PROSTATE CANCER SCREENING IN POPULATION OF EASTERN NEPAL: A FIELD STUDY

STUDY REPORT

SUBMITTED TO:

NHRC, Ramshah path Kathmandu, Nepal.

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Dated: 18th September,2011

To,
The President
NHRC,
Ramshah Path, Kathmandu, Nepal

Subject: To submit the Report of the study "*PROSTATE CANCER SCREENING IN POPULATION OF EASTERN NEPAL: A FIELD STUDY*".

Respected Sir,

With due respect, kindly accept my heartful thanks for providing the grant for the study. This grant was of great help to me during the execution of the study. This study was a great learning experience in my carrier. I hope that the results of the study will be of great help to the Nepalese Population. Sir with these words I am submitting 6 copies of the report of my study. Please provide me feedbacks if there are things to correct.

Thanking You

Yours sincerely
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Dr. Narayan Prasad Belbase

Abbreviations

ASTRO-American Society for Therapeutic Radiology and Oncology

BMI-Body Maass Index

BPH-Benign Prostatic Hyperplasia

B.P.K.I.H.S- B.P.Koirala Institute of Health sciences

CaP-Carcinoma Prostate

CLIA- Chemicluminescence Assay

COPD-Chronic Obstructive Pulmonary Disease

DRE- Digital Rectal examination

FDA- U.S. Food and Drug Administration

HIFU- High-Intensity Focused Ultrasound

PSA-Prostate Specific Antigen

MRI-Magnetic Resonance Imaging

MRS-Magnetic Resonance Spectroscopy

PCPT-Prostate Cancer Prevention Trial

PIN-Prostatic Intraepithelial Neoplasia

PSMA- Prostate- Specific Membrane Antigen External Beam Radiotherapy

SPECT- Single Photon Emission Computed Tomography

TRUS-Trans Rectal Ultrasonography

CONTENTS

INTRODUCTION

Prostate cancer is the second most frequently diagnosed cancer and the sixth leading cause of cancer death in males, accounting for 14% (903,500) of the total new cancer cases and 6% (258,400) of the total cancer deaths in males in 2008 (**Jemal et al, 2011).** Descriptive epidemiology has shown wide ethnic/racial differences in the incidence of Prostate carcinoma. The highest incidence rate group (100/100,000/year) includes African Americans in the United States; intermediate rates (20–50/100,000/year) are observed in Canada, South America, and European countries; and lowest rates (10/100,000/year) in Japan, China, and India **(Watanbe et al, 2000).** Temporal trends in incidence rates in countries with higher uptake of PSA testing such as the United States, Australia, Canada, and the Nordic countries followed similar patterns (**Jemal et al, 2011)**.

Prostate cancer has a highly variable natural history, ranging from an indolent and silent entity throughout a man's entire life to one that grows rapidly, metastasizing to lymph nodes and bone, with a median life expectancy of 24 to 36 months after bony metastases are detected. It is largely asymptomatic until metastases are present**.** The medical community has advocated early detection and treatment of prostate cancer for nearly a century. As early as 1905, the noted urologist Hugh H. Young, concluded that careful digital rectal examination (DRE) could identify prostatic changes that herald the first signs of cancer. For the next 75 years, this was the only screening test available, but an imperfect one **(Brawley et al, 2009**. In the early 1980s, clinicians reacted with optimism to initial studies using a blood protein, prostate–specific antigen (PSA), as a screening test for this disease because of an increasing death rate and the poor performance of the DRE (**Catalona et al, 1991**).

Early diagnosis of prostate cancer is hindered by the lack of symptoms. Therefore, early detection requires a simple, safe, inexpensive, and effective test. Digital rectal examination (DRE) is notoriously imprecise, lacks sufficient sensitivity, and is more likely to detect disease when it is advanced. Only 30% to

40% of cancers detected by DRE can be expected to be organ confined. When prostate cancer is detected by PSA, a majority of tumors are organ confined and clinically significant (**Crawford et al, 1996).**

Despite progress in the treatment of advanced or metastatic prostate cancer it is well recognized that the only possibility of a significant reduction in prostate cancer death is treatment of localized disease. It is reasonable to assume that the recently observed decrease in deaths from prostate cancer is due to earlier diagnosis with serum PSA and transrectal ultrsonography of the prostate coupled with improved treatment of localized disease by surgery, radiotherapy, brachytherapy and endocrine therapy **(Labrie et al, 1999).**

Proof of the potential benefits of screening and treatment of localized prostate cancer can only be obtained from prospective and randomized studies comparing the incidence of death from prostate cancer in a group of men screened and treated early with a parallel group of men receiving standard medical care.

In Nepal, to the best of our knowledge (after extensive search on PUBMED, CINAHL, ERIC, and CIJE) though accurate data regarding prevalence of prostate cancer has not been published, **Annual Report 2009** from B.P. Koirala Memorial Cancer Hospital, Bharatpur shows that out of 170 genitourinary malignancies, 31 i.e (18.23%) were carcinoma prostate. Among the 31 carcinoma prostate detected 4 underwent radical prostatectomy for early carcinoma prostate and 27 underwent bilateral orchiectomy for advanced disease. Another similar data from the study 'Clinico-Epidemiological study of genitourinary malignancies at B. P. Koirala Institute of Health Sciences (2006-2008)' done in B. P. Koirala Institute of Health Sciences, Dharan, Nepal shows that out of 139 cases of genitourinary carcinoma, 24 (17.26%) were carcinoma prostate **(Hai et al, 2008)**.

So this study was undertaken as a trial to explore the situation of prostate cancer in a cohort of healthy population of Eastern Nepal and also to assess the feasibility of screening prostate cancer.

AIMS AND OBJECTIVES

Primary objective:

- To explore the situation of prostate cancer in population of Eastern Nepal.

Secondary objectives:

- To assess the importance and feasibility of screening of prostatic cancer in population of Eastern Nepal.

LITERATURE REVIEW

The prostate gland is the male organ most commonly afflicted with either benign or malignant neoplasms. It comprises the most proximal aspect of the urethra. Anatomically it resides in the true pelvis, separated from the pubic symphysis anteriorly by the retropubic space (space of Retzius).

Epidemiology of carcinoma prostate

Prostate cancer is the fourth most common male malignant neoplasm worldwide. Its incidence 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) **(Quinn and Babb, 2002)**. As in the United States, prostate cancer incidence has increased in many countries since the early 1990s. Although much of the increase can be correlated with the introduction of PSA screening, some of the increase predates screening **(Gronberg, 2003)**. Mortality also varies widely among countries, being highest in Sweden (23 per 100,000 per year) and lowest in Asia (<5 per 100,000 per year in Singapore, Japan, and China) **(Quinn and Babb, 2002)**. Mortality rates increased slowly for most countries between 1985 and 1995 **(Quinn and Babb, 2002).**

There are multiple complex causes for the worldwide and ethnic variations in prostate cancer incidence**.** Access to and quality of health care, accuracy of cancer registries, and penetrance of PSA screening affect how rates of disease are reported. Before reliable data were available from African countries, rates of prostate cancer in Africa were thought to be much the same as those in Asia. However, in Uganda and Nigeria, prostate cancer is common, and it is the most common cancer in men in Nigeria **(Gronberg, 2003).**

Environment also plays an important role in modulating prostate cancer risk around the world**.** Japanese and Chinese men in the United States have a higher

risk for development of prostate cancer and dying of it than do their relatives in Japan and China **(Muir et al, 1991; Shimizu et al, 1991).** Likewise, prostate cancer incidence and mortality have increased in Japan as the country has become more westernized **(Landis et al, 1999).** However, Asian Americans have a lower prostate cancer incidence than white or African American men do, indicating that genetics still plays a role in determining prostate cancer predisposition.

Age at Diagnosis

Prostate cancer is rarely diagnosed in men younger than 50 years, accounting for less than 0.1% of all patients. Peak incidence occurs between the ages of 70 and 74 years, with 85% diagnosed after the age of 65 years **(Ries et al, 2004)**. At 85 years of age, the cumulative risk of clinically diagnosed prostate cancer ranges from 0.5% to 20% worldwide, despite autopsy evidence of microscopic lesions in approximately 30% of men in the fourth decade, 50% of men in the sixth decade, and more than 75% of men older than 85 years **(Sakr et al, 1993; Gronberg, 2003)**. PSA-based screening has induced an important age migration effect; the incidence of prostate cancer in men 50 to 59 years has increased by 50% between 1989 and 1992 **(Hankey et al, 1999)**, with important implications for deciding on the need for, type of, and complications after therapy.

Stage at Diagnosis

In addition to changes in prostate cancer incidence and mortality during the past several decades, there has been a substantial shift to more favorable stage at presentation in men with newly diagnosed disease. This clinical stage migration is largely if not exclusively accounted for by PSA screening **(Mettlin et al, 1993).** Since the introduction of PSA testing, the incidence of local-regional disease has increased, whereas the incidence of metastatic disease has decreased **(Newcomer et al, 1997)**. Diagnosis of local-regional disease increased 18.7% annually in white men between 1988 and 1992 and then decreased, on average, 9.8% annually through 1995 **(Hankey et al, 1999)**. In contrast, the incidence of metastatic disease decreased 1.3% annually from 1988 to 1992 and then 17.9%

annually through 1995. Non palpable cancers (AJCC clinical stage T1c) now account for 75% of newly diagnosed disease **(Derweesh et al, 2004)**. Concomitant with these changes, the percentage of men treated for clinically localized disease with radical prostatectomy increased substantially **(Hankey et al, 1999)**. Clinical stage migration has also been associated with improvements in 5- and 10-year survival rates, which for all stages combined now are 100% and 92%, respectively **(American Cancer Society, 2005)**.

The use of PSA has also resulted in a substantial downward pathologic stage migration as evidenced by an increasing incidence of organ-confined disease at radical prostatectomy **(Jhaveri et al, 1999; Derweesh et al, 2004)**. The improvement in pathologic stage has been seen for tumors of clinical stages T1 to T3 and for all tumor grades and has resulted in improved cancer-specific survival after external radiation or surgery for patients treated late in the PSA era. **(Jhaveri et al, 1999; Derweesh et al, 2004; Kupelian et al, 2005)**.

