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Study of Prostate Specific Antigen, Alkaline Phosphatase and Vitamin B12 in Prostate Cancer

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Authors' contributions

This work was carried out in collaboration between all authors. Author RVB designed the study and collected the data. Author SMD managed the literature searches and wrote the first draft of the manuscript. Author NY performed the statistical analysis and computations. Author VWP drafted the manuscript and managed the analyses of the study. Author LGA selected subjects for the study. All authors read and approved the final manuscript.

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ABSTRACT

Objective: This study aimed to find the relative risks of prostate cancer incidence associated with screening by serum prostate-specific antigen (PSA), alkaline phosphatase (ALP) and vitamin B12 levels.
Methods: Serum samples of 488 subjects above 40 years without treatment or puncture/rectal examination were screened for PSA levels using Chemiluminescence. Prostate cancer cases and control groups were analysed for vitamin B12 using Chemiluminescence and alkaline phosphatase using fully automated chemistry analyser. The relation of ALP and Vitamin B12 to levels of PSA in prostate cancer was examined.
Results: Incidence rate for the screening on the risk of prostate cancer by PSA levels and metastasis involvement was significant. Out of 488 screened subjects, 347 were within normal range according to age reference values, 30 were showing prostate cancer, and 111 were with the high risk of metastasis. Results of the case-control analysis showed a positive correlation among ALP and PSA levels and negative with vitamin B12.

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Conclusions: Benefits of PSA screening varies with age group according to blood PSA levels. For men with a PSA level in different age groups screening and treatment depends upon individual decision, pain and clinical examination.

Keywords: Prostate cancer; PSA; alkaline phosphatase; vitamin B12.

1. INTRODUCTION

Prostate cancer is a common malignant tumour in the urinary system with increased incidence and mortality in recent years. In the nineteenth century, prostate cancer was described as a "very rare disease". It is now the most common male cancer and the second or third most common cause of cancer-related death in men. Although knowledge of the aetiology of prostate cancer is still an area of investigation, evidence of nutritional and dietary targets for primary prevention is accumulating. In the review nutrition, dietary interventions and prostate cancer: the latest evidence, Lin and colleagues provide an overview of recent literature on the possible influences of diet and nutrients on prostate cancer outcomes [1].

PSA was first described in 1971 and purified in 1979 in seminal plasma and the prostate. PSA is a single chain glycoprotein with 240 amino acids synthesised by the epithelial cells of prostatic acini and ducts and is secreted as a normal constituent of seminal fluid [2,3,4]. Serum prostate-specific antigen (PSA) level can, predict the lesion range of prostate cancer and is essential for its early detection and follow-up; PSA and alkaline phosphatase (ALP) are significant predictors for bone metastasis [5,6,7, 8,9]. PSA is a protein produced by both normal and cancerous prostate cells, and a high PSA value can be a sign of cancer [10,11,12,13]. Compared to the bone scan, serum markers showed advantages in their reproducibility, non-invasiveness, and relatively low cost. Alkaline phosphatase (ALP) is essential predictors for bone metastasis. The folate-mediated one-carbon metabolism, which involves B-vitamins as enzymatic co-factors, is characterised by the transfer of methyl groups and has been hypothesised to affect carcinogenesis by inducing epigenomic changes and influencing synthesis of DNA. Although some prospective studies reported no association, vitamin B12 concentration has been associated with increased prostate cancer risk [14,15]. Interpretation of these findings is challenging because of the heterogeneous nature of Prostate Cancer, with many tumours remaining small and asymptomatic for long durations of time, whereas some develop into aggressive forms and are ultimately lethal [16,14]. Due to lack of symptoms in the onset of prostate cancer as, most patients get their clinical examination done when metastases symptoms are produced, lead to fracture and bone pain that severely affect the quality of life and prognosis. Therefore the identification of risk factors, early diagnosis and treatment of prostate cancer bone metastases is of great significance [17,18,19,20,21].

2. MATERIALS AND METHODS

Screening of 488 subjects for serum PSA levels was done from January 2014 to December 2016. Subjects of male gender above 40 years of age from O.P.D. and I.P.D. of Medicine, Surgery and Urology departments of Sir J. J. Group of Hospitals, Mumbai were included in the study. Ethical Clearance approval was taken from the institutional ethics committee of Grant Govt. Medical College and Sir J. J. Group of Hospitals, Mumbai and informed consent along with details of patients were taken prior to the study. Subjects did not receive treatment or puncture/rectal examination at least a week before blood collection. Peripheral venous blood samples were collected in plain vacutainer, centrifuged and serum sample was preserved at -80°C and processed. From the screened subjects, 30 cases with prostate cancer having high serum PSA levels were selected along with 30 controls for the further study. Estimation of PSA and Vitamin B12 levels was done by solid-phase sequential Chemiluminescent immunometric assay (Chemiluminescence Immulite 1000) and Alkaline Phosphatase (ALP) levels by fully automated chemistry analyser (ADVIA). Statistical evaluation was done using ANOVA test using Minitab 17 software.

