. 2010). PSA density is estimated by dividing the prostatic volume (ml) by the tPSA concentration (ng/ml). After finding that a cut-off of 0.10 ng/ml² resulted in a detection rate of 77% of Gleason score 7 tumors compared to tPSA alone, 64% (n = 947). Nordström et al. (2018) recommended that PSA density might guide doctors more on biopsy decisions. Additionally, after determining that the marker was crucial for the diagnosis of aggressive PCa, Verma et al. (2014) and Sebastianelli et al. (2019) both proposed using PSA density to avoid needless biopsies (Verma 2014, Sebastianelli et al. 2019). There are still a lot of restrictions with the way that PSA measurement is currently done to diagnose PCa. Based on population-

based estimations, the benefit-to-harm ratio of the PSA test is negative. Individualized PSA-based screening appears to have a bright future as a part of multivariate risk stratification, which is done by utilizing various nomograms and risk prediction algorithms. The present aim is to find other biomarkers that may be utilized in primary care alongside PSA to distinguish BPH from PCa (Alberts et al. 2015).

Total serum PSA and BPH progression

Several studies have shown a connection between total serum PSA and BPH progression, which is determined by prostate growth, worsening of LUTS, or the emergence of quantifiable clinical events such as AUR or BPH-related surgical treatments. The capacity of blood PSA to predict prostate volume was investigated in a study that included 4448 participants from several trials conducted in Europe and North America (Roehrborn et al. 1999). Ages of the patients in this combined cohort ranged from 40 to 79, and they all had BPH diagnoses but no prostate cancer. Both serum PSA and prostate volume demonstrated a substantial log-linear association with age. To identify which men were most likely to have a prostate volume greater than 30, 40, or 50 ml, specific thresholds for total serum PSA levels were established using age-corrected curves and the receiver operating characteristic (ROC). With a threshold serum PSA of greater than or equal to 1.6, 2.0, or 2.3 ng/ml for men in their fifth, sixth, or seventh decades, respectively, and a predicted prostate volume of greater than or equal to 40 ml (assuming a specificity of 0.70 and a sensitivity of 0.65-0.70, the area under the curve (AUC) for all ages combined ranged from 0.75 to 0.77. This was the first comprehensive study to demonstrate a substantial relationship between prostate volume and blood PSA levels in BPH-affected males. The slope of the correlation between age on the x-axis and serum PSA on the y-axis dramatically rose as men's ages grew.