RISK FACTORS

Although the specific causes of prostate cancer initiation and progression are not yet known, considerable evidence suggests that both genetics and environment play a role in the origin and evolution of this disease**.** Classic and molecular epidemiology have identified a number of potential risk factors associated with the development of prostate cancer **(Presti et al, 2008).**

Familial and Genetic Influences

For investigative purposes, prostate cancer may be conveniently divided into three phenotypes: sporadic, familial, and hereditary. Sporadic cancers occur in individuals with a negative family history. Familial prostate cancer is defined as cancer in a man with one or more affected relatives. Hereditary prostate cancer is a subset of the familial form and has been operationally defined as nuclear families with three or more affected members, prostate cancer in three successive generations, or two affected individuals diagnosed with cancer before the age of 55 years **(Klein, 2007).**

Evidence for major prostate cancer susceptibility genes that segregate in families has been obtained from several complex segregation analyses, with the majority supporting a dominant and the remainder supporting a recessive or X-linked mode of inheritance. At least eight candidate prostate cancer susceptibility genes have been reported, including RNase L/HPC1, ELAC2/HPC2**,** SR-A/MSR1, CHEK2, BRCA2, PON1, OGG1, and MIC1. Individually, these genes are likely to account for only a small fraction of the observed genetic predisposition to prostate cancer **(Klein, 2007).**

Molecular Epidemiology

In molecular epidemiologic studies of prostate cancer, the association of biomarkers of exposure measured in blood or other tissues is evaluated in relation to incidence or mortality. These biomarkers capture aspects of diet, environmental contaminants and factors for which concentrations are partly inherently determined.

a) Androgens

Androgens influence the development, maturation, and maintenance of the prostate, affecting both proliferation and differentiation of the luminal epithelium. There is little doubt that a lifetime of variable exposure of the prostate to androgens plays an important role in prostate carcinogenesis. Long-term absence of androgen exposure to the prostate appears to protect against the development of cancer, but a dose-response relationship between androgen levels and cancer risk has not been established. In particular, whether normal-range androgen concentrations are associated with risk of prostate cancer remains unclear. Androgen receptor mediates testosterone and dihydrotestosterone activity by initiating transcription of androgen-responsive genes. Numerous studies have identified a shortened CAG trinucleotide repeat length in exon 1 to be associated with increased risk as well as advanced, hormone-refractory disease **(Klein, 2007).**

Estrogens

Estrogens have been postulated to protect against prostate cancer by inhibition of prostate epithelial cell growth but alternatively to increase risk by eliciting inflammation in concert with androgens **(Naslund et al, 1988)** or by the production of mutagenic metabolites **(Yager, 2000)**. Estradiol promotes prostate epithelial cell growth through binding of estrogen receptor-α and inhibits growth by effects mediated through estrogen receptor-β **(Harkonen and Makela, 2004)**. Estrogen receptor-β may play an important role in initiation of prostate cancer. In estrogen receptor-β knockout mice, there is prostatic epithelial cell hyperplasia characterized by arrested cellular differentiation, an ideal milieu for the development of an epithelium-derived cancer **(Imamov et al, 2004)**.

b) Insulin-like Growth Factor Axis

Insulin-like growth factor 1 (IGF-1) is a peptide hormone that promotes growth in adolescence and childhood and is correlated with adult lean body mass. IGF-1 promotes proliferation and inhibits apoptosis in normal prostate and tumor cells in vitro **(cohen et al, 1994)**. A positive association between plasma IGF-1 level and prostate cancer is supported by several studies **(Mantzoros et al, 1997; Harman et al, 2000; Khosravi et al, 2001)**, with a summary adjusted odds ratio of 1.49 (95% confidence interval, 1.14 to 1.95) comparing high and low IGF-1 concentrations in a meta-analysis **(Klein, 2007).**

c) Vitamin D, Vitamin D Receptor, and Calcium

Vitamin D (1, 25-dihydroxyvitamin D_3) is an essential vitamin that is a part of the steroid hormone superfamily. Human sources are dietary intake and through sunlight exposure, which converts inactive to active vitamin D in the skin. Interest in vitamin D as a determinant of prostate cancer risk comes from several epidemiologic observations **(Peehl et al, 2003)**:

1. Men living in northern latitudes with less sunlight-derived ultraviolet exposure have a higher mortality rate from prostate cancer.

2. Prostate cancer occurs more frequently in older men, in whom vitamin D deficiency is more common because of both less ultraviolet exposure and age-related declines in the hydroxylases responsible for synthesis of active vitamin D.
3. African Americans, whose skin melanin blocks ultraviolet radiation and inhibits activation of vitamin D, have the highest worldwide incidence and mortality rates for prostate cancer.
4. Dietary intake of dairy products rich in calcium, which depresses serum levels of vitamin D, are associated with a higher risk of prostate cancer.
5. Native Japanese, whose diet is rich in vitamin D derived from fish, have a low incidence of prostate cancer.

In addition, prostate cancer cells express vitamin D receptor, and several studies have demonstrated an antiproliferative effect of vitamin D on prostate cancer cell lines by inducing cell cycle arrest **(Krishnan et al, 2003)**.

d) Sexual Activity

Sexual activity has been hypothesized to expose the prostate to infectious agents, which may increase the risk of prostate cancer, akin to the causal relationship between human papillomavirus and cervical cancer in women. Some studies have found a link among early sexual intercourse, number of sexual partners, and prostate cancer **(Honda et al, 1988)**, although not consistently **(Ewings and Bowie, 1996; Giles et al, 2003; Fernandez et al, 2005)**.

e) Vasectomy

A relationship between vasectomy and prostate cancer risk was initially suggested in 1993 with a relative risk of 1.6 based on two large cohort studies **(Giovannucci et al, 1993).**

Smoking

Cigarette smoke may be a risk factor for prostate cancer because it is a source of cadmium exposure, increases circulating androgen levels, and causes significant

cellular oxidative stress. Both case-control and cohort studies have produced conflicting results, and none has demonstrated a clear dose-response relationship, although some studies have suggested an association with more advanced stage at diagnosis and increased prostate cancer–related mortality **(Bostwick et al, 2004).**

f) Dietary Fat

Prostate cancer incidence and mortality rates around the world correlate highly with the average level of fat consumption, especially for polyunsaturated fats **(Klein, 2007)**. Potential mechanisms of action include fat-induced changes in the hormonal milieu and induction of oxidative stress. High levels of dietary fat stimulate proliferation of prostate cancer cells both in vitro and in vivo, and animal models have shown that a fat-free diet can reduce the growth of androgen-dependent tumors in the Dunning model **(Wang et al, 1995; Aronson et al, 1999).**

g) Obesity

Obesity as measured by body mass index (BMI) has been suggested to be a risk factor for prostate cancer because of their common occurrence in middle-aged men and clear links to colon and breast cancer risk **(Madigan et al, 1998).**

Treatment of obesity through reduction in fat intake and increased exercise has been shown to reduce oxidative stress, suggesting that lifestyle modification could be important in reducing the risk of prostate cancer **(Roberts et al, 2002)**.

Cohort studies have examined the relationship between anthropometric variables and prostate cancer risk with conflicting results **(Andersson et al, 1997; Giovannucci et al, 1997; Schuurman et al, 2000)**, although two studies have suggested a protective effect for higher BMI in men 60 years and younger **(Giovannucci et al, 2003 ; Porter and Stanford, 2005).** There is an inverse relationship between circulating androgen levels and measures of obesity **(Svartberg et al, 2004; Chia et al, 2007; Culp et al, 2009)**.This observation may explain why higher BMI is associated

with lower serum PSA concentration **(Baillargeon et al, 2005),** which in obese men could lead to ascertainment bias against biopsy, perhaps explaining the previously noted protective effect of obesity on prostate cancer risk.

h) Alcohol Consumption

Alcohol consumption is of interest for risk of prostate cancer because of its association with other cancers, its effect on estrogen and testosterone, and the high content of polyphenolic compounds with antioxidant activity in red wine. A review of relevant epidemiologic studies showed no increased risk for prostate cancer among light to moderate drinkers **(Breslow and Weed, 1998)**. A later prospective cohort study found a dose-dependent increase in prostate cancer risk highest in those imbibing more than three hard liquor drinks per day (relative risk, 1.85) during a period of 11 years **(Sesso et al, 2001)**. There was no association with wine or beer consumption and prostate cancer risk, although the wine consumption was not separated into red or white varieties. Another study concluded that prostate cancer risk was unassociated with total alcohol consumption but that consumption of one to three glasses of red wine per week had a protective effect (relative risk, 0.82), even when adjusted for age, PSA screening, total lifetime number of female sexual partners, and smoking **(Marieke Schoonen et al, 2005).**

PROSTATIC INTRAEPITHELIAL NEOPLASIA

PIN and atypical small acinar proliferation (ASAP) are thought to be precursor lesions. Men found to have either lesion may be at an increased risk of prostate cancer and warrant repeat biopsy certainly if an extended core biopsy was not performed initially. High-grade PIN (HGPIN) is characterized by cellular proliferations within preexisting ducts and glands, with nuclear and nucleolar enlargement similar to prostate cancer. However, unlike cancer, HGPIN retains a basal cell layer identifiable by immunohistochemistry **(Presti et al, 2008).** Of the 11 studies with at least 50 cases of high-grade PIN on needle biopsy with follow-up, the mean risk of cancer was 26.4% **(Epstein, 2006)**.

Carcinoma Prostate

Over 95% of the cancers of the prostate are adenocarcinomas. Of the other 5%, 90% are transitional cell carcinomas, and the remaining cancers are neuroendocrine (small cell) carcinomas or sarcomas. Approximately, 60–70% of cases of CaP originate in the peripheral zone, while 10–20% originate in the transition zone, and 5–10% in the central zone. Although prostate cancer is most often thought to be multifocal, the use of widespread screening and extended biopsy techniques has resulted in the increasing detection of unifocal and smaller cancers **(Presti et al, 2008)**

CLINICAL FINDINGS

A. Symptoms

Most patients with early-stage Carcinoma prostate are asymptomatic. The presence of symptoms often suggests locally advanced or metastatic disease. Obstructive or irritative voiding complaints can result from local growth of the tumor into the urethra or bladder neck or from its direct extension into the trigone of the bladder. Metastatic disease to the bones may cause bone pain. Metastatic disease to the vertebral column with impingement on the spinal cord may be associated with symptoms of cord compression, including paresthesias and weakness of the lower extremities and urinary or fecal incontinence **(Presti et al, 2008).**

B. Signs

A physical examination, including a DRE, is needed. Induration, if detected, must alert the physician to the possibility of cancer and the need for further evaluation (ie,PSA, TRUS, and biopsy). Locally advanced disease with bulky regional lymphadenopathy may lead to lymphedema of the lower extremities. Specific signs of cord compression relate to the level of the compression and may include weakness or spasticity of the lower extremities and a hyperreflexic bulbocavernosus reflex **(Presti et al, 2008)**

C. Laboratory Findings

Azotemia can result from bilateral ureteral obstruction either from direct extension into the trigone or from retroperitoneal adenopathy. Anemia may be present in metastatic disease. Alkaline phosphatase may be elevated in the presence of bone metastases. Serum acid phosphatase may be elevated with disease outside the confines of the prostate **(Presti et al, 2008)**

D. Tumor Markers—Prostate-Specific Antigen

PSA is a serine protease produced by benign and malignant prostate tissues. It circulates in the serum as uncomplexed (free or unbound) or complexed (bound) forms.Normal PSA values are those ≤4 ng/mL. Current detection strategies include the efficient use of the combination of DRE, serum PSA, and TRUS with systematic biopsy. Unfortunately, PSA is not specific for Carcinoma prostate, as other factors such as BPH, urethral instrumentation, and infection can cause elevations of serum PSA**.**

PSA is widely known to be associated with age. Since PSA is produced in the prostate and the prostate generally enlarges after age 50, the increase in PSA levels with age is understandable. The following studies also shows that with increasing age PSA increases**.**

Study	Country	PSA value(ng/ml) by age groups(years)		
		50-59	60-69	70-79
Liu et al (2008)	China	3.20	4.10	5.37
Lee et al (2000)	Korea	2.4	3.9	6.3
Malati and Kumari (2004)	India	1.6	2.0	2.47

Although the last two factors can usually be clinically ascertained, distinguishing between elevations of serum PSA resulting from BPH and those related to Carcinoma prostate remains the most problematic. Serum PSA concentrations are decreased by treatment with agents that lower serum testosterone such as

LHRH agonists and antagonists used to treat prostate cancer as well as with 5-alpha-reductase inhibitors used to treat BPH.