3. RESULTS

The age wise distribution of screened subjects showed a higher incidence of PSA levels in individuals aged 50 years and above. The screened subjects were distributed according to the different levels of serum PSA in relation to age (Tables 1, 2).

In our study, 30 subjects in a different distribution of age groups above 40 years, those with normal serum PSA levels were included in the control group, and high levels were further classified according to PSA levels. 30 subjects with higher values of serum PSA with prostate cancer were included in the case group. The levels of alkaline phosphatase were increased and showed metastasis with the involvement of bones as the disease progresses. But vitamin B12 levels were within normal range in control as well as in patients with risk of prostate cancer. Low levels were found as the disease progresses to prostate cancer.

The positive correlation was established between different PSA and Alkaline phosphatase which was significantly increased in prostate cancer as compared to control. A negative correlation was established between PSA and vitamin B12 (Table 3 and Graph 1). This study shows that as PSA and alkaline phosphatase increases leading to prostate metastasis and vitamin B12 decreases as the disease progresses (Table 4 and Graph 1).

4. DISCUSSION

Before PSA testing, most prostate cancers were detected with a digital rectal examination or in patients presenting with symptoms of advanced disease, often too late for curative care [22]. Therefore, early diagnosis of prostate cancer is of great significance for treatment [17].

Table 1. Age wise distribution of screened subjects

Age Groups (years)	21 – 40	41 – 50	51 – 60	61 – 70	Above 70
No. of Men	14	25	126	225	98

Table 2. PSA levels distribution of screened subjects

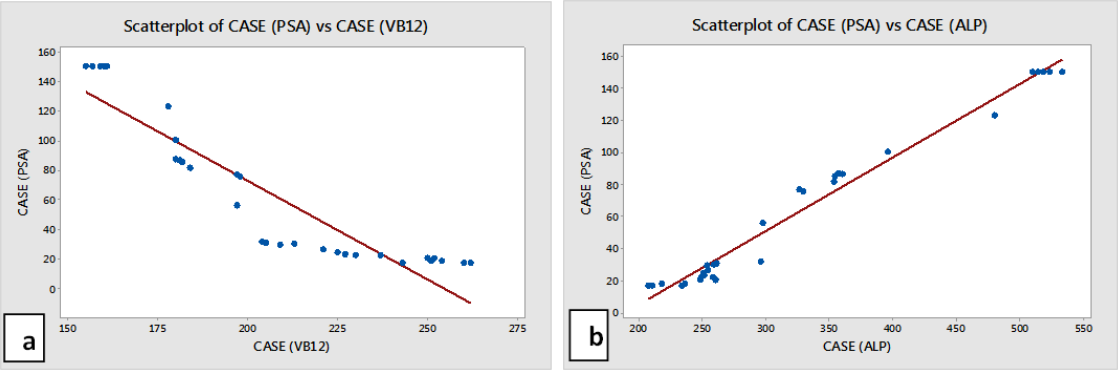
PSA Levels (ng/ml)	≤0.5	0.6–1.0	1.1–2.0	2.1–3.0	3.1–4.0	4.1 – 10	10.1-50	> 50
No. of Men	56	95	99	54	44	86	40	14
Age of Men (yrs) Mean ±SD	63.39± 10.65	60.11 ± 10.06	63.86 ± 9.18	64.93± 9.49	64.98± 7.97	65.10 ± 7.37	64.53 ± 10.72	63.86 ± 10.63
PSA (ng/ml) Mean ± SD	0.31 ± 0.13	0.72 ± 0.13	1.45 ± 0.28	2.43 ± 0.32	3.50 ± 0.31	6.24 ± 1.70	16.79 ± 6.34	108.71 ± 35.01

Table 3. Age, PSA, alkaline phosphatase and vitamin B12 levels in control and prostate cancer

Group	Age (years)	PSA (ng / ml)	ALP (IU/L)	Vitamin B12 (pg / ml)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
Control (N=30)	59.7 ±10.91	0.78 ± 0.39	89.3 ± 17.43	519.27±116.72
Prostate cancer cases (N=30)	61.8 ±10.84	63.03 ±49.52	327.43 ± 106.48	207.07± 34.14

Table 4. Correlations among Prostate Specific Antigen (PSA), Alkaline Phosphatase (ALP) and vitamin B12 levels in control and case (Prostate cancer) groups

Groups	r-values	p- value
Control (PSA) / Case (PSA)	0.92	0.00
Control (PSA) / Case (ALP)	0.90	0.00
Control (PSA) / Case (VB12)	-0.92	0.00
Control (ALP) / Case (PSA)	-0.13	0.48
Control (ALP) / Case (ALP)	-0.13	0.49
Control (VB12) / Case (PSA)	-0.20	0.29
Control (VB12) / Case (ALP)	-0.20	0.29
Control (VB12) / Case (VB12)	0.07	0.71
Case (PSA) / Case (ALP)	0.99	0.00
Case (PSA) / Case (VB12)	-0.92	0.00