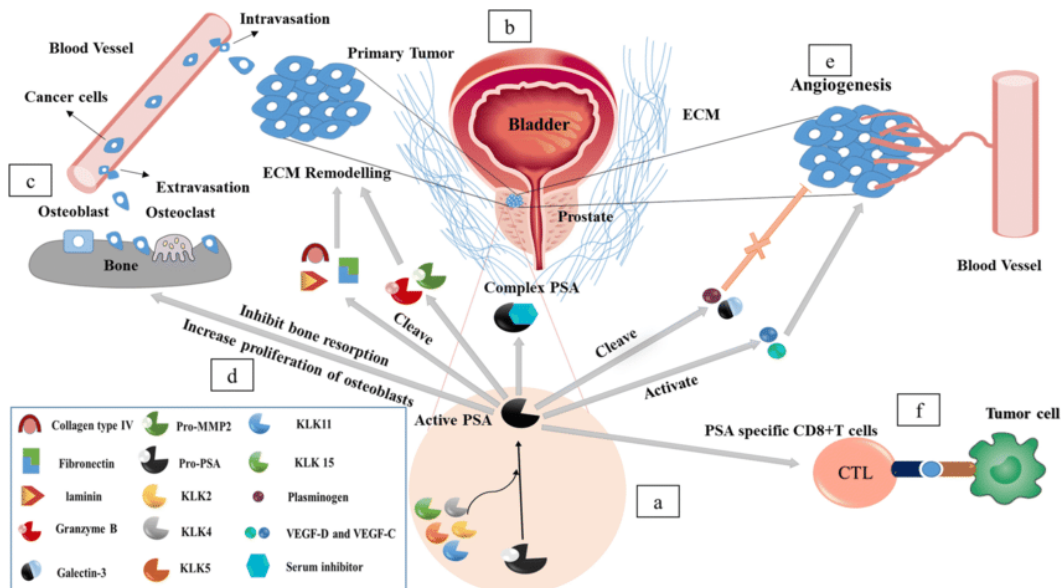


Fig. 4 (a-f): a) Other KLKs such as KLK2, KLK4, KLK5, KLK11, and KLK15 can cleave pro-PSA and release active PSA, b) PSA cleaves proteins including collagen type IV, fibronectin, and laminin and is able to activate Granzyme B and pro-MMP2 leading to ECM remodeling, c) PSA has been shown to be involved in the EMT process leading to metastasis of the primary tumor, d) PSA also has a potential to inhibit bone resorption leading to osteogenesis. Exposure of osteoblasts to PSA in vitro led to cell proliferation, e) PSA

cleaves plasminogen leading to inhibition of new endothelial tube formation and thus angiogenesis inhibition. PSA cleaves galectin-3, a mediator of VEGF and basic bFGF-mediated angiogenic response. In contrast, PSA activates tumor-derived VEGF-C and VEGF-D which may lead to the production of angiogenic and lymph-angiogenic tumors, f) PSA-specific epitopes can activate CTLs leading to the killing of the cancer cells, thus has a role to play in the immune response. (https://www.researchgate.net/figure/PSA-has-a-multi-faceted-role-in-prostate-cancer-progression-a-Other-KLKs-such-as-KLK2_fig1_336862214).

fPSA and BPH progression

Numerous studies have demonstrated that the level of fPSA and the ratio of fPSA/total PSA can distinguish between benign and malignant prostatic diseases, with much lower levels in patients with prostate cancer (Catalona et al. 2000). In a group of 681 LUTS patients, Morote et al. (2000) assessed total PSA, fPSA, and prostate volume. The prostate volume significantly correlated with both total serum PSA and free PSA, with $r = 0.51$ ($P 0.001$) and $r = 0.61$ ($P 0.001$), respectively. In the range of 10% to 20% of the observed prostate volume, fPSA produced 67% of the anticipated values and 91.2% of the actual results. For intervals of between 10% and 20%, total serum PSA was predicted to increase at rates of 63.0% and 90.9%, respectively (Morote et al. 2000).

PSA as a marker of prostate cancer disease progression

There is continuous discussion regarding the significance of PSA as a prognostic indicator in men who have been diagnosed with prostate cancer, in addition to the issue surrounding PSA-based screening.

PSA as a prognostic factor in early-stage prostate cancer

It is known that early-stage prostate cancer tumors release PSA, which can be used as a biomarker to track treatment response and disease progression and to help doctors make treatment decisions. Before surgery, PSA levels can be used to forecast how radical prostatectomy would turn out. Preoperative PSA levels were substantially correlated with advanced, high-grade illness and biochemical markers (Freedland et al. 2005).

Other studies have demonstrated that PSA is a long-term, independent predictor of all pathologic stages of prostate cancer (Chun et al. 2007). Monitoring PSA levels after treatment for localized prostate cancer enables early detection of recurring cancer before any other method might. Particularly, it has been demonstrated that the PSA doubling time (PSA-DT) stratifies the risk of clinical progression for males whose PSA is growing following aggressive treatment (Freedland et al. 2005, D'amico et al. 2004). These studies show that PSA predicts whether a patient will develop advanced prostate cancer after receiving treatment.

PSA as a prognostic factor in advanced prostate cancer

The usefulness of PSA as a prognostic indicator declines with prostate cancer progression. The tumour may grow without an accompanying rise in PSA levels, either because little PSA is produced (for example, because tumour cells have dedifferentiated) or because PSA production is being inhibited by antiandrogen therapy. As the disease progresses, prostate cancer tumours become significantly more heterogeneous, both between patients and, crucially, within the same patient. This causes variation in tumour PSA expression, which may cause false positive or false negative PSA test findings (Shah et al. 2004).

