Clinical Pattern of Prostate Cancer among Sudanese Patients Treated at Gezira Hospital for Renal Disease and Surgery and the National Cancer Institute, University of Gezira, Sudan (2009 – 2013)

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Date:  /10/2014
Dedication

With all my due love and respect, I dedicate this humble work to the soul of my father, my mother, my wife and daughters, brothers and sisters and to my respected Teachers to whom I owe who I am today.

Mohammed Elhassan Abdarahman
Acknowledgment

I would like to express my special thanks with deepest appreciation and gratitude to my supervisors Prof. Mohammed El imam and Dr. Dafalla Abu Idris for their encouragement, guidance and help through the writing of this thesis.
Clinical Pattern of Prostate Cancer among Sudanese Patients Treated at Gezira Hospital for Renal Disease and Surgery and the National Cancer Institute, University of Gezira, Sudan (2009 – 2013)

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Abstract

Prostate cancer is a significant burden to men's health. It is now one of the leading causes of cancer related death in human male worldwide. In Sudan the incidence of prostate cancer is increasing. The objective of this study is evaluation of the clinical pattern of prostate cancer among Sudanese patients treated at Gezira NCI. This is a descriptive retrospective hospital based study which was conducted on 424 patients with prostate cancer treated at Gezira NCI from 1/2009 -12/2013. The descriptive data of the patients included in this study is provided by Gezira NCI registry and patients medical records. The data were analyzed using social package for scientific statistic (SPSS). Chi-square test was used to test for association between variables. This study showed that 65.3% of the patients were from the Gezira state, 33.7% from out state and 0.9% unknown. The majority( 91.3%) were married and 8.7% were unmarried. The bulk of the patients were in the age group 71-80(36%) and the age group 61-70 years (35.5%) while less than 1% were less than 50 years. Concerning education level most of the patient were illiterate (37.3%), 26.7% were khalwa graduates, 23.3% were primary educated, 7.1% had education to high school level, 1.2% were intermediate educated and 4.4% had university and higher education.

The study showed that more than 50% of our patients were farmers, 31.1% worked in the private sector, 7.5% were drivers and (10.6%) were government employee. Regarding BMI 32.8% had normal weight, 24.5% were under weight, 6.1% were overweight, 3.1% were obese and 0.2% were morbidly obese. In the study when considering LUTs(frequency, urgency, hesitancy, straining, weak stream, dysuria), frequency complained about by 84.7% and urine retention 50.9% represented the dominant presenting symptoms while those with backache were 14.4% and those with haematuria were 9%, 6.8% presented with neurological symptoms, and 4.5% presented with renal impairment. Concerning findings on DRE, hardness represented 67.6%, nodularity 62.3%, asymmetry 10.1% while those with obliterated median sulcus were 12%, 13.4% were hypertensive, 4% were diabetic, 2.4% were both hypertensive and diabetic, 78.3% were neither hypertensive nor diabetic and 0.9% were unknown. Socially 3.3% were alcohol consumers, 25% were smokers and snuffers, 14.9% were both alcohol consumers and snuffer and 55% were not alcoholic nor smokers. 80.9% of the patients showed no family history of malignancies, 4.2% had positive family history of malignancies and 14.7% were unknown. The finding on PSA testing of the patients showed that 96.6% had PSA level above 4ng/ml and 1.7% had PSA level less than 4ng/ml. Histopathology reports showed that 100% were adenocarcinoma and the 63.2% of patients had Gleason score above 7, 18.4% less that 7 and 15.8% had Gleason score of 7. When staging the disease 1.7% had organ confined disease, 40.3% had locally advanced one while 58% had metastatic disease. Bone metastases were found in 46.7%, 1.4% had liver metastasis, 0.2% had lung metastasis and 0.2% had para-aortic lymph nodes metastasis. The conclusion is that the incidence of Prostate Cancer has increased. This is most probably due to introducing PSA testing and ultrasound guided biopsy. Prostate cancer is a multi-factorial disease but age, race, and family history still are the main risk factors. Other risk factors have inconsistent evidence. Adenocarcinoma represents the most common type of prostate cancer. Low education level, low socioeconomic status and decrease awareness about prostate cancer are most probably the cause of the advanced stage of the disease on presentation. Bones are the most common site of distant metastases for prostate cancer and PSA is considered as a good tool for diagnosis of the disease and prediction of bone metastasis.
النمط الاكلينيكى لسرطان البروستات بين المرضى السودانيين الذين تلقوا علاجهم بمستشفى ودمدنى لامراض وجراحة الكلى ومركز الجراحة لعلاج الأورام، ودمدنى، ولاية الجزيرة، السودان (2009-2013)