Graph 1. Correlations graph (a) Case PSA and Vitamin B12 (b) Case PSA and ALP

Table 1 shows age-wise distribution of screened subjects for PSA, in which the group 61 – 70 years were having more subjects. No tumour marker has caused a greater change in our approach to cancer detection prognosis, and monitoring than PSA for prostate cancer. Table 2 levels of PSA distribution, their mean age, no. of subjects were more in the range of PSA level 4 – 10 ng/ml and are at initial stage of prostate cancer. In the above group nutritional status along with alkaline phosphatase should be monitored as they are at the high risk of developing bone involvement. In our study, in 488 screened subjects, there were 140 subjects having PSA levels above 4ng/ml, out of which only 30 subjects with higher values [PSA levels (Mean ± SD) 63.03 ± 49.52 ng/ml] were selected due to limitation of study. Further, correlation of PSA levels in these subjects were studied with alkaline phosphatase and vitamin B12 levels and found in some similar studies from other authors [17,18,23,22,14,15,24]. In this study, the evidence for PSA's effectiveness as a screening tool is 6% of the total screened subjects were having prostate cancer and about 22.7% were having high levels of serum PSA showing high risk of prostate cancer for bone involvement [22,23]. Similar study show direct relationship between preoperative serum PSA and tumour volume as determined from radical prostectomy specimens (Kabalin et al., 1995) and also as a general rule, as prostate cancer progresses it produces more PSA [2,25].

Although there are numerous reports addressing bone scan findings in relation to PSA level, only a few has the serum ALP level also assessed. Case-control Table 3 displays age, PSA, ALP and vitamin B12 values in pre-operative bone involvement group with significantly increased PSA and alkaline phosphatase levels and low levels of vitamin B12 as compared to control. ALP is particularly valuable in identifying the subgroup of patients whose metastatic disease with increase in PSA [26]. Observation that total serum alkaline phosphatase might be elevated in prostate cancer patients actually preceded the establishment of acid phosphatase as marker for that disease. Alkaline phosphatase is considered a non-specific tumour marker, being neither organ nor tumour specific but widely used as a marker for tumours of the skeleton [27] According to the some previous studies, PSA and ALP are stated to be important predictors for bone metastases [17,28]. Table 4 indicates correlation amongst case/control, case/case in different parameters. PSA shows significant positive correlation in case/control. In cases with prostate cancer along with bone involvement shows significant positive correlation with PSA levels and as increase in ALP Graph 1b. Similarly a retrospective cohort study conducted by Metwalli et al. (2015) indicate that the addition of ALP to PSA based stratification methods may significantly enhance clinical ability to identify men at the greatest risk for developing bone metastases. Alkaline Phosphatase Velocity (APV) appears to be a strong independent predictor of bone metastases and overall survival in men with rising PSA [18].

We have seen negative correlated of PSA with Vitamin B12 in pre operative cases Table 4 and Graph 1a. Similar study of Stefan de Vogel et al. (2013) showed the associations of prostate cancer risk with circulating folate and vitamin B12 have been investigated in several large population-based studies [14]. A meta-analysis of prospective cohort studies suggested that relatively high folate concentration is associated with modestly increased prostate cancer risk [15]. In addition; during follow-up study indicate

high folate concentrations at prostate cancer diagnosis were associated with increased cancer cell proliferation or with faster increases of PSA levels, suggesting that high folate levels may enhance progression of localized prostate cancer [14].

Observational studies suggested that high dietary folate intake is associated with decrease in prostate cancer risk. Some prospective studies reported no association of vitamin B12 concentration with increased risk of prostate cancer [14,15,24].

Although knowledge of the etiology of prostate cancer is still an area of investigation, evidence of nutritional and dietary targets for primary prevention is accumulating. Modern management of prostate cancer now includes active surveillance, which is, monitoring the disease and delaying curative intervention until signs of disease progression. Its high-risk disease is multidisciplinary, and to make progress in the treatment of advanced prostate cancer with the advent of new drugs and gene expression studies. As more expensive therapies for metastatic prostate cancer are being brought to market, it is increasingly important to be able to accurately identify appropriate patients in order to avoid overtreatment and unnecessary expense. Clinical application of alkaline phosphatase increase or doubled in conjunction with PSA doubling time could enable physicians to reserve more effective, toxic and expensive therapies for those who need them most [1,17,10,18].

5. CONCLUSION

The results of present study conclude that the higher values of PSA were mostly found in patients of age above 50 years. For men with a PSA level in different age groups screening and treatment depends upon individual decision, pain and clinical examination. The values of ALP and nutritional status should be monitored in high-risk group of PSA values which might lead to bone metastasis in prostate cancer. Thus, PSA and ALP can be useful as prognostic markers of clinical benefit. Future biomarkers might help to improve customised therapy of treatment options.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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