Relevant studies

A study named "Metabolomics Profiling Discriminates Prostate Cancer from Benign Prostatic Hyperplasia within the Prostate-Specific Antigen Gray Zone" showed Lipid metabolism was linked to the most highly enriched pathways in PCa participants, including glycerophospholipid and glycolipid metabolisms. Lipids and lipid-like compounds were the predominant metabolites within the top 50 differential metabolites selected

using fold-change threshold >1.5 or $<2/3$, variable importance in projection (VIP) > 1 , and Student's t-test threshold $p < 0.05$. Eighteen lipid or lipid-related metabolites were selected including 4-oxoretinol, anandamide, palmitic acid, glycerol 1-hexadecanoate, DL-dihydrosphingosine, 2-methoxy-6Z-hexadecenoic acid, 3-oxo-nonadecanoic acid, 2-hydroxy-nonadecanoic acid, N-palmitoyl glycine, 2-palmitoylglycerol, hexadecenal, D-erythro-sphingosine C-15, N-methyl arachidonoyl amine, 9-octadecenal, hexadecyl acetyl glycerol, 1-(9Z-pentadecenoyl)-2-eicosanoyl-glycero-3-phosphate, 3Z,6Z,9Z-octadecatriene, and glycidyl stearate. Selected metabolites effectively discriminated PCa from BPH when PSA levels were in the range of 4–10 ng/ml (area under the curve is >0.80). Notably, the 18 identified metabolites were negatively corrected with total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and Apo-B levels in PCa patients; and some were negatively correlated with high-density lipoprotein cholesterol (HDL-C) and Apo-A levels. However, the metabolites were not correlated with triglycerides (TG). The results of this study show that metabolic reprogramming, particularly in lipid metabolism, is a crucial characteristic of PCa. With a PSA level in the grey range of 4-10 ng/ml, the 18 lipid or lipid-associated metabolites discovered in this study could be used as diagnostic indicators for differentiating between PCa patients and BPH sufferers (Xu et al. 2021).

A previous study showed, after de-duplication, 563 search results were evaluated by title and abstract, and 75 full-text papers were examined. Nineteen studies were eligible for inclusion, of which one was from a screening study cohort and 18 were carried out in secondary care settings. Transrectal ultrasound-guided biopsy (TRUS), typically only performed on patients with increased PSA levels or abnormal prostate exams, was the reference test utilized in all investigations. The estimated sensitivity of PSA for prostate cancer was 0.93 (95% CI 0.88, 0.96) and the estimated specificity was 0.20 (95% CI 0.12, 0.33) based on data compiled from 14,489 patients. The hierarchical summary receiver operator characteristic curve's area under it had a 95% confidence interval of 0.72 (0.68, 0.76). At least one QUADAS-2 domain was found to have a significant risk of bias for every study. This study concluded that, PSA is quite sensitive but not very specific for detecting prostate cancer in symptomatic patients. The certainty of this estimate is however diminished by substantial flaws in the reference test and research design. The majority of PSA testing is done in primary care, where there is very little evidence to support its use (Merriel et al. 2022).

A study by Jung et al. (2000) titled Role of free to total prostate specific antigen ratio in serum in the diagnosis of prostatic enlargement revealed that, in order to distinguish BPH from prostate cancer, serum PSA and the free/total PSA ratio must differ in a highly significant way. Free/total PSA ratio was highly significant in differentiating between BPH and carcinoma prostate ($p < 0.001$) and carcinoma prostate and control ($p < 0.001$). Free/total PSA ratio decreased biopsies by 81-85% in BPH and prostate cancer, respectively, in patients with somewhat high PSA. When separating BPH from prostate cancer, total PSA and free/total PSA performed substantially better overall in terms of specificity, positive predictive value, and efficiency (Jung et al. 2000).