ملخص الدراسة

يشكل سرطان البروستات خطرا كبيرا على صحة الرجال. ويعتبر الآن واحداً من الأسباب الرئيسية لوفيات السرطان عند الرجال في جميع أنحاء العالم. في السودان، تكون الإصابة بسمنة دفعًا للإصابة بسرطان البروستات. الهدف من الدراسة هو تقييم السطح السريري لسرطان البروستات بين المرضى الذين تلقوا العلاج بمركز علاج الأورام في السودان. هذه الدراسة دراسة وصفية مزدوجة مستقبليّة وتتطرق إلى أمور أخرى أهميتها. أجريت بعد تلقي المرضى الذين يعانون من سرطان البروستات بالعلاج الشامل في مركز الجزيرة في السودان. كانت نسبة المرضى الذين تلقوا العلاج بالمركز 50%. استخدمت الدراسة مجموعة من الأدوات التشخيصية، مثل الفحص الفيورين، وقياس مستويات البروستات الخاص، والتخطيط السطحي، والتشخيص الخصوب، وقياس مستويات البروستات الخاص. هذه الدراسة تكشفت أن البروستات ذات النوع الأكثر شيوعاً بين الرجال السودانيين هو نوع البروستات النووي، والذي يعتمد على الأعراض البدنية، ويفترض في تقييم حالات السرطان. كما توضح الدراسة أن السرطان الأكرونيون لدى الرجال السودانيين يعاني من داخل الجسم ويعاني من بالخارج، ويعاني من في الخارج. هذه الدراسة تؤكد على أهمية الوعي بالسرطان، وتعمل على ارتفاع المستوى التعليمي لدى المرضى، والحد من السمنة، وتحفيز المرضى على أخذ العلاجات المناسبة. النتائج تشير إلى أن سرطان البروستات هو السرطان الأكثر شيوعاً بين الرجال السودانيين.
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Abbreviations

ACP    American College of Physicians
ACS    American cancer society
AUA    American Urological Association
BMI    Body mass index
BPH    Benings prostatic Hyperplasia
BPSA   Benign prostatic specific Antigen
CPSA   Complex prostatic specific Antigen
DHT    Dihydrotestosterone
DRE    Digital Rectal Examination
ERSPC  European Randomized Study of Screening for prostate Cancer
ESMO   European Society for medical Oncology
F/T PSA Free/total prostatic specific Antigen
G      Grade "Histological"
HIFU   High Intensity Focused Ultrasound
HIV    Human Immunodeficiency Virus
IGF    Insulin-like growth factor
IGFBP  Insulin-like growth factor Binding protein
LHRH   Luteinizing Hormone Releasing Hormone
LUTs   Lower Urinary Tract symptoms
MRI    Magnetic Resonance Imaging
NSAID  Non Steroidal Anti Inflammatory Drug
PCA3   Prostatic cancer antigens3
PCa    Prostatic Carcinoma
PIA    Proliferative inflammatory Atrophy
PIN    Prostatic intraepithelial Neoplasia
PLCO   Prostate Lung Colorectal and ovaries
PSA    Prostatic Specific antigen
PSADT  Prostatic Specific Antigens Velocity Doubling Time
PSAV   Prostatic Specific Antigens Velocity
RS     Reactive Stroma
SEER   Surveillance Epidemiology and End Results
TNM    Tumor, Node, Metastasis
TRUS   Trans Rectal Ultrasound
USPSTF United States Preventive Services task Force
UTI    Unitary Tract Infection
CHAPTER 1

Introduction and literature review

1.1. Introduction to Prostate Cancer(1-20)

Although the prostate was first described by Venetian anatomist Niccolo Masia in 1536 and illustrated by Flemish anatomist Andreas Vesalius in 1538, prostate cancer was not identified until 1853(1). Prostate cancer appears to impact the world’s populations differently with widely varying incidence and mortality rates(2). It is now considered as the fourth most common male malignant neoplasm worldwide (3). The incidence of prostate cancer has increased significantly over the past two decades, in some areas almost exponential (4-6). This increased incidence is explained by introduction of PSA test(7,8).

Autopsy studies shows that the prevalence of the prostate cancer is increasing sharply with age, and foci of prostate cancer can be detected in up to 70-80% of 80 years old male who died of other causes (9-11).

There is limited knowledge on the etiology of the prostate cancer. Racial differences in the incidence of clinical prostate cancer and tendency to familial accumulation suggest a genetic component, but there are others factors( infectious, dietary, hormonal, …) that appear to play a role in the development of prostate cancer(12).

Prostate cancer may be asymptomatic or may cause symptoms similar to those of Benign Prostatic Hyperplasia (BPH), and by spreading locally and to the distant part of the body may cause additional symptoms e.g. (bone pain, neurological symptoms)(13,14).