Interestingly, serum PSA levels are decreased in men with high body mass indexes compared to normal weight men. The positive predictive value of a serum PSA between 4 and 10ng/mL is approximately 20–30%. For levels in excess of 10ng/mL, the positive predictive value increases from 42% to 71.4%. Given that most men with elevated serum PSA levels do not have prostate cancer, there is great interest in identifying markers with greater sensitivity and/ or specificity. Candidate markers include novel auto-antibodies or other prostate antigens (early prostate cancer antigen) **(Presti et al, 2008)**. Numerous strategies to refine PSA for cancer detection have been explored. Their common goal is to decrease the number of false-positive test results. This would increase the specificity and positive predictive value of the test and lead to fewer unnecessary biopsies, lower costs, and reduced morbidity of cancer detection. Attempts at refining PSA have included PSA velocity (change of PSA over time), PSA density (standardizing levels in relation to the size of the prostate), age-adjusted PSA reference ranges (accounting for age-dependent prostate growth and occult prostatic disease), and PSA forms (free versus protein bound molecular forms of PSA).

1. PSA velocity—PSA velocity refers to the rate of change of serum PSA. A retrospective study has shown that men with prostate cancer have a more rapidly rising serum PSA in the years before diagnosis than do men without prostate cancer. Patients whose serum PSA increases by 0.75ng/mL/y appear to be at an increased risk of harboring cancer. However, PSA velocity must be interpreted with caution **(Presti et al, 2008).**

2. PSA density—PSA levels are elevated approximately 0.12ng/mL/g of BPH tissue. Thus, patients with enlarged glands due to BPH may have elevated PSA levels. The ratio of PSA to gland volume is termed the PSA density. Some investigators advocate prostate biopsy only if the PSA density exceeds 0.1 or 0.15, while others have not found PSA density to be useful. Problems with this

approach include the facts that (1) epithelial-stromal ratios vary from gland to gland and only the epithelium produces PSA, and (2) errors in calculating prostatic volume may approach 25%. The positive predictive value of PSA density is slightly higher than the use of a PSA level >4ng/mL in several series (30–40% versus 20–30%). Instead of adjusting the PSA to total prostate volume, some have advocated adjusting it to transition zone volume (PSA transition zone density). However, like PSA density, such calculations are subject to error, require TRUS, and do not seem to be superior to the use of PSA in most patients **(Presti et al, 2008).**

3. Racial variations in CaP detection— Previously, it was noted that in men without prostate cancer, African American men presented with higher baseline serum PSA and PSA density. In addition, African American men had worse outcomes (cancer recurrence and mortality) compared to Caucasian, Hispanic, and Asian American men.

Differential screening practices were recommended based on these results. However, more contemporary analyses suggest that these discrepancies are disappearing. In addition, much of any variation noted may be more strongly related to education, insurance status, and access to health care than ethnicity **(Presti et al, 2008).**

4. Molecular forms of PSA—The most recent refinement in PSA has been the recognition of the various molecular forms of PSA—free and protein-bound.

Approximately 90% of the serum PSA is bound to alpha-1-antichymotrypsin, and lesser amounts are free or are bound to alpha-2-macroglobulins. In the latter form, no epitopes to the antibodies used in the current assays are available, while PSA bound to alpha-1-antichymotrypsin may have 3 of its 5 epitopes masked. Early studies suggest that prostate cancer patients demonstrate a lower percentage of free PSA than do patients with benign disease. A large multicenter study has reported that in men with a normal DRE and a total PSA level between

4 and 10ng/mL, a 25% free PSA cut off would detect 95% of cancers while avoiding 20% of unnecessary biopsies**.** The cancers associated with > 25% free PSA were more prevalent in older patients and generally were less threatening in terms of tumor grade and volume **(Catalona et al, 1998).**

E. Prostate Biopsy

Prostate biopsy should be considered in men with an elevated serum PSA, a DRE, or a combination of the two. Prostate biopsy is best performed under TRUS guidance using a spring-loaded biopsy device coupled to the imaging probe. Biopsies are taken throughout the peripheral zone of the prostate, rather than just sampling an area abnormal on the basis of DRE or TRUS. Traditionally, 6 (sextant) biopsies were taken along a parasagittal line between the lateral edge and the midline of the prostate at the apex, mid gland, and base bilaterally. However, several investigators have shown that increasing the number (≥10) and performing more laterally directed biopsies of the peripheral zone will increase detection rates 14–20% over the more traditional sextant technique. Using TRUS guided biopsy of the prostate, the cancer detection rate was30.5%-39.3% **(Catalona et al, 1991; Rabah and Arafa, 2010; Niang et al, 2011)**. Although a small number of prostate cancers will originate in the transition zone, specific transition zone biopsies add little to overall cancer detection rates when an extended-pattern biopsy is performed. There is ongoing interest in the use of even more extended biopsy schemes “saturation biopsy” or use of a transperineal approach to improve cancer detection, usually in those who have had a negative biopsy, but are thought to be at an increased risk of prostate cancer based on a persistently abnormal serum PSA. Prostate biopsy is usually performed using local anesthesia and pre procedure antibiotic prophylaxis. Although prostate biopsy is usually very well tolerated by patients, approximately10–24% of those undergoing the procedure will find it very painful. The use of local anesthesia, either applied topically along the anterior rectal wall, injected into or adjacent to the prostate, or a combination of the two, decreases pain associated with procedure. Hematospermia and hematuria are

common occurring in approximately 40–50% of patients. Minor rectal bleeding may occur, as well. High fever is rare occurring in 2.9–4.2% of patients.

F. Imaging

1. TRUS—TRUS is useful in performing prostatic biopsies and in providing some useful local staging information if cancer is detected. Almost all prostate needle biopsies are performed under TRUS guidance. This allows uniform spatial separation and sampling of the regions of the prostate and also makes lesion-directed biopsies possible. If visible, Carcinoma prostate tends to appear as a hypoechoic lesion in the peripheral zone **(Presti et al, 2008).**

2. Endorectal magnetic resonance imaging (MRI)—

Use of an endorectal coil improves cancer detection and staging compared to the use of a standard body coil. Routine use of this technology may not alter treatment decisions compared to the information gained by assessment of more standard clinopathologic information. Use of magnetic resonance spectroscopy (MRS) in conjunction with MRI may improve the accuracy of imaging **(Hricak 2005).**

3. Axial imaging (CT, MRI)—Cross-sectional imaging of the pelvis in patients with CaP is selectively performed to exclude lymph node metastases in high-risk patients who are thought to be candidates for definitive local therapy, whether it be surgery or irradiation. Both MRI and computed tomography (CT) are used for this purpose. Intravenous administration of super paramagnetic nano particles, which gain access to lymph nodes by means of interstitial-lymphatic fluid transport, at the time of high-resolution MRI, appears to improve visualization of small nodal metastases **(Presti et al, 2008).**

4. Bone scan— When prostate cancer metastasizes, it most commonly does so to the bone .Soft tissue metastases (eg, lung and liver) are rare at the time of initial presentation. Although a bone scan has been considered a standard part of the initial evaluation of men with newly diagnosed prostate cancer, good evidence

has been accumulated that it can be excluded in most of these men on the basis of serum PSA. However, patients with PSA 15 ng/mL or greater, locally advanced disease (T3B, T4) are at higher risk for bone metastases and should be considered for bone scan **(Presti et al, 2008).**

5. Antibody imaging—ProstaScint is a murine monoclonal antibody to an intracellular component of the prostate- specific membrane antigen (PSMA), which is conjugated to 111 indium. After infusion of the antibody, single photon emission computed tomography (SPECT) images are usually obtained at 30 minutes to access vasculature and at 72–120 hours. It has been approved by the U.S. Food and Drug Administration (FDA) for use in the evaluation of patients prior to treatment and for detecting the site of recurrent disease in patients who have biochemical relapse after initial treatment **(Presti et al, 2008).**

SCREENING FOR CARCINOMA PROSTATE

The case for Carcinoma Prostate screening is supported by the following: PSA improves detection of clinically important tumors without significantly increasing the detection of unimportant tumors; most PSA-detected tumors are curable; prostate cancer mortality is declining in regions where screening occurs; and curative treatments are available. If screening is undertaken, it appears that the use of both DRE and serum PSA is preferable to either one used alone. Although many recommend that screening be undertaken at age 50, some have advocated for earlier screening starting at age 40.The mean age of the population at screening ranged from 62.1 years to 65.5years **(Seo et al , 2007; Ganpule et al, 2007; Niang et al, 2011)**. Although annual screening is most often recommended, some feel that men with very low serum PSA level (≤1 ng/mL) may be able to be screened at less frequent intervals (every 2 or 3 years).

What constitutes a serum PSA at which biopsy is recommended is a matter of debate. Although a normal PSA is considered to be 4ng/mL or less, this value was set in men of all ages and prostate volumes. As mentioned earlier, younger men, with less BPH, should have lower levels. In addition, recent information suggests

that many men with serum PSA concentrations in the normal range, even with a normal DRE, may harbor significant disease. In the PCPT trial of finasteride for chemoprevention of prostate cancer discussed earlier, the prevalence of prostate cancer was 6.6% among men with a PSA level of up to 0.5 ng/mL, 10.1% among those with values of 0.6–1 ng/mL, 17% among those with values of 1.1–2 ng/mL, 23.9% among those with values of 2.1–3 ng/mL, and 26.9% among those with values of 3.1–4 ng/mL **(Thompson et al, 2003; Thompson et al, 2004).** For PSA >4.0 ng /ml sensitivity ranged from 0.78-1.00 **(Harvey et al, 2009; Catalona et al, 1994).** The positive predictive value for PSA >4.0ng/ml ranged from 28%-35% **(Woolf, 1995; Niang et al, 2011).**Even more importantly, the prevalence of high grade cancers varied from 12.5% to 25% in these low ranges. Therefore, there is no PSA cut point where cancer can be excluded. Based on these results, some have suggested lowering the PSA cut point for biopsy to 2 or 2.5ng/ml. Both DRE and PSA can detect occult prostate cancer. Reported values for the sensitivity, specificity, and positive predictive value of DRE and PSA may not reflect true values; however, because the number of false-negative cases is often unknown, studies traditionally screen volunteers, whose cancer risk may differ from the general population, and fine-needle biopsies may miss cancerous lesions. DRE has a reported sensitivity of 45%-68% in asymptomatic men **(Catalona et al, 1991; Lee et al, 1988; Mettlin et al, 1991)**, but values as low as 18%-22% have been reported (**Optenberg et al, 1990**). The reported positive predictive value of DRE is 6%-34% (**Chodak et al, 1989; Lee et al, 1988; Mettlin et al, 1991**). The specificity and/or positive predictive value of PSA may be enhanced by measuring PSA density (PSA value divided by gland volume measured by transrectal ultrasound), PSA velocity (annual rate of change of PSA), the free PSA ratio, age - adjusted PSA reference ranges, or increasing the cut-off value. When DRE and PSA are used as screening tests for prostate cancer detection, detection rates are higher with PSA than with DRE and highest with a combination of the two tests **(Catalona et al, 1994; Littrup et al, 1994; Stone et al, 1994; Schroder et al, 1998)**. The cancer detection rate using PSA >4.0ng/ml and DRE ranged from 1.0%-3.7%

(Mettlin et al, 1991; Galic et al, 2003; Ganpule et al, 2007; Rabah and Arafa, 2010). One concern related to screening is the fact that some cancers may be detected which would never result in clinically significant disease in the patient if left untreated, a phenomenon called over detection. Some have estimated that between 29% and 48% of cancers detected by an aggressive screening program are such cancers **(Etzioni et al, 2002; Draisma et al, 2003)**. This underscores the importance of informed consent before screening is undertaken and the need to discuss all treatment options, including active surveillance, in those found to have the disease. Screening should be undertaken in men who are healthy enough to benefit from it. Screening may be highly encouraged in certain populations with a higher disease prevalence and/or mortality such as African American men and those with a strong family history of the disease.