A study by Benson et al. (1992) showed that in order to be helpful in the routine evaluation of prostate disease, isolated prostate specific antigen (PSA) tests in asymptomatic individuals have not shown appropriate sensitivity and specificity. They have employed a ratio of serum PSA and prostate volume, or prostate specific antigen density (PSAD), to improve the precision of serum PSA. Prostate volume in this study was calculated from magnetic resonance imaging determinations of benign prostatic hypertrophy (BPH) or from the dimensions of the surgical specimen of cancer using the formula, length \times width \times depth \times 0.5 = volume. A total of 61 patients with prostatic disease clinically confined to the prostate glands (41 with prostate cancer undergoing radical prostatectomy and 20 with BPH) were evaluated. The mean PSAD for prostate cancer was 0.581 while that for BPH was 0.044 ($p < 0.002$). No patient with BPH had a PSAD of greater than 0.117 and only 1 patient had a density of 0.1 or greater. Of 34 patients with a PSAD of 0.1 or greater 33 had prostate cancer. Only 2 of the 41 prostate cancer patients and 14 of the BPH patients had a

PSAD of 0.05 or less. There were 11 patients with a PSAD of greater than 0.05 and less than 0.1, including 6 with prostate cancer (1 with P0 disease) and 5 with BPH. Of the 6 prostate cancer patients 5 had a PSA of 4.0 or less and among the 5 patients with BPH 4 had a serum PSA of greater than 4.0 and 1 had a PSA of greater than 10. These results suggest that PSAD may be useful in distinguishing BPH and prostate cancer.

Implications for research and practice

National recommendations advise using the PSA test as part of the evaluation of patients with LUTS to check for the existence of prostate cancer, mostly in a primary care setting (Mottet et al. 2021, Carter et al. 2013). It is well recognized that there is a paucity of primary care evidence for the use of PSA to diagnose prostate cancer, but this is not the only ailment for which secondary care evidence has been used to inform primary care recommendations (Funston et al. 2020). Despite this, there is a significant knowledge gap since secondary care data (or screening data) do not transition to primary care due to spectrum bias. To remedy this vacuum, high-quality research in primary care populations are required. Future studies should report not only on prostate cancer specifically but also on cancer that is clinically important. The development of multiparametric magnetic resonance imaging and other improved prostate cancer detection procedures (Merriell et al. 2022). Greater understanding of PSA's significance in the early diagnosis of symptomatic prostate cancer is required. Incorporating extra pertinent clinical data into multivariable risk models could help improve PSA performance (Ferraro et al. 2021). Nevertheless, just one has been approved for use in primary care (Aladwani et al. 2020). Clinical recommendations recommend having a balanced conversation with patients about the potential benefits and drawbacks of using PSA testing to diagnose prostate cancer. Primary care providers are generally aware of the limits of PSA testing (Evans et al. 2007, Roland et al. 2018). Numerous PSA alternatives have been studied in-depth and while some show promise in terms of boosting detection confidence for prostate cancer, none have yet made their way into primary care settings (Eldred-Evans et al. 2021, Kim et al. 2020).

Conclusion

In symptomatic patients, PSA has a high sensitivity and a low specificity for the detection of prostate cancer. There were no studies that evaluated the accuracy of PSA in a primary care population since published research suffer from a number of biases that presumably overstate its accuracy. There is an urgent need for research into the usefulness of PSA for the detection of clinically relevant prostate cancer in primary care. Such a study's main objective would be to identify patients with cancer who required severe treatments while preventing the problem of over diagnosis of clinically unimportant prostate cancer from getting worse.

References

- Aladwani M, Lophatananon A, Ollier W and Muir K (2020). Prediction models for prostate cancer to be used in the primary care setting: a systematic review. *BMJ Open* 10(7): 034661.
- Alberts AR, Schoots IG and Roobol MJ (2015). Prostate-specific antigen-based prostate cancer screening: past and future. *International Journal of Urology* 22(6): 524-532.
- Alcaraz A, Hammerer P, Tubaro A, Schröder FH and Castro R (2009). Is there evidence of a relationship between benign prostatic hyperplasia and prostate cancer? Findings of a literature review. *European Urology* 55(4): 864-875.
- Benson MC, Whang IS, Pantuck A, Ring K, Kaplan SA, Olsson CA and Cooner WH (1992). Prostate specific antigen density: a means of distinguishing benign prostatic hypertrophy and prostate cancer. *The Journal of Urology* 147(3): 815-816.
- Buck ER and Berry SJ (1987). DNA synthetic in the canine prostate. Effects of androgen and estrogen treatment. *Prostate* 10: 45-56.