The principal tools for evaluating prostate cancer include a combination of digital rectal examination (DRE), and prostate specific antigen promoting decision to perform a transrectal ultrasound(TRUS) guided prostate biopsy(15,16,17).

Treatment of prostate cancer involve surgery, radiation, chemotherapy, cryotherapy, HIFU, hormonal therapy, antiandrogens or some combinations (18-20).
1.2: Prostate gland

1.2.1: Embryology (21):

The prostate develops from the outgrowth from prostatic segment of the urethra, that grows into the surrounding mesenchyme. This outgrowth and branching start at week 10 during embryo growth. By week 12 there are 5 groups of tubules that form the lobes of the prostate. The first group makes up the middle lobe. The second and third groups make up the right and left lateral lobes. The fourth group is the posterior lobe that starts from the floor of the urethra and the fifth group is the anterior lobe.

The normal formation of the prostate gland requires the presence of dihydrotestosterone (DHT) which is synthesized from fetal testosterone by action of 5 alpha reductase. This enzyme is localised in the urogenital sinus and external genitalia of humans. Consequently deficiencies of 5 alpha reductase will cause rudimentary or undetectable prostate, in addition to severe abnormalities of the external genitalia although the epididymis, vas deferens and seminal vesicles remain normal.

1.2.2: Anatomy (21, 22, 23)

The prostate gland, a part of a man's reproductive and urinary systems, is shaped like an inverted pyramid. It has a base, an apex, anterior, posterior and inferolateral surfaces. Normal prostate gland is approximately 20 – 25 g in volume, 3 cm in length, 4 cm wide and 2 cm in depth.

As men get older the prostate gland becomes variable in size secondary to benign prostatic hyperplasia. The gland is located posterior to the pubic symphysis, superior to the perineal membrane, inferior to the bladder and anterior to the rectum. The prostate is enclosed by a capsule composed of collagen, elastin and large amount of smooth muscle.

The prostate is covered by 3 distinct layers of fascia on the anterior, lateral and posterior aspects. The anterior and anterolateral fascia is in direct continuity to the true capsule. Laterally, the fascia fuses with the levator fascia. The posterior aspect is covered by the rectovesical (Denonvilliers) fascia.

The gland is supported anteriorly by the puboprostatic (pubovesical) ligaments and inferiorly by the external urethral sphincter and perineal membrane.
The prostate consists of approximately 70% glandular tissue and 30% fibromuscular stroma. The glandular part produces the fluid portion of the semen. The muscular part control urine flow and ejaculation while the fibrous part provides the supportive structure of the gland.

Lowsley described the lobar structure of the prostate in 1912 and he suggested that the gland is composed of five lobes anterior, posterior, middle and two laterals.

I- **Anterior lobe:**

This Term is used to describe the anterior portion of the gland lying in front of the urethra. It is devoid of glandular tissue being formed completely of fibromuscular tissue.

II- **Median lobe:**

It is the cone shaped portion of the gland situated between the two ejaculatory ducts and the urethra.

III- **Latera lobes (right and left):**

Form the main mass of the gland and are continuous posteriorly. They are separated by the prostatic urethra.

IV- **Posterior lobe:**

Is used by some to describe the posteromedial part of the lateral lobes that can be palpated through the rectum during DRE.

Lowsley’s concept of a 5-lobed prostate has been replaced by McNeal’s concept of zonal architecture. In this scheme, the prostate has 3 glandular zones each with its own ductal system. The peripheral zone, the transition zone and the periurethral glands have a similar histologic appearance and are derived from the urogenital sinus. However, the central zone is histologically distinct from the other 3 zones and is derived from mesonephric tissues (ie, wolffian tissue).

**Peripheral zone**

The peripheral zone constitutes almost about 75% of the normal prostate gland. It occupies the distal part of the gland, the area around the urethra distal to the
verumontanum. The acini are small, round, and smooth-walled, and their ducts drain into the urethra distal to the verumontanum. The stroma is loosely woven with randomly oriented muscle fibers. Approximately 70% of Prostate Ca cases arise in this zone.

Central zone

The central zone constitutes 25% of the normal prostate and occupies the part of the prostate behind the proximal prostatic urethra. The ejaculatory ducts pass through the central zone. The acini are large and irregular with significant intraluminal folds and ridges. They are also surrounded by muscular tissues that closely follows the shape of the acini. Approximately 5-10% of PCa cases arise in this zone.

Transition zone

The transition zone makes up approximately 5-10% of the normal prostate gland (see the image below). The transition zone lies on either side of the proximal prostatic urethra lateral to the internal sphincter. The glandular architecture is similar to that of the peripheral zone; however, the stroma is more compact. The transition zone is where BPH originates and where approximately 20% of PCa cases arise.