MATERIALS AND METHODS

Type of the study: A Field study.

Duration of study: 8 months (1st November 2010 to 31st July 2011).

Materials and methods:

This study was a field trial study conducted in the Department of General Surgery at B. P. Koirala Institute of Health Sciences, Dharan, Nepal. The Study was approved by "The Institute Protocal and Ethical Committees".

Settings:

This study was conducted in the Department of General surgery at B. P. Koirala Institute of Health Sciences, Dharan, Nepal in Surgical Outpatient Department its Teaching District Hospitals (Dhankuta, Inaruwa, Bhadrapur and Rangeli) representing four different regions of Eastern Nepal, through health camps from 1st November 2010 to 31st July 2011.

Inclusion Criteria: All males above 50 years of age attending outpatient department of surgery in B.P.K.I.H.S, teaching district hospitals and screening camps.

Exclusion criteria:

- Males already diagnosed to have carcinoma prostate,
- Those who did not give consent for enrollment,
- Those who did not give consent for trucut biopsy of prostate, and
- Those with a history of coagulopathies or sepsis.

Males above 50 years visiting Surgical Outpatient Department in BPKIHS were enrolled in the study. Screening camps were organized in the selected Teaching district hospitals of BPKIHS. Standing posters regarding information about carcinoma prostate were displayed in the study settings. Information was also broadcasted via local radio centers asking men to participate actively in the

study. Men above 50 years were invited to participate in the study and were explained the nature, objectives and benefits of the study. Written consent was taken from each of them regarding their willingness to be enrolled in the study. Digital rectal examination (DRE) was done by the trained professionals after collecting blood for serum prostatic specific antigen (PSA). Focussed group discussions were conducted in the camps to assess the feasibility of screening carcinoma prostate. Any patient diagnosed with prostate cancer was offered treatment according to its stage and grade as well as the general health condition of the patient. The patient was made aware of all the treatment options, including watchful waiting, radical prostatectomy, and radiation therapy. Those with a negative biopsy were offered continual annual screening.

Data collection and processing:

A total of 1521 males more than 50 years of age were assessed and screened after meeting inclusion criteria. For all subjects a predesigned proforma were filled. Blood samples were collected from all individuals included in the study prior to Digital rectal examination (DRE). Three ml of blood was taken in a plain vial, centrifuged and the serum was stored at -20 degree Celsius until analysis. PSA was estimated using Chemicluminescence Assay (CLIA) method (Acculite Kit, by Monobind, California, USA). Serum prostatic specific antigen (PSA) above 4ng/ml was considered abnormal. In DRE prostate was considered abnormal if the consistency of prostate was hard, there was evidence of nodularity, induration, asymmetry and absence of median sulcus. Trucut biopsy was done for all individuals with abnormal PSA/DRE findings. Glycerine suppository enema was given prior to the biopsy. Adequate antibiotic coverage was given with oral Metronidazole and Ofloxacin for 5 days.

Estimation of sample size:

The sample size was calculated based on 899 per 100000 population with confidence interval of 95% for prostate cancer .The sample size came out to be 2000.

Primary Data Analysis:

Collected data were entered in Microsoft excel-2007 and imported into SPSS 11.5 version for statistical analysis. For descriptive statistics mean, standard deviation, proportion, percentage and diagrammatic presentation was done. For inferential statistics chi-square test, t-test were carried out to find out the significant differences between the dependent and independent variables where level of significance was considered p=0.05.

RESULTS

This was a field trial study, conducted in the Department of Surgery, B.P.K.I.H.S, Dharan, Nepal. The duration of the study was eight months from 1st November 2010 to 31st July 2011. Though the calculated study sample was 2000 healthy males more than 50 years of age, we could conduct the study only on 1521 individuals due to lack of adequate fund. Out of these 1521 individuals 98% were married, 10% of the participants were having secondary schooling and 5% of the participants were having higher secondary education. Among the enrolled population 5 did not come for follow up and 6 did not give consent for Trucut biopsy. These 11 individuals had high PSA. Consent for Trucut biopsy was not given because of the fear of being diagnosed to have carcinoma prostate.

DEMOGRAPHICS:

AGE

In our study we had 682(45.2%) subjects in the age group of 50-60 years, 489(32.4%) subjects in the age group of 61-70 years and 339(22.4%) subjects in the age group of more than 70 years respectively. The majority of the population in our study were in the age group 50-60 years (45.2%). The age range of the study population was 50 to 100 years with the mean age of 63.63±9.76 years. The age distribution of the study population is shown in figure 1.

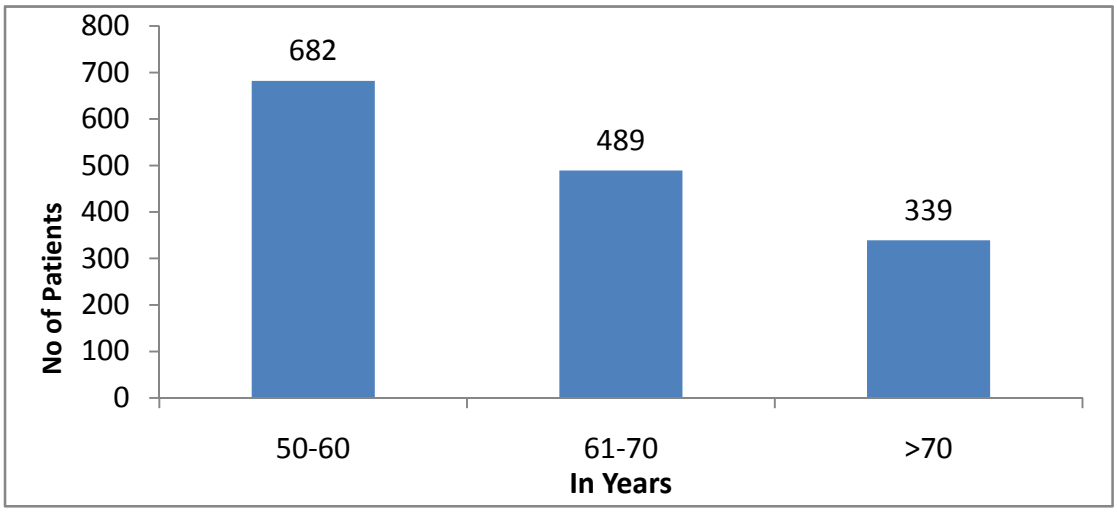

Figure 1: Age Distribution of the study population

DISTRICT

Enrolled patients in the study were from all over the eastern region of Nepal. Most of the subjects 644 (45.2%) were from Sunsari district, followed by neighboring Jhapa 281 (18.6%), Morang 226 (15%) and Dhankuta 120 (7.9%) districts. Rest of the subjects 239 (15.8%) were from Saptari, Siraha, Ilam, Udaypur, Sankhuwasabha, Taplejung and Tehrathum districts. The district distribution is shown in figure 2.

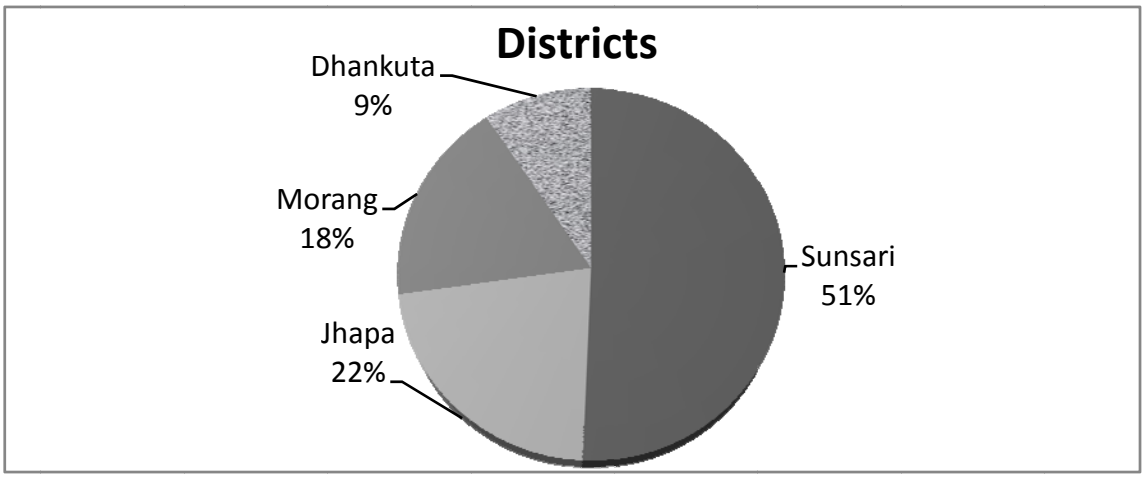

Figure 2: District wise distribution

KNOWLEDGE ABOUT CARCINOMA PROSTATE

In this study 189 (12.5%) individuals told that they have heard of carcinoma prostate and the same percent knew that it occurs in male at the neck of Urinary Bladder. Twelve and half percent individuals told that it can be detected by blood test. Twenty seven (1.78%) individuals told that carcinoma prostate occurs in both male and female. Only 175 (11.59%) individuals were able to tell that carcinoma prostate occurs in old age.

Table 1: Knowledge about Carcinoma prostate

Response	No. of individuals(n)	Percentage (%)
Yes	189	12.5
No	1321	87.5
Total	1510	100

COMORBID CONDITIONS IN THE STUDY POPULATION

In the study population 462 (30.6%) individuals had Hypertension, 121 (8.0%) individuals had Diabetes and 152 (10.1%) had Chronic obstructive Pulmonary Disease.

RISK FACTORS:

RACE OF THE STUDY POPULATION:

Nepalese population chiefly comprises of Aryans and Mongolians race. In our study majority of the population were Aryans 900 (59.60%) and rest were Mongolians 610 (40.40%). The following figure 3 shows these findings.