- Carter HB, Albertsen PC, Barry MJ, Etzioni R, Freedland SJ, Greene KL, Holmberg L, Kantoff P, Konety BR, Murad MH and Penson DF (2013). Early detection of prostate cancer: AUA Guideline. *The Journal of Urology* 190(2): 419-426.
- Catalona WJ, Southwick PC, Slawin KM, Partin AW, Brawer MK, Flanigan RC, Patel A, Richie JP, Walsh PC, Scardino PT and Lange PH (2000). Comparison of percent free PSA, PSA density, and age-specific PSA cutoffs for prostate cancer detection and staging. *Urology* 56(2): 255-260.
- Chokkalingam AP, Nyrén O, Johansson JE, Gridley G, McLaughlin JK, Adami HO and Hsing AW (2003). Prostate carcinoma risk subsequent to diagnosis of benign prostatic hyperplasia: A population-based cohort study in Sweden. *Cancer: Interdisciplinary International Journal of the American Cancer Society* 98(8): 1727-1734.
- Chun FKH, Briganti A, Gallina A, Hutterer GC, Shariat SF, Antebie E, Walz J, Roehrborn C, Salonia A, Rigatti P, Saad F, Huland H, Montorsi F, Graefen M and Karakiewicz PI (2007). Prostate-specific antigen improves the ability of clinical stage and biopsy Gleason sum to predict the pathologic stage at radical prostatectomy in the new millennium. *European Urology* 52(4): 1067-1075.
- Cooner WH, Mosley BR, Rutherford Jr, CL, Beard JH, Pond HS, Terry WJ, Igel TC and Kid DD (1990). Prostate cancer detection in a clinical urological practice by ultrasonography, digital rectal examination and prostate specific antigen. *The Journal of Urology* 143(6): 1146-1152.
- Dai X, Fang X, Ma Y and Xianyu J (2016). Benign prostatic hyperplasia and the risk of prostate cancer and bladder cancer: a meta-analysis of observational studies. *Medicine* 95(18): e3493.
- D'amico AV, Moul J, Carroll PR, Sun L, Lubeck D and Chen MH (2004). Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. *The Journal of Urology* 172(5S): S42-S47.
- De Angelis G, Rittenhouse HG, Mikolajczyk SD, Shamel LB and Semjonow A (2007). Twenty years of PSA: from prostate antigen to tumor marker. *Reviews in Urology* 9(3): 113-123.
- Duskova K and Vesely S (2015). Prostate specific antigen. Current clinical application and future prospects. *Biomedical Papers of the Medical Faculty of Palacky University in Olomouc*, 159(1): 018-026.
- Eldred-Evans D, Burak P, Connor MJ, Day E, Evans M, Fiorentino F, Gammon M, Hosking-Jervis F, Klimowska-Nassar N, McGuire W and Padhani AR (2021). Population-based prostate cancer screening with magnetic resonance imaging or ultrasonography: the IP1-PROSTAGRAM study. *JAMA Oncology* 7(3): 395-402.
- Etzioni R, Gulati R, Cooperberg MR, Penson DM, Weiss NS and Thompson IM (2013). Limitations of basing screening policies on screening trials: the US Preventive Services Task Force and prostate cancer screening. *Medical Care* 51(4): 295.
- Evans R, Edwards AG, Elwyn G, Watson E, Grol R, Brett J and Austoker J (2007). It's a maybe test': men's experiences of prostate specific antigen testing in primary care. *British Journal of General Practice* 57(537): 303-310.
- Ferraro S, Bussetti M, Bassani N, Rossi RS, Incarbone GP, Bianchi F, Maggioni M, Runza L, Ceriotti F and Panteghini M (2021). Definition of outcome-based prostate-specific antigen (PSA) thresholds for advanced prostate cancer risk prediction. *Cancers* 13(14): 3381.
- Freedland SJ, Humphreys EB, Mangold LA, Eisenberger M, Dorey FJ, Walsh PC and Partin AW (2005). Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. *Journal of the American Medical Association* 294(4): 433-439.