Arterial supply:

i- The arterial supply to the prostate is primarily from the inferior vesical artery which originates from the anterior division of the internal iliac artery. The inferior vesical artery branches into two main arterial branches to feed the prostate. The first arterial branch is the urethral artery that enters the prostatovesical junction posterolaterally and travels inward perpendicular to the urethra toward the bladder neck. They turn caudally and parallel to urethra to supply the transition zone. The capsular artery is the second main branch of the prostate. It runs posterolateral to the prostate and enters the prostate at right angles to supply the glandular tissue.

ii- Middle rectal artery:

iii- Internal pudendal artery
**Venous Drainage:**

The veins join to form a plexus around the sides and base of the prostate. This prostatic venous plexus, between the fibrous capsule of the prostate and the prostatic sheath, drains into the internal iliac veins. The prostatic venous plexus is continuous superiorly with the vesical venous plexus and communicate posteriorly with the internal vertebral venous plexus.

**Innervation:**

The autonomic innervations of the prostate arise from the pelvic plexuses formed by the parasympathetic, visceral, efferent and preganglionic fibres that arise from the sacral levels (S2–S4) and the sympathetic fibres from the thoracolumbar levels (L1 – L2).

The pelvic plexus is located beside the rectum approximately 7cm from the anal verge with its midpoint located at the level of the tips of the seminal vesicles.

The sympathetic and parasympathetic fibres that come from the pelvic plexuses travel to the prostate via the cavernous nerves. The cavernous nerves run posterolateral to the prostate in the lateral prostatic fascia. The parasympathetic nerves end at the acini and lead to prostatic secretion. The sympathetic nerves lead to contraction of the smooth muscle of the capsule and the stroma.

The pudendal nerve is the major nerve supply leading to somatic innervations of the striated sphincter and the levator ani. The preprostatic sphincter and the vesicle neck or internal sphincter is under alpha-adrenergic control.

**lymphatic drainage:**

The lymphatic drainage of the prostate primarily drains to the obturator and the internal iliac lymphatic channels. There is also lymphatic communication with the external iliac, presacral and the para-aortic lymph nodes.

**1.2.3: Histology(24):**

The prostate gland is the largest accessory sex gland. It is a collection of 30 to 50 tubuloalveolar glands that surround the proximal urethra. The glands are arranged in three concentric layers: a mucosal layer of short glands that secrete directly into the urether; a submucosal layer of glands; and the outer or main glands. Both the submucosal and main glands have ducts that carry their secretions to the prostatic urethra.
The epithelium of the prostate gland is generally simple columnar although patches of cuboidal, squamous or pseudostratified epithelium may be found.

The prostatic alveoli especially those of older male usually contain concretions of variable form and size that may be as large as 2 mm in diameter. These are also called corpora amylacea. They are believed to be formed by precipitation of the secretory material around cell fragments. They may become calcified.

1.2.4: Physiology(25,26,27):

(1) Secretory function:

The main function of the prostate is to secrete slightly alkaline fluid, milky or white in appearance,¹ that usually constitutes 50 – 75% of the volume of the semen along with spermatozoa and seminal vesicles fluid². This secretion contains protein and non protein components.

Table 1: Prostate secretion

<table>
<thead>
<tr>
<th>Protein</th>
<th>Non protein</th>
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<tr>
<td>Acid phosphatise</td>
<td>Citrate</td>
</tr>
<tr>
<td>PSA</td>
<td>Spermine</td>
</tr>
<tr>
<td>Leucine aminopeptidase</td>
<td>Spermidine</td>
</tr>
<tr>
<td>Plasminogen activator</td>
<td>Putrescine</td>
</tr>
<tr>
<td>Complement C₃ and C₄</td>
<td>Zinc</td>
</tr>
<tr>
<td>Transferrin and transferritin</td>
<td>Myooinositol</td>
</tr>
<tr>
<td>Growth factors</td>
<td>Cholesterol</td>
</tr>
<tr>
<td>Annexin</td>
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- Phosphatase catalyse the reaction by which phosphoryl choline converts to cholin which is used as a nutrient by sperm.
• Zinc maintains quartenary structure of sperm chromatin.
• PSA aids liquefaction of seminal fluid.
• Citrate act as a buffer for seminal fluid.
• Plasmin antimicrobial protein that compacts UTI.

(2) Ejaculatory function:

The prostate contains the ejaculatory duct that releases sperm during ejaculation. The ejaculatory duct opens to allow semen to pass from the ducts deferens into the urethra and eventually out of the body. During orgasm smooth muscle tissue in the prostate contracts in order to push semen through the urethra.