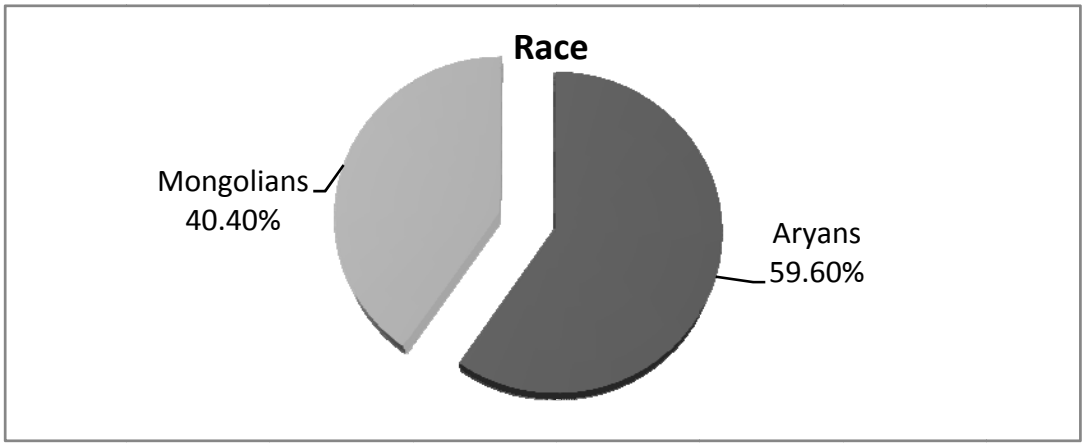

Figure 3: Race of the study population

BODY MASS INDEX (BMI)

In our study 1036 (68.6%) individuals had normal body mass index (BMI), 392 (26%) were overweight and 48 (3.2%) individuals were obese. The distribution of BMI is shown figure 4.

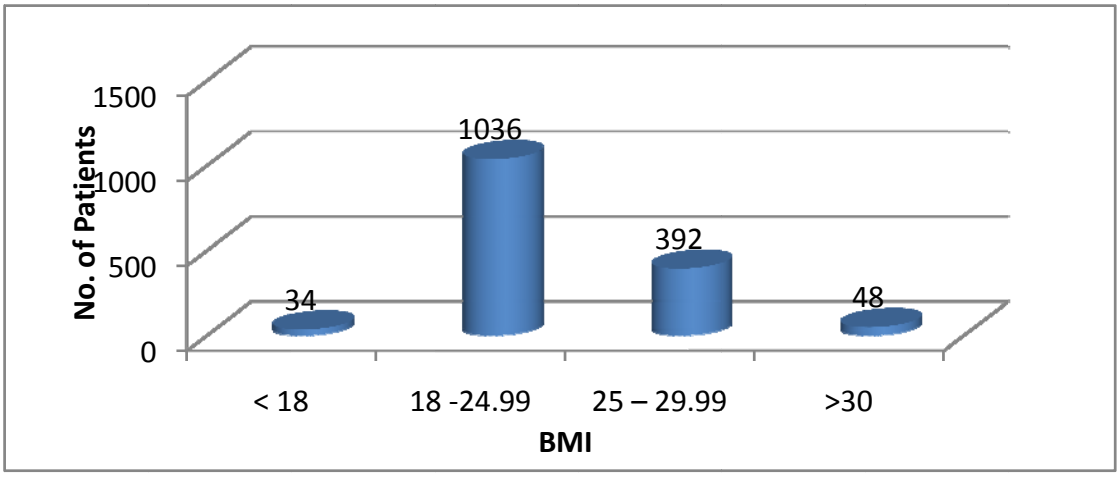

Figure 4: Distribution of Body Mass Index

ALCOHOL INTAKE

We found alcohol consumption in 107 (7.08%) individuals and this is shown in table 2.

Table 2: Alcohol intake in the study population

Alcohol intake	No. of individuals (n)	Percentage (%)
Yes	107	7.08
No	1403	92.92
Total	1510	100

SMOKING

Smoking was found in 89 individuals i.e. 5.8% of the study population and this is shown in figure 5:

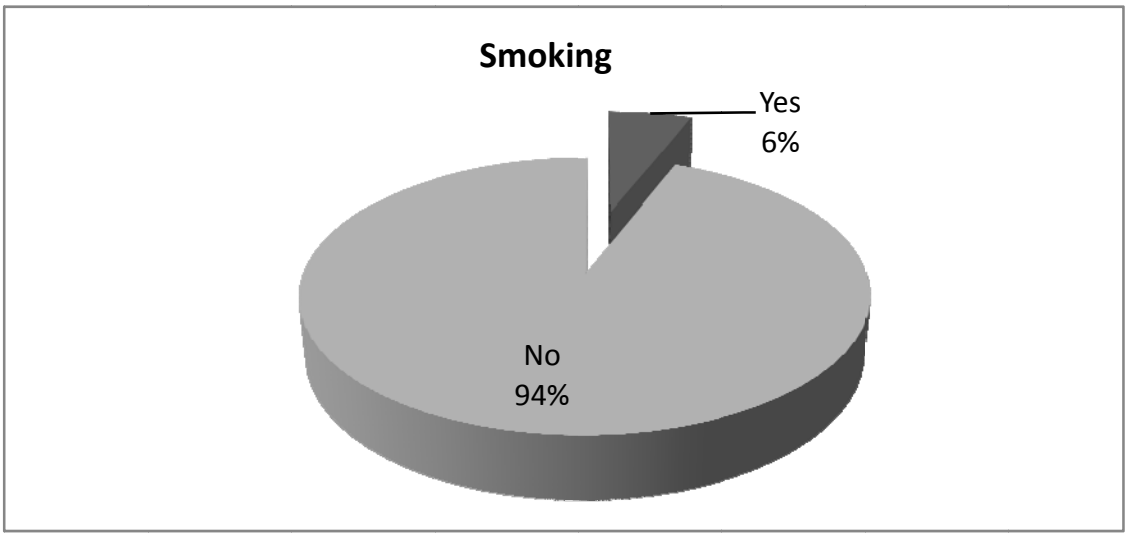

Figure 5: Distribution of smoking in the study population

CLINICAL EXAMINATION:

SUSPICIOUS FINDINGS IN DIGITAL RECTAL EXAMINATION

We found abnormal DRE in 26(1.72%) individuals only. Abnormal findings in DRE are shown in Table 3.

Table 3: Suspicious findings in Digital Rectal Examination

DRE Findings	No. of individuals (n)	Percentage (%)
Negative	1484	98.28
Positive	26	1.72
Total	1510	100

INVESTIGATIONS:

PSA LEVEL IN SERUM

Maximum individuals 1452 i.e.96.2% had PSA less than or equal to 4.0 ng/ml. Abnormal PSA i.e. PSA more than 4 ng/ml was found in 58 (3.8%) individuals. The minimum level of PSA in the study was 0.01 and maximum PSA value was 132.5ng/ml. The distribution of PSA in serum is as shown figure 6.

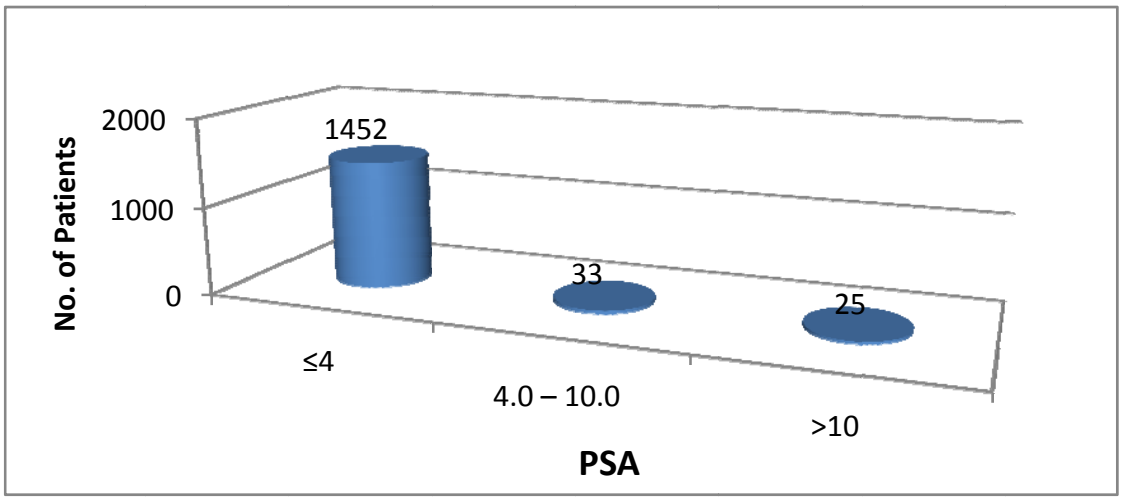

Figure 6: PSA Distribution

HISTOPATHOLOGY EXAMINATION (HPE) REPORT ON TRUCUT BIOPSY

On the basis of raised PSA value and abnormal DRE findings, 58 (3.84%) individuals were subjected to digitally guided trucut biopsy out of which 47 (3.11%) individuals had histopathological features of Benign Prostatic Hyperplasia (BPH) and 11 (0.73%) individuals had adenocarcinoma prostate. The trucut findings are shown in Table 4.

Table 4: Trucut Biopsy Findings

HPE	No. of individuals(n)	Percentage (%) (Total Biopsy, n=58)	Percentage (%) (Total Sample, n=1510)
BPH	47	81.03	3.11
Adenocarcinoma Prostate	11	18.97	0.73
Total	58	100	3.84

RELATION BETWEEN AGE AND PSA

It was found that with increasing age, PSA value also increased and this was statistically significant, where p value was less than 0.001. The relation between age and PSA is shown in Table 5.

Table 5: Relation between Age and PSA

Age(years)	PSA(ng/ml)			P value	Remarks
	PSA ≤ 4	PSA 4.0 – 10	PSA >10		
50-60	673	7	2	< 0.001	Significant
61-70	468	14	7		
>70	311	12	16		
Total	1452	33	25		

AGE AND MEAN PSA

With increased age, the mean PSA also increased and it was statistically significant, where p value was less than 0.001. This relation is shown in the table below.

Table 6: Distribution of Age and Mean PSA

Age (Years)	Mean PSA ±SD (ng/ml)	P value	Remarks
50-60	0.91±1.23	0.001	Significant
61-70	2.03±3.71		
>71	3.44±8.41		

RACE AND MEAN PSA

Although PSA was seen higher in the Aryans than the Mongolians, it was not statistically significant where the p value was >0.05 and this is shown in the table 7.

Table 7: Mean PSA distribution with the Race of the study population

Race	Mean PSA ±SD PSA (ng/ml)	P value	Remarks
Aryans	1.88 ± 3.35	0.711	Not significant
Mongolians	1.79± 6.155		

RELATION BETWEEN BODY MASS INDEX AND PSA

With increasing body mass index, serum PSA decreased and this inverse relation was statistically significant, where p value was < 0.001**.** The distribution of PSA with BMI is shown in figure 7.

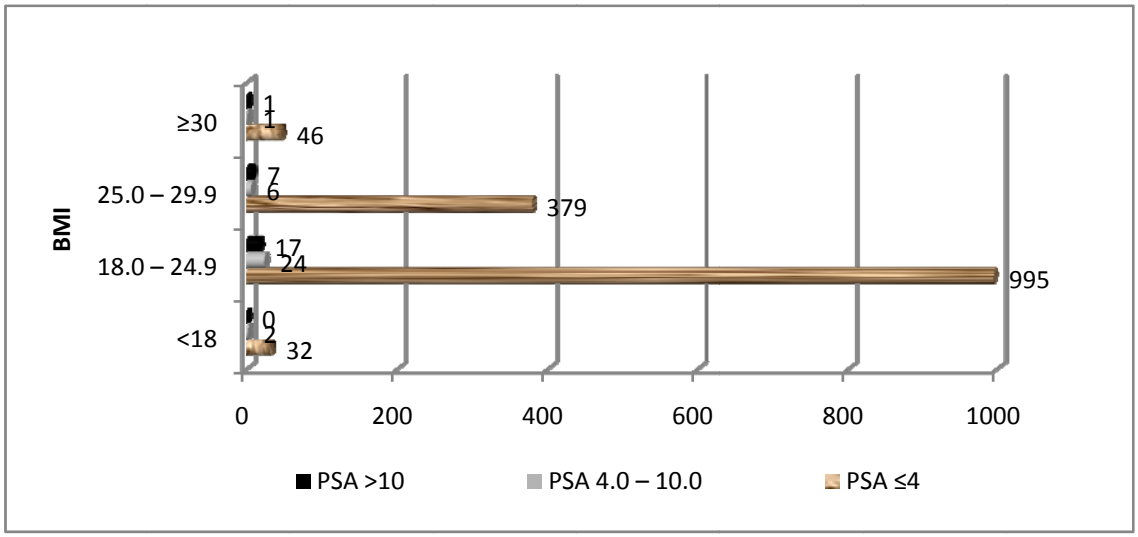

Figure 7**:** Relation between BMI and PSA

SUSPICIOUS DRE FINDINGS AND SERUM PSA

As shown in the Table below, suspicious DRE was found in 26 individuals and all of them were having PSA more than 4.0ng/ml. This was statistically significant, where p value was less than 0.001

Table 8: Suspicious DRE Findings and Serum PSA

DRE Findings	PSA (ng/ml)			P value	Remarks
	≤ 4	4 .0 - 10.0	>10		
Positive	0	1	9	< 0.001	Significant
Negative	1452	32	16		
Total	1452	33	25		

RELATION BETWEEN RACE AND HPE RESULT

Among the detected 11 cases of adenocarcinoma prostate in the study, 5 were Mongolians and 6 were Aryans. This finding was not statistically significant (p value was 0.257).

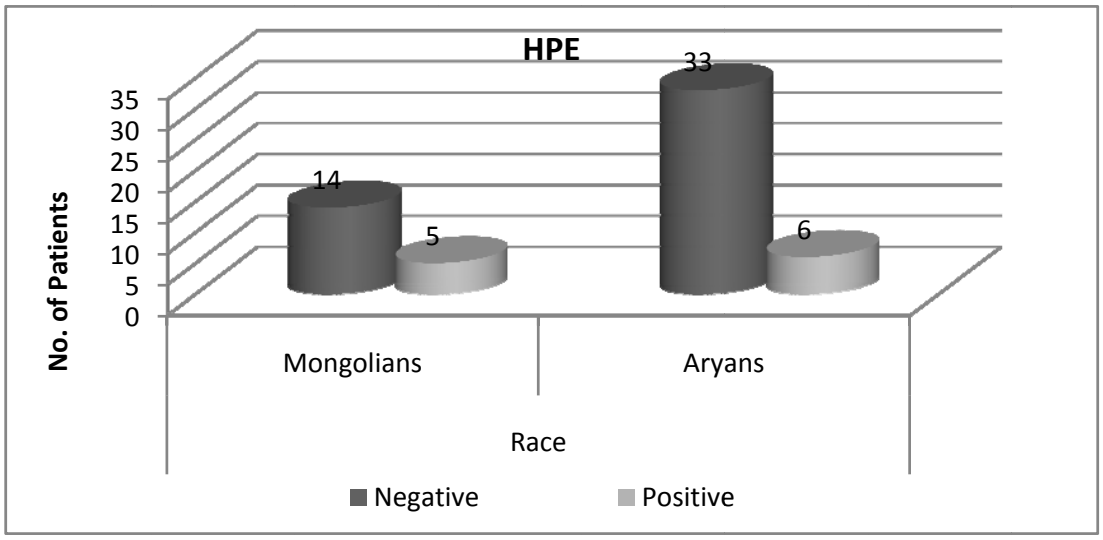

Figure 8: Relation between Race and HPE result

RELATION BETWEEN HPE RESULT AND ALCOHOL INTAKE

There was no significant relation between alcohol intake and incidence of carcinoma prostate. The p value was more than 0.05 and it was not significant .This is shown in the table below.

Table 9: Relation between HPE result and alcohol intake

HPE result	Alcohol intake		Total	P value	Remarks
	No	Yes			
Negative	30	17	47	0.404	Not significant
Positive	6	5	11		
Total	36	22	58		

RELATION BETWEEN HPE RESULT AND SMOKING

Smoking and carcinoma prostate were not statistically related and the p value was more than 0.05. The relation between smoking and HPE result is shown in table 10.

Table 10: Relation between HPE result and smoking

HPE result	Smoking		Total	P value	Remarks
	No	Yes			
Negative	26	21	47	0.398	Not significant
Positive	5	6	11		
Total	31	27	58		

DRE Findings and HPE

As shown in the figure below abnormal findings in DRE was found in 26(1.72%) individuals. All of them underwent digitally guided trucut biopsy of the prostate and adenocarcinoma prostate was found in 10(0.66%) individuals only. One individual with negative DRE (but high PSA value) had adenocarcinoma prostate on trucut biopsy. The specificity of DRE was 65.95% sensitivity 90.9% and positive predictive value 38.46%.

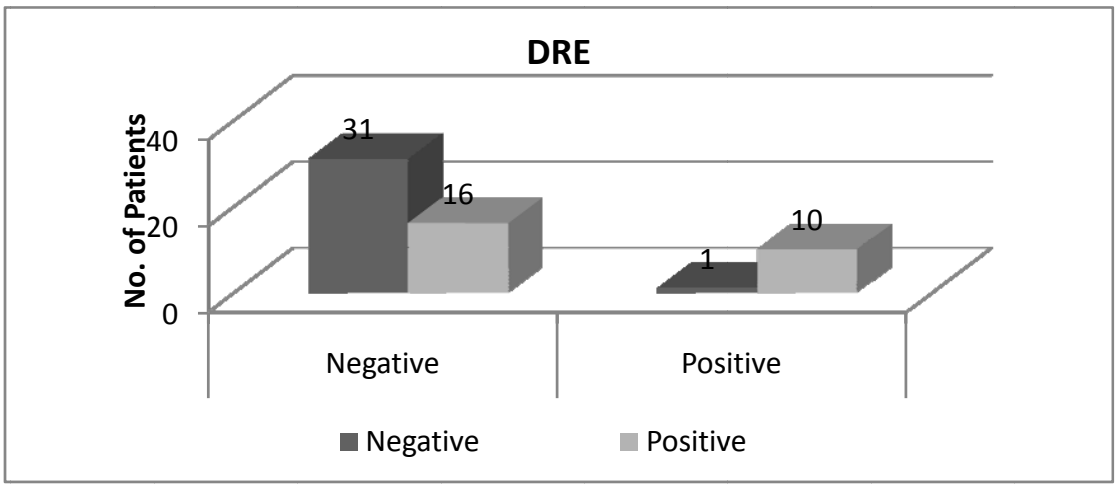

Figure9: DRE findings and HPE

PSA AND HPE

In the study population 58 individuals (3.84%) underwent trucut biopsy of the prostate on the basis of raised PSA. Out of which, eleven individuals (0.73%) were found to have adenocarcinoma prostate on histopathology report. In this study the sensitivity of PSA more than 4ng/ml in detecting carcinoma prostate was 100% and the positive predictive value for serum PSA was 18.96%. Of the 11 detected carcinoma prostate 10(0.66%) were having PSA more than10ng/ml. The relation between PSA and HPE is shown in the Figure below.

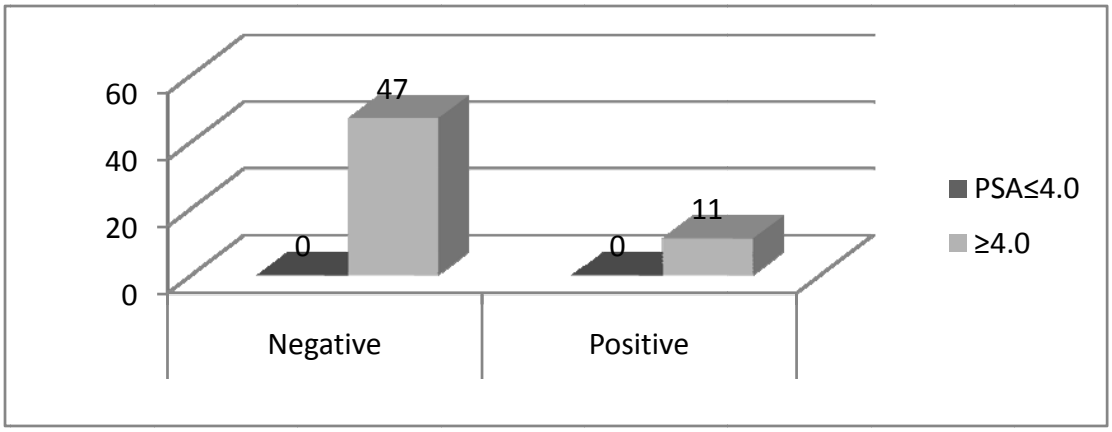

Figure 10 : PSA and HPE

COMBINATION OF DRE FINDINGS AND PSA WITH HPE

DRE and Serum PSA both were abnormal in twenty-six individuals (1.72%). Eleven (0.73%) individuals had adenocarcinoma prostate on histopathology with trucut biopsy. The sensitivity of DRE in combination with PSA came out to be 100% and the positive predictive value for the combination of both was 42%. The figure below shows this relation.