- Funston G, Hamilton W, Abel G, Crosbie EJ, Rous B and Walter FM (2020). The diagnostic performance of CA125 for the detection of ovarian and non-ovarian cancer in primary care: A population-based cohort study. *PLoS Medicine* 17(10): 1003295.
- Gosselaar C, Kranse R, Roobol MJ, Roemeling S and Schröder FH (2008). The interobserver variability of digital rectal examination in a large randomized trial for the screening of prostate cancer. *The Prostate* 68(9): 985-993.
- Hammarsten J and Högstedt B (2004). Clinical haemodynamic, anthropometric metabolic and insulin profile of men with high-stage and high-grade clinical prostate cancer. *Blood Pressure* 13(1): 47-55.
- Hendriksen PJ, Dits NF, Kokame K, Veldhoven A, Van Weerden WM, Bangma CH, Trapman J and Jenster G (2006). Evolution of the androgen receptor pathway during progression of prostate cancer. *Cancer Research* 66(10): 5012-5020.
- Hsing AW, Gao YT, Chua Jr S, Deng J and Stanczyk FZ (2003). Insulin resistance and prostate cancer risk. *Journal of the National Cancer Institute* 95(1): 67-71.
- Islam MA, Haque MJ and Islam SMS (2022a). The role of free prostate-specific antigen in the diagnosis of prostate carcinoma: A cross-sectional study in Rajshahi, Bangladesh. *Journal of Bio-Science*, 30(1): 79-89.
- Islam MA, Haque MJ, Hossain MM and Islam SMS (2022b). Prospective analysis of percent free prostate-specific antigen as a better predictor of early diagnosis of prostate cancer. *Journal of Bio-Science*, 30(2): 67-77.
- Islam MA, Haque MJ, Hossain MM and Islam SMS (2023). Ability of free/total serum PSA ratio in diagnosing prostate cancer and benign prostatic hyperplasia. *TAJ- The Journal of Teachers Association RMC, Rajshahi*, 36(2): 101-109.
- Jung K, Elgeti U, Lein M, Brux B, Sinha P, Rudolph B, Hauptmann S, Schnorr D and Loening SA (2000). Ratio of free or complexed prostate-specific antigen (PSA) to total PSA: which ratio improves differentiation between benign prostatic hyperplasia and prostate cancer?. *Clinical Chemistry* 46(1): 55-62.
- Kim L, Boxall N, George A, Burling K, Acher P, Aning J, McCracken S, Page T and Gnanapragasam VJ (2020). Clinical utility and cost modelling of the phi test to triage referrals into image-based diagnostic services for suspected prostate cancer: the PRIM (Phi to Refine MRI) study. *BMC Medicine* 18(1): 1-9.
- McVary KT (2006). BPH: epidemiology and comorbidities. *The American Journal of Managed Care* 12(5 Suppl): S122-8.
- Merriel SW, Pocock L, Gilbert E, Creavin S, Walter FM, Spencer A and Hamilton W (2022). Systematic review and meta-analysis of the diagnostic accuracy of prostate-specific antigen (PSA) for the detection of prostate cancer in symptomatic patients. *BMC Medicine* 20(1): 1-11.
- Morote J, Encabo G, Lopez M and De Torres IM (2000). Prediction of prostate volume based on total and free serum prostate-specific antigen: is it reliable? *European Urology* 38(1): 91-95.
- Mottet N, Van den Bergh RC, Briers E, Van den Broeck T, Cumberbatch MG, De Santis M, Fanti S, Fossati N, Gandaglia G, Gillessen S and Grivas N (2021). EAU-EANM-ESTRO-ESUR-SIOG guidelines on prostate cancer-2020 update. Part 1: screening, diagnosis, and local treatment with curative intent. *European Urology* 79(2): 243-262.
- Nordström T, Akre O, Aly M, Grönberg H and Eklund M (2018). Prostate-specific antigen (PSA) density in the diagnostic algorithm of prostate cancer. *Prostate Cancer and Prostatic Diseases* 21(1): 57-63.
- Ørsted DD and Bojesen SE (2013). The link between benign prostatic hyperplasia and prostate cancer. *Nature Reviews Urology* 10(1): 49-54.