(3) Urination:

The prostate also plays a part in controlling the flow of urine. The urethra runs from the bladder through the prostate and out through the penis. The muscle fibres of the prostate are wrapped around the urethra and are under involuntary nervous system control. These fibers contract to slow and stop the flow of urine.

1-3: Prostate cancer:

1-3-1: Definition(28):

It is one of the most common type of cancer in men which develops in the prostate. Usually it grows slowly and initially remains confined to the prostate gland where it may not cause serious harm, however there are cases of aggressive prostate cancer that can spread quickly.

1-3-2: Epidemiology:

1-3-2-1Incidence

The incidence of prostate cancer varies worldwide(29,30), with the highest rates found in the United States, Canada and Scandinavia and the lowest rates are found in China and other parts of Asia(31,32). These differences are caused by genetic susceptibility, exposure to unknown external risk factor or differences in health care and cancer registration or even a combination of these factors(32). Similarly, prostate cancer mortality varies worldwide with the highest rates reported in the Caribbean and Scandinavia and the lowest rates in China, Japan and countries of the former Soviet Union(36). The number of men older than 65 years is expected to increase 4-fold worldwide between the years 2000 and 2050 representing an increase from 12.4% of the population in 2000 to 19.6% in 2030(33,34).
1-3-2-2 Mortality:

Only one in six American men diagnosed with prostate cancer will eventually die from it. Prostate cancer is the second leading cause of cancer death among U.S. men after lung cancer(35).

The Pattern of mortality worldwide reflects that of incidence, although the mortality rates show less variation between countries. Nevertheless, mortality rates are still higher in Western nations than in lower-risk, Asian countries. The world's highest mortality rates were seen in the Caribbean nations of Barbados, the Bahamas, and Trinidad and Tobago where there are large populations of men of African descent. Mortality was higher in Scandinavian countries and part of Northern Europe than in the U.S. and lowest of all in the Asian countries of South Korea, Philippines and Japan.

The pronounced excess risk of prostate cancer in western nations suggests that factors associated with westernization, such as diet and obesity, may be positively associated with prostate cancer etiology. In addition, prostate cancer's disproportionate impact on African-Americans and Caribbean men suggests that factors associated with African ancestry may also play a role in prostate cancer etiology. While it is not known whether the risk factors explaining the observed patterns are environmental, lifestyle or genetic, it is likely that a complex interplay of these factors is associated with prostate cancer development.

Despite its high morbidity, the etiology of prostate cancer remains largely unknown. Advancing age, race and a family history of prostate cancer are the only established risk factors. Many putative risk factors including androgens, diet, physical activity, sexual factors, inflammation and obesity have been implicated but their roles in prostate cancer etiology remain unclear.

1-3-2-3 Risk Factors:

1. Age and Ethnicity:

Prostate cancer is a disease associated with aging. In the United State more than 70% of all cases of prostate cancer are diagnosed in men over 65 years of age(36), but after this age, the incidence and mortality rates increase exponentially(29). The probability of developing prostate cancer increases from 0.005% among individuals aged < 39 years to 2.2%( 1 in 45) for those aged 40 to 59 years and 13.7% ( 1 in 7 ) for those aged 60 to 79 years(36). Overall, the lifetime risk
of developing prostate cancer is 16.7% (1 in 6). The results of autopsy studies, however, suggest that the probability of developing histologic evidence of prostate cancer is even higher. Carter et al. (30) showed that 20% of men aged 50 to 60 years and 50% of those aged 70 to 80 years had histologic evidence of malignancy. It has been estimated that a 50-year-old man has a lifetime risk of 42% for developing histologic evidence of prostate cancer, a 9.5% risk of developing clinical disease and a 2.9% risk of dying of prostate cancer (37).

African Americans are among the highest rates of prostate cancer in the world (257.3 per 100,000 men) (36). The incidence among African Americans is nearly 60% higher than among whites. The mortality rate for African Americans was 2.3 times higher than for whites, 3.3 times higher than for Hispanics and 5 times higher than for Asians / Pacific Islanders (36). Data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) program indicate that a higher percentage of African Americans present with metastatic disease but they are not more likely than whites to present with high-grade lesions (38, 39).

2: Hormonal Factors:

The growth and differentiation of the prostate is under androgen control. Men who underwent castration before puberty and those with congenital abnormalities in androgen metabolism do not develop prostate cancer. Moreover, androgen blockade with 5α – reductase inhibitors is effective in causing involution of benign prostatic hyperplasia (BPH), whereas androgen ablation either surgically or with luteinizing hormone – releasing hormone agonists is an effective strategy in the treatment of advanced prostate cancer. Nevertheless plasma testosterone or dihydrotestosterone concentrations determined either prospectively or at the time of cancer diagnosis have not been convincingly associated with increased risk of prostate cancer (40).

Vitamin D, another steroid hormone, is obtained primarily from dermal synthesis in response to sunlight exposure. Vitamin D and its analogs have potent anti-proliferative, pro-differentiative and pro-apoptotic effects on prostate cancer cells. In addition, vitamin D inhibits prostate tumor growth in vivo. In general, laboratory data are consistent and support the hypothesis that vitamin D may protect against prostate cancer. However, results from epidemiologic studies investigating serum levels of vitamin D have been inconsistent (41).

In addition to steroid hormones, insulin-like growth factors (IGFs) have been implicated in prostate cancer. IGF-I and IGF-II are polypeptides that function as both
tissue growth factors and endocrine hormones with mitogenic and anti-apoptotic effects on prostate epithelial cells. There are at least six known IGF binding proteins (IGFBPs) that can bind to IGFs and thus prevent activation of the IGF receptor which mediates IGF effects.

Epidemiologic studies have evaluated the roles of the IGF axis in prostate cancer and many have reported a positive association with IGF-I and an inverse association with IGFBP3 (42-47). In addition results from studies, particularly the prospective studies, indicate that IGF1 prostate cancer association may be strongest for advanced disease. However, the roles of IGF2 and the others IGFBPs are less clear.

3: Diet:

Ecologic studies have shown a strong correlation between the incidence of prostate cancer and dietary fat intake(48). A western diet, typically high in fat, has been linked to a higher risk for prostate cancer by increasing production and availability of both androgens and estrogens while Asian and vegetarian diets (low-fat, high-fiber) are associated with lower circulating levels of these hormones(48).

Fat intake is the most studied dietary risk factor for prostate cancer. Most epidemiologic studies have investigated the role of total, saturated, and/or animal fat. Findings from these studies, although mixed, suggest a possible positive association with monounsaturated, animal, and saturated fats, and an inverse association with omega-3 fat. The results for polyunsaturated fat are less consistent (49,50). Consumption of meat, particularly red meat and processed meat, is also consistently linked to an increased risk of prostate cancer. However, it is unclear whether the excess risk is due to the high-fat content, mutagens such as heterocyclic amines that are induced during high-temperature cooking animal proteins, or other unidentified factors(51).

Numerous recent epidemiologic studies have also investigated whether intake of fatty fish is associated with reduced prostate cancer risk. Fatty fish are rich in potentially tumor-inhibitory marine fatty acids, such as omega-3. However, a recent review of 17 studies(52), including 8 prospective studies, found suggestive but inconsistent results.

Although consumption of fruits and vegetables is associated with a reduced risk of several cancers, their role in prostate cancer is less clear. The only consistent finding is an inverse association with consumption of tomatoes and tomato paste,
which has been largely attributed to the antioxidant effect of lycopene(53). A recent review concluded that there is modest evidence that intake of cruciferous vegetables, including broccoli, cabbage, cauliflower and Brussels sprouts is inversely associated with prostate cancer risk, possibly due to their content of isothiocyanates(54). In addition, intake of allium vegetables, including onions, garlic, and chives, were inversely associated with prostate cancer in a case-control study in China(55). This protective effect may be due to the tumor inhibitory properties of organosulfur compounds.

Dietary calcium, from either dairy products or supplement consumption, has been linked to prostate cancer. Because of its role in the regulation of vitamin D synthesis. Calcium may down-regulate vitamin D's anti-proliferative effects on prostate cancer. Recent data suggest a threshold effect that only very high calcium intake (≥2000mg/day) may be associated with disease(56).

Chronic excess of zinc, a mineral obtained largely through dietary supplements, may be positively associated with prostate cancer risk although in vitro studies demonstrating mitogenic effects of zinc on prostate cancer suggest that it may reduce risk(57).

A large body of epidemiological evidence support the hypothesis that selenium (an essential trace element found largely in grains fish and meat) may reduce prostate cancer risk in humans (58). Molecular data show that selenium prevents clonal expansion of tumors by causing cell cycle arrest, promoting apoptosis and modulating p53 dependent DNA repair mechanism. Vitamin E supplementation is associated with a reduced risk of prostate cancer(59,60).

4: Obesity:

In epidemiologic studies, obesity usually measured by body mass index (BMI; weight in kg divided by the square of height in meters, kg/m). abdominal obesity (ratio of waist to hip circumference)and bone mass may be associated with prostate cancer. Risk of prostate cancer mortality increased significantly in association with higher baseline BMI (P<0.001). Men with a BMI of 35.0 to 39.9 had a 34% greater risk of dying of prostate cancer than those with a normal BMI. Although the findings on overall obesity are mixed, recent data suggest that obesity is more consistently related to aggressive prostate tumors and that abdominal obesity
may be associated with an increased risk of prostate cancer even in relatively lean men (62,62).

Data from the Framingham study suggest that high bone mass may increase risk of prostate cancer by 60% to 90%. A total of 1012 white men who had hand radiographs between 1967 and 1970 were observed until 1999. The prostate cancer incidence rate for patients with the lowest quartile of bone mass was 3.8 per 1000 person – years, whereas it was 7.4 and 6.5 per 1000 person-years in the third and highest quartiles respectively. The biologic mechanism underlying this relation is unclear but cumulative exposure to higher levels of androgen, IGF-1 and calcium was suggested.

In addition, higher serum levels of insulin have been linked to an increased risk of prostate cancer (63) and higher serum levels of leptin (the product of the obesity gene Ob) have been linked to larger tumor volume (>5cm) (64).

Although obesity's role in prostate cancer is not clearly defined, it is linked to numerous putative prostate cancer risk factors including high meat and fat intake, hormone metabolism and insulin metabolism. Furthermore, the prevalence of obesity correlates with prostate cancer risk across populations. Thus it is likely that obesity may provide a link between westernization and increased prostate cancer risk.

5: Physical activity:

Physical activity may decrease levels of total and free testosterone, reduce obesity and enhance immune function(65) all of which may lead to protection from prostate cancer. However, perhaps due to challenges in classifying physical activity and/or identifying the age/time periods during which such activity may be most protective, results from numerous epidemiologic studies are equivocal (65,66).

6: Occupation:

Occupation is highly correlated with socioeconomic status and lifestyle factors. There is a large body of literature on prostate cancer and occupation and one consistent result from these studies is that farmers and other agricultural workers have a 7-12% increased risk. (67,68). Though this percentage could reflect lifestyle factors such as the increased intake of meat and fats exposure to chemicals may also play a role. In addition to agriculture, workers in heavy industry, rubber manufacturing and newspaper printing may be at elevated risk(67) suggesting that exposure to certain
chemicals or other factors common in these work environments may increase the risk of prostate cancer.

7: Chronic inflammation:

An association of prostate cancer with chronic inflammation of the prostate (chronic prostatitis) has long been suspected. Studies of prostatitis and prostate cancer reported an overall relative risk of 1.6(69).

Results from pathologic and molecular surveys suggest that the earliest stages of prostate cancer may develop in lesions generally associated with chronic inflammation (70,71). De Marzo et al. showed that almost all forms of focal prostatic glandular atrophy are proliferative and that such proliferative inflammatory atrophied (PIA) lesions often contain inflammatory infiltrates and are frequently found adjacent to or near high-grade prostatic intraepithelial neoplasia (PIN), a precursor of prostate cancer(70,71). Inflammation may lead to tumorigenesis by stimulating angiogenesis, enhancing cell proliferation and damaging DNA through radical oxygen species such as nitric oxide.

Additional support for the role for chronic inflammation in prostate cancer comes from the observation that a higher intake of fish and use of aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with reduced prostate cancer risk (72). In two large prospective studies, higher intake of fish was associated with a lower risk of total prostate cancer and metastatic prostate cancer (73,74). Being abundant in fatty fish, omega-3 fatty acids are known antagonists of arachidonic acid and suppress the production of pro-inflammatory cytokines (75). In addition, use of anti-inflammatory agents especially NSAIDs such as ibuprofen or aspirin has also been related to lower prostate cancer risk in epidemiologic studies (76-79) and a recent meta-analysis of 12 of these studies concluded that aspirin use was associated with a 15% reduction in prostate cancer risk (80).

8: Sexually transmitted disease:

Sexually transmitted diseases (STDs) have been linked to prostate cancer. One large, population based study showed 2 – 3 fold increase in prostate cancer risk associated with STDs, particularly syphilis and recurrent gonorrhea infections (81). Other studies reported associations of human papillomavirus-16, – 18 and -33 serology with an increased risk of prostate cancer (82,83) while a study of a human
immunodeficiency virus (HIV) infected population found that duration of HIV infection was associated with increased prostate cancer risk (84).

A recent meta-analysis of 17 studies concluded that a higher number of sexual partners is associated with increased prostate cancer risk possibly through increased opportunity for sexually transmitted infections(69). Although the mechanisms are not clear, sexually transmitted bacterial or viral agents have been implicated with the induction of chronic inflammation of the prostate potentially leading to prostate cancer.

9: Sexual frequency:

Recent studies have indicated that increased sexual frequency may be associated with an increased risk of prostate cancer, because it may serve as an indicator for either a greater opportunity of infection or higher androgenic activity(69,85,86). A recent prospective study which is not as vulnerable to recall bias as case-control studies reported that ejaculation frequency is not associated with risk; in fact, there was some suggestion that very high ejaculation frequency during a man's 20's (>21 times per month) is associated with reduced risk(87).

10: Vasectomy:

Several but not all studies investigating the association between vasectomy and prostate cancer risk suggest a modest positive association(88). Vasectomy is linked to elevations in anti-spermatozoa antibodies, reduced hormone concentrations in the semen and reduced prostatic secretion(89). Whether these conditions can influence prostate carcinogenesis needs to be clarified.

11: Benign prostatic hyperplasia:

The relationship between benign prostatic hyperplasia (BPH) and prostate cancer is not well established. BPH is currently not considered a precursor to prostate cancer since prostate cancer occurs mostly in the external, peripheral zone of the prostate and BPH is more common in the internal transition and periurethral zones. Nevertheless because both conditions are common in elderly men and because they may coexist within the prostate they appear to share risk profiles making it difficult to elucidate the independent role, if any, of BPH in prostate cancer etiology. The epidemiologic evidence for BPH as a risk factor for prostate cancer remains weak and inconsistent(90), with the largest study to date (over 85,000 BPH patients) showing
only a marginally elevated age-adjusted risk of prostate cancer among BPH patients versus the general population (<2% in 10 years)(91).

12: Diabetes Mellitus:

Men with diabetes mellitus appear to have a lower risk of developing prostate cancer. In a population-based cohort study conducted in Sweden, men hospitalized for diabetes had a 9% lower risk of prostate cancer and those hospitalized for a diabetic complication had an 18% lower risk than men in other population-based registers(92). In a hospital-based, case-control study, diabetes was associated with a 40% lower risk of prostate cancer overall and a 53% lower risk of regional or advanced prostate cancer(93). This effect was found mainly in whites and Hispanics but not in African Americans.

13: Family history and Genetic Susceptibility:

The risk of developing prostate cancer doubles for men who have a father or brother affected by prostate cancer and increases further when multiple first-degree relatives are affected(94,95). Epidemiologic studies indicate that men with a positive family history are diagnosed at an earlier age – on average 6 to 7 years earlier – than those without affected first-degree relatives(96). These studies estimate that 5% to 10% of all prostate cancer cases and up to 40% of those occurring at <55 years of age may have a hereditary basis(95,96). Other than being diagnosed at an earlier age, hereditary prostate cancer does not differ clinically from disease that arises sporadically.

14: Other factors:

Several other risk factors such as smoking, use of alcohol and liver cirrhosis have been investigated but their roles in prostate cancer are weak or unclear based on data in the current literature(235-237).

1-3-3: Presentation( Symptoms & Signs)(97):

Prostate cancer may not cause symptoms or signs in its early stage. Early warning signs of Prostate Ca to consider:

- Difficulty in passing urine.
- A slow stream, often with dribbling at the end.
- Inability to start or stop the flow of urine.
- Frequent need to pass urine / especially at night.
• Swelling in legs.

These early symptoms may be related to other factors such as inflammation of the prostate called prostatitis or benign enlargement of the prostate.

Late warning signs of Prostate Ca. Include:

- Inability to pass urine.
- Lower back pain.
- Blood in the urine or semen.
- Painful ejaculation.
- Erectile dysfunction.
- Bone pain.
- Lower limbs paresthesia or paraplegia.
- Incontinence.
- Renal function impairment.

1-3-4: DIAGNOSIS:

The main diagnostic tools to obtain evidence of PCa include DRE, serum concentration of PSA and transrectal ultrasonography (TRUS) and biopsy. Its definite diagnosis depends on the histopathologic verification of adenocarcinoma in prostate biopsy cores or operative specimens.

1-3-4-1: Digital rectal examination (DRE):

Most prostate cancers are located in the peripheral zone of the prostate and detected by DRE when the volume is about 0.2 mL or larger. Abnormal prostate findings include nodules, asymmetry or induration. In about 18% of all patients, PCa is detected by a suspicious DRE alone irrespective of the PSA level(98). Suspicious DRE is a strong indication for prostate biopsy as it is predictive for more aggressive (Gleason score ≥ 7) prostate cancer (99,100).

1-3-4-2: Prostate – specific antigen (PSA):

i. PSA test originally approved by FDA in 1986 to monitor the progression of the prostate cancer in men who had already been diagnosed with the disease.
In 1994 the FDA approved the use of PSA test in conjunction with a digital rectal examination to test asymptomatic men for prostate cancer.

ii. PSA is a kallikrein-like serine proteases produced almost exclusively by the epithelial cells of the prostate. It has a half-life of 2.2 days. For practical purposes, it is organ-specific but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. The level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS (101).