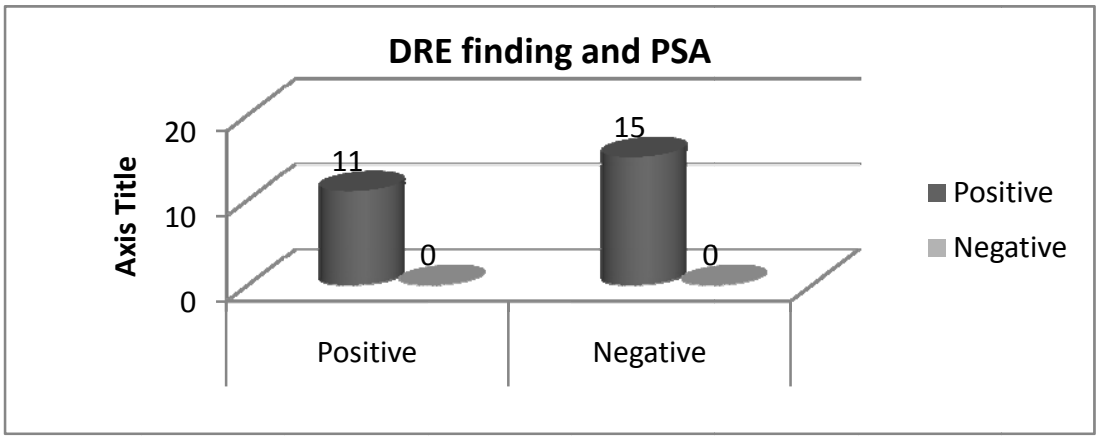

Figure 11: Combination of DRE Findings and PSA with HPE

CANCER DETECTION RATE

The overall cancer detection rate in this study was **0.73%** and those detected were locally advanced.

PROFILE OF INDIVIDUALS WITH CARCINOMA PROSTATE

In the study population, among those who were diagnosed to have adenocarcinoma prostate, the maximum PSA was 132.5 and highest Gleason score was 9. The following table shows the distribution of the patients, their age, PSA value, and Gleason score.

Table 11: profile of individuals with carcinoma prostate

Serial no.	Age (years)	PSA (ng/ml)	HPE	Gleason score
1	65	52.4	Adenocarcinoma prostate	4+3=7
2	55	17.9	Adenocarcinoma prostate	3+2=5
3	75	132.5	Adenocarcinoma prostate	4+5=9
4	70	8.01	Adenocarcinoma prostate	2+3=5
5	80	59.91	Adenocarcinoma prostate	4+4=8
6	67	12.94	Adenocarcinoma prostate	3+4=7
7	65	49.51	Adenocarcinoma prostate	5+3=8
8	83	36.26	Adenocarcinoma prostate	3+4=7
9	77	10.32	Adenocarcinoma prostate	2+1=3
10	82	18.32	Adenocarcinoma prostate	2+3=5
11	75	25.42	Adenocarcinoma prostate	2+2=4

FEASIBILITY OF SCREENING CARCINOMA PROSTATE

In the study most of the population came forward for screening on a request made in local radios and newspapers. In focused group discussions conducted in the camps majority of them told that such programmes are useful and must be conducted regularly. There was no hesitation among the individuals regarding blood sampling and digital rectal examination**.**

DISCUSSION

This field trial study, one of its kinds, was conducted in the outpatient department of surgery, and teaching district hospitals of B. P. Koirala Institute of Health sciences during a period of 8 month from 1st November 2010 to 31st July 2011. It included 1521 healthy males >50 years of age, who gave consent for enrollment in the study. Out of this study population only 1510 were analysed as 5 subjects were lost to follow up and 6 did not give consent for trucut biopsy.

AGE:

Prostate cancer is a disease associated with ageing. Prostate cancer is rarely diagnosed in men younger than 50 years, accounting for less than 0.1% of all patients. Peak incidence occurs between the ages of 70 and 74 years, with 85% diagnosed after the age of 65 years.

The following table shows the mean age of the study population in different studies.

Study	Country	Study population	Mean age (in Years)
Seo et al (2007)	Korea	4967	66.1± 9.1
Ganpule et al (2007)	India	1919	62.1± 9.5
Niang et al (2011)	Senegal	572	65.5
Present study	Nepal	1521	63.63± 9.76

Thus our age distribution is comparable to that of above mentioned studies.

DISTRICTS

The enrolled patients in our study were from all over the eastern region of Nepal. Most of the patients were from Sunsari district followed by neighbouring district Jhapa. This study was conducted in B. P. Koirala Institute of Health Sciences, Dharan, Sunsari, Nepal and Sunsari is the local district, which may be the reason for majority of patients from the same district.

RACE:

The Nepali population is mainly divided into Indo-Aryan and Tibeto-Mongolian ethnicities. In this study the Aryans were 900 (59.60%) and Mongolians 610 (40.40%). This is in accordance to the general population of Nepal which harbours more than 50% Aryan population.

RISK FACTORS:

- **ALCOHOL CONSUMPTION:**

Alcohol consumption is of interest for risk of prostate cancer because of its association with other cancers, its effect on estrogen and testosterone, and the high content of polyphenolic compounds with antioxidant activity in red wine. Study done by Breslow and Weed, in 1998, showed no increased risk for prostate cancer among light to moderate drinkers. A later prospective cohort study done by Sesso et al, 2001 found a dose-dependent increase in prostate cancer, risk being highest in those imbibing more than three hard liquor drinks per day (relative risk, 1.85) during a period of 11 years There was no association with wine or beer consumption and prostate cancer risk, although the wine consumption was not separated into red or white varieties. Another study done by Marieke Schoonen et al, in 2005, concluded that prostate cancer risk was unassociated with total alcohol consumption but that consumption of one to three glasses of red wine per week had a protective effect (relative risk, 0.82), even when adjusted for age, PSA screening, total lifetime number of female sexual partners, and smoking.

In the current study, alcohol consumption was seen in 107 (7.08%) individuals and it was not statistically associated with incidence of carcinoma prostate. Thus our study is in accordance with above study findings.

- **SMOKING HABIT**

Cigarette smoke may be a risk factor for prostate cancer because it is a source of cadmium exposure, increases circulating androgen levels, and causes significant

cellular oxidative stress. Both case-control and cohort studies done by Bostwick et al in 2004 have produced conflicting results, and none has demonstrated a clear dose-response relationship between smoking and carcinoma prostate.

In our study, smoking was found in 89 (5.8%) individuals. Cigarette smoking in the current study was also not statistically associated with incidence of carcinoma prostate.

SERUM PSA VALUE: PSA is a 33-kD glycoprotein that acts as a serine protease. The presence of prostate disease (prostate cancer, BPH, and prostatitis) is the most important factor affecting serum levels of PSA. PSA elevations may indicate the presence of prostate disease, but not all men with prostate disease have elevated PSA levels. Furthermore, PSA elevations are not always specific for prostate cancer.

In the study conducted by Ganpule et al, 2007, in a population of 1919 healthy males, PSA was >4 ng/ml in 10.7% population. In a similar study conducted by Catalona et al, 1991, in a population of 1653 individuals, PSA was > 4ng/ml in 8.3% population. In the study done by Chia et al, 2007, in a population of 3,486 males PSA was >4ng /ml in 7.3% of the study population.

In our study PSA was > 4ng/ml in 3.8% population which is quite lower in comparision to the study findings discussed above.

This difference may be because in the study done by Ganpule et al, 2007, the population of elderly males (age more than 60 years) were more than in our study (59.08% vs.54.8%) and PSA is directly related to age. In the study done by Catalona et al abnormal PSA is more than ours because they had repeated the PSA of normal individuals after 6 months, which we did not do. Also, our study sample was relatively smaller than the above mentioned studies.

AGE AND PSA

PSA is widely known to be associated with age. Since PSA is produced in the prostate and prostate generally enlarges after age 50, the increase in PSA levels with age is understandable. Table below clearly shows similar scenario in various Asian populations.

Study	Country	Population (n)	PSA value (ng/ml) by age groups (years)		
			50-59	60-69	70-79
Liu et al (2008)	China	8422	3.20	4.10	5.37
Lee et al (2000)	Korea	5805	2.4	3.9	6.3
Malati and Kumari (2004)	India	583	1.6	2.0	2.47

In our study also, increase in age was associated with rise in PSA which was statistically significant (p value < 0.001). Thus finding of our study is similar to above studies.

BMI AND PSA

Obesity as measured by body mass index (BMI) has been suggested to be a risk factor for prostate cancer because of their common occurrence in middle-aged men and clear links to colon and breast cancer risk. Studies done by Giovannucci in 2003 and Porter and Stanford in 2005 have suggested a protective effect for higher BMI in men 60 years and younger. Since there is an inverse relationship between circulating androgen levels and measures of obesity as studied by Svartberg et al in 2004 this may explain why higher BMI is associated with lower serum PSA concentration which in obese men could lead to ascertainment bias against biopsy, perhaps explaining the previously noted protective effect of obesity on prostate cancer risk.

Also in the study done by Chia et al, 2008, there was a significant inverse relation between BMI and PSA level. In a similar study done by Culp S et al, 2009, there was significant inverse relation between BMI and PSA.

In our study also there was significant inverse relation between BMI and PSA.

RACE AND PSA

Prostate-specific antigen (PSA) determination is currently the most widely used serum marker for both prostate cancer screening and follow-up after anticancer treatment. Moreover, another issue is that PSA levels in relation to the presence of prostate cancer exhibit ethnic differences. The normal currently used PSA reference levels were derived from studies of mainly white men. Therefore, the reference levels may not be directly applicable to Asian patients.

In a study done by Chia et al, 2007, in a population of 3,486 the mean of PSA of Chinese population i.e Mongolian was 1.60ng/ml and Indian population i.e Aryans was 1.23ng/ml.

In our study the mean PSA for Mongolian race was 1.79ng/ml and that for Aryan race was 1.88ng/ml. This difference may be due to small population sample in our study

MEAN PSA LEVEL

Men with prostate cancer generally exhibit elevated levels of PSA in their serum; this tumor marker is now frequently used for prostate cancer screening, diagnosis and monitoring of response to therapy. To date, studies conducted to establish normal serum PSA values have involved study populations that have included North America, Europe, Japan, Korea and China. To our knowledge, there are no reports of population studies involving Nepal.

In the studies shown in the table the mean PSA level for different age group was as:

Study	Country	PSA value (ng/ml) by age groups (years)		
		50-59	60-69	70-79
Liu et al (2008)	China	3.20	4.10	5.37
Lee et al (2000)	Korea	2.4	3.9	6.3
Malati and Kumari (2004)	India	1.6	2.0	2.47

Our study showed the mean PSA level with age as depicted by the table below which is almost comparable to the study done by Malati and Kumari in 2004 in Indian population.

	PSA value(ng/ml) by age groups (years)		
Present study	50-60	61-70	>70
	0.91	2.03	3.44

PSA AND HISTOPATHOLOGY:

PSA is a member of the human kallikrein gene family. PSA is secreted in high concentrations (mg/mL) into seminal fluid, where it is involved in liquefaction of the seminal coagulum and it is normally found in low concentration in serum (ng/mL). The effectiveness of PSA as a screening method for prostate cancer is debated. However, it has been proved that use of PSA increases detection rates of prostate cancer and leads to the detection of prostate cancers that are more likely to be confined when compared with detection without the use of PSA. This has been documented in population-based data, observational studies, and randomized screening trials.

In study done by Harvey et al, 2009, PSA sensitivities ranged from 0.78 to 1.00 and specificities from 0.06 to 0.66.

In the study done by Catalona et al, 1994, in 6,630 individuals PSA had a sensitivity of 80 percent in detecting prostate cancer.

In the study done by Woolf, 1995 the reported positive predictive value of PSA in screening studies was 28 to 35 percent.

In the study done by Niang et al, 2011 in a population of 572, the sensitivity of PSA level was 95.5% and the positive predictive value was 31.8%.

In our study the sensitivity of PSA was 100% and positive predictive value was 18.96%.

The positive predictive value in our study is lesser than the above study because we did not have the facility of TRUS guided biopsy.

RACE AND CARCINOMA PROSTATE

Descriptive epidemiology has shown wide ethnic/racial differences in the incidence of carcinoma prostate. The highest incidence rate group (100/100,000/year) includes African Americans in the United States; intermediate rates (20–50/100,000/year) are observed in Canada, South America, and European countries; and low rates (10/100,000/year) in Japan, China, and India. The incidence of prostate cancer varies from country to country, with the highest incidence being found in the Western world and the lowest in Asian countries. Owing to the low incidence of prostate cancer, there could be different views regarding the use of PSA in Asian countries, especially for the early detection/screening of prostate cancer.

Although we could not find studies comparing cancer detection rate among Aryans and Mongolians, our study showed that there was no significant difference in the incidence of carcinoma prostate in the two groups.

DIGITAL RECTAL EXAMINATION VERSUS HISTOPATHOLOGY:

Before the availability of PSA testing, physicians relied solely on DRE for early detection of prostate cancer. DRE is a test with only fair reproducibility in the hands of experienced examiners that misses a substantial proportion of cancers and detects most cancers at a more advanced pathologic stage, when treatment is less likely to be effective.

In the study done by Catalona et al, 1991 in a population of 1653 suspicious DRE finding was noted in 1.5% study population. In similar study done by Rabah and Arafa, 2010 in a study population of 2100 abnormal DRE was found in 5% population.

In our study DRE finding was abnormal in 1.72**%** population.

The sensitivity, specificity and positive predictive value of different studies is shown in the table below:

	Lee et al(1988) (n=784)	Mettlin et al (1991) (n=2425)
Cancer detection rate	1.3	1.4
Sensitivity	45	58
Specificity	97	96
Positive predictive value	34	28

In our study the sensitivity for DRE was 90.9%, specificity 65.95% and positive predictive value was 38.46%.

The cancer detection rate for DRE in our study was 0.67%.

This difference may be due to lack of TRUS guided biopsy in our study.

COMBINATION OF DRE FINDINGS AND PSA WITH HPE:

The combination of DRE and serum PSA is the most useful first-line test for assessing the risk of prostate cancer being present in an individual. According to Catalona et al, 1994; Littrup et al, 1994; Stone et al, 1994 and Schroder et al, 1998; when DRE and PSA are used as screening tests for prostate cancer detection, detection rates are higher with a combination of the two tests.

In our study also the sensitivity of DRE in combination with PSA came out to be 100% and positive value for the combination of both was 42% which was more than that detected by PSA or DRE alone.

HISTOPATHOLOGY FINDINGS:

The following table shows yield of TRUS guided biopsy in different studies.

Study	Study population	No. of trucut biopsy	Percentage Yield of trucut biopsy
Catalona et al (1991)	1653	112	37 (37.03%)
Niang et al (2011)	572	72	22 (30.6%)
Rabah and Arafa (2010)	2100	132	52 (39.3)

In our study the trucut biopsy for prostate cancer was positive in 18.97% of the total biopsies

This difference is because our trucut biopsy was digitally guided which has less sensitivity compared to TRUS guided biopsy.

OVERALL CANCER DETECTION RATE:

Cancer detection rate in our study was 0.73% and it was lesser than that detected by the studies shown in the table below. The detection rate in our study was less because our sample size was smaller than the study groups and we did not had the facility of TRUS guided biopsy of the prostate.

Study	Study population	Cancer detection rate
Mettlin et al (1991)	2425	1.4%
Galic et al (2003)	1,000	3.7%
Ganpule et al (2007)	1919	1%
Rabah and Arafa (2010)	2100	2.5%

FEASIBILITY OF SCREENING CARCINOMA PROSTATE

This was the first field trial study conducted in eastern Nepal attempting to clarify the burden of prostate cancer and to study the feasibility of prostate cancer screening.

In the present study it was seen that most of the population came forward for screening on the request made in local radios and newspapers. In focused group discussions conducted in the camps majority of them told that such programmes are useful and must be conducted regularly. There was no hesitation among the individuals regarding blood sampling and digital rectal examination**.**

Despite being an absolutely new introductory programme, we found that this programme was heartily welcomed by the local population with open hands. Also we found this programme to be needy to the Nepalese people like the vast campaining programmes being conducted for infectious diseases. Such screening programmes should also be encouraged for other cancers as well.

SUMMARY

This field trial study was conducted in the Department of Surgery, B.P.K.I.H.S, Dharan Nepal on outpatient department basis including teaching district hospitals of Eastern Nepal of the Institute. The duration of the study was of 8 months from 1st November 2010 to 31st July 2011. The study population was of 1521 healthy males with age more than 50 years who gave consent for enrollment in the study.

- Age ranged from 50 to 100 years with the mean age of 63.63 ± 9.76 years. The majority of the population in the study were in the age group of 50-60 years (45.2%).
- Enrolled patients in the study were from all over the eastern region of Nepal. Most of the subjects were from Sunsari district 644 (45.2%), followed by neighboring Jhapa 281(18.6%), Morang 226(15%) and Dhankuta 120(7.9%). The rest of the study population was from - Saptari, Siraha, Ilam, Udaypur, Sankhuwasabha, Taplejung and Tehrathum districts.
- In the study population 59.6% individuals were from Aryan descent and 40.4% were from Mongolian descent.
- In the study majority of the population 1036 (68.6%) had normal body mass index (BMI), 392 (26%) were overweight and 48 (3.2%) individuals were obese.
- In the study 189 (12.5%) individuals had heard of carcinoma prostate and the same percent knew that it occurs in male at the neck of Urinary Bladder. Twelve and half percent individuals said that it can be detected by blood test. Of the study population 27(1.78%) individuals said that carcinoma prostate occurs in both male and female. Only 175 (11.59%) individuals were able to say that carcinoma prostate occurs in old age.
- Alcohol as a risk factor was present in 7.08% study population and smoking as a risk factor was present in5.8% study population. In this study smoking

and alcohol consumption were not statistically related with the incidence of carcinoma prostate.

- In the study population maximum individuals 1452 (96.2%) had PSA less than or equal to 4.0 ng/ml. Abnormal PSA i.e. PSA more than 4 ng/ml was found in 58 (3.8%) individuals. The minimum level of PSA in the study was 0.01 and maximum PSA value was 132.5ng/ml.
- In this study it was found that with increasing Body Mass Index, serum PSA was decreasing.
- There was no statistical difference in the cancer detection rate among the two race i.e. Aryans and Mongolians.
- In the study abnormal DRE was found in 26(1.72%) individuals.
- In the study population 58 (3.84%) individuals underwent trucut biopsy of the prostate on the basis of raised PSA .Out of which, eleven individuals were found to have carcinoma prostate. In this study the sensitivity of PSA more than 4ng/ml in detecting carcinoma prostate was 100% and the positive predictive value for serum PSA was 18.96%. Of the 11 detected carcinoma prostate 10 were having PSA more than10 ng/ml.
- Abnormal finding in DRE was found in 26(1.72%) individuals. All of them underwent trucut biopsy of the prostate and adenocarcinoma prostate was found in 10 indivuduals .Only 1 individuals with negative DRE (but high PSA) had adenocarcinoma prostate on trucut biopsy. The specificity of DRE was 65.95%, sensitivity 90.9% and positive predictive value 38.46%.
- The sensitivity of DRE in combination with PSA was 100% and positive predictive value for the combination of both was 42% which was more than that detected by PSA or DRE alone.
- The overall cancer detection rate in this study was **0.73%** and that detected were locally advanced. All those having negative biopsy but positive PSA and DRE findings are kept on constant follow up.

CONCLUSION

- The cancer detection rate in a cohort of healthy population of Eastern Nepal, is 0.73%.
- As this study has been conducted successfully, it can be concluded that it is feasible to screen prostatic cancer in population of Eastern Nepal.

RECOMMENDATIONS

- Further studies should be conducted in Eastern and other parts of Nepal to know the true burden of carcinoma prostate.
- With the help of NGOS, various social organization and local clubs such studies can be conducted on large scale.
- Carcinoma prostate is evolving as one of the most common male malignancies worldwide and most of the population in our study were unaware of the disease, so various awareness programmes should be launched through National television, local radio centres and national and local newspapers to propagate the nature, clinical features and prognosis of the disease.

LIMITATIONS

- Lack of adequate fund was the major limitation.
- The unavailability of TRUS and TRUS guided biopsy was one of the important limiting factor as its absence hampered the cancer detection rate in biopsy.

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प्रश्नावली

आइ.डी: .....

नाम: ..... उमेर: ..... लिङ्ग: ..... जाति: .....

ठेगाना: ..... टेलिफोन नं.: .....

उचाई: ..... तौल: .....

कृपया राम्रोसँग चिन्ह लगाउनुहोला

- तपाईले पोष्टेट क्यान्सरको बारेमा सुन्नु भएको छ? छ/छैन
- यदि छ भने, यो रोग कसलाई हुन्छ ? महिला/पुरुष
- यो क्यान्सर कुन ठाउँमा लाग्छ ? टाँउको/घाँटी/पेट/पिसाव थैलीको मुखमा
- यो क्यान्सर कसलाई हुन्छ ? बच्चाहरुलाई/तन्नेरीहरुलाई/बुढाहरुलाई

लक्षणहरु:

- खान मन नलाग्ने छ/छैन
- तौल घटेको छ/छैन
- ढाड दुख्ने छ/छैन

अरु समस्याहरु:

- चक्तचाप (ब्लड-पेसर) रोग छ/छैन
- चिनी रोग छ/छैन
- सिओपिडी- दम, श्वास प्रश्वासको रोग छ/छैन
- धुम्रपान छ/छैन कति वर्ष देखि .....
- मद्यपान छ/छैन कति वर्षदेखि .....

अन्य जाँच:

- PSA: .....
- DRE: .....

  .....
- USG: .....

  .....
- TRUCUT BIOPSY REPORT: .....

मञ्जुरीनामा

म स्वेच्छिक रुपले प्रोस्टेट ग्रन्थि को क्यान्सर सम्बन्धि प्रारम्भिक जाँच मा भाग लिन मञ्जुर छु । डाक्टरहरुले जाँच को क्रममा हुने प्रक्रियाको बारेमा बुझाइ सक्नु भएके छ । साथै भविष्य मा आवश्यक परे मलद्धार को बाटो बाट सुई हाली प्रोस्टेट ग्रन्थि को मासु जाँच्ने जानकारी र त्यस बाट हुने सम्भावित खतरा को जानकारी पनि दिनुभएको छ ।

मञ्जुरी दिनेको नाम .....

सहि .....

ठेगाना .....

मिति .....

GLIMPSES OF THE SCREENING CAMP

Banner kept by local social organization

People attending screening camp

Curious people at screening camp

Filling the proforma

Collecting blood for PSA

Waiting for DRE

Explaining the need for screening carcinoma prostate

With Volunteers at screening Camp