- Roehrborn CG, Boyle P, Gould AL and Waldstreicher J (1999). Serum prostate-specific antigen as a predictor of prostate volume in men with benign prostatic hyperplasia. *Urology* 53(3): 581-589.
- Roland M, Neal D and Buckley R (2018). What should doctors say to men asking for a PSA test? *The BMJ* 362. Doi: <https://doi.org/10.1136/bmj.k3702>.
- Sasidharan S, Srinivasakumar KP, Poddar S, Bhaumik A, Das SK and Nair HJ (2022). Benign prostatic hyperplasia (BPH): A comprehensive analysis of the malaise and summarizing possible management options through phytotherapeutic agents. *Health Journal* 17(2): 81-88.
- Schenk JM, Kristal AR., Arnold KB, Tangen CM, Neuhauser ML, Lin DW, White E and Thompson IM (2011). Association of symptomatic benign prostatic hyperplasia and prostate cancer: results from the prostate cancer prevention trial. *American Journal of Epidemiology* 173(12): 1419-1428.
- Sebastianelli A, Morselli S, Vitelli FD, Gabellini L, Tasso G, Venturini S, Cito G, Vignolini G, Raspollini MR, Gacci M and Serni S (2019). The role of prostate-specific antigen density in men with low-risk prostate cancer suitable for active surveillance: results of a prospective observational study. *Prostate International* 7(4): 139-142.
- Shah RB, Mehra R, Chinnaiyan AM, Shen R, Ghosh D, Zhou M, MacVicar GR, Varambally S, Harwood J, Bismar TA and Kim R (2004). Androgen-independent prostate cancer is a heterogeneous group of diseases: lessons from a rapid autopsy program. *Cancer Research* 64(24): 9209-9216.
- Skinder D, Zacharia I, Studin J and Covino J (2016). Benign prostatic hyperplasia: A clinical review. *Journal of the American Academy of Physician Assistants* 29(8): 19-23.
- Sokoll LJ, Sanda MG., Feng Z, Kagan J, Mizrahi IA, Broyles DL, Partin AW, Srivastava S, Thompson IM, Wei JT and Zhang Z (2010). A prospective, multicenter, National Cancer Institute Early Detection Research Network study of [-2] proPSA: improving prostate cancer detection and correlating with cancer aggressiveness. *Cancer Epidemiology, Biomarkers and Prevention* 19(5): 1193-1200.
- Verma A, Onge JS, Dhillon K and Chorneyko A (2014). PSA Density Improves Prediction of Prostate Cancer. *Canadian Journal of Urology* 21(3): 7312-21.
- Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M et al. (2012). Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010". *Lancet* 380(9859): 2163-2196. doi:10.1016/S0140-6736(12)61729-2.
- Wingo PA, Landis S and Ries LA (1997). An adjustment to the 1997 estimate for new prostate cancer cases. *Cancer: Interdisciplinary International Journal of the American Cancer Society* 80(9): 1810-1813.
- Xu B, Chen Y, Chen X, Gan L, Zhang Y, Feng J and Yu L (2021). Metabolomics profiling discriminates prostate cancer from benign prostatic hyperplasia within the prostate-specific antigen gray zone. *Frontiers in Oncology* 11: 730638.

(Manuscript received on 15th September 2023 and revised on 9th November 2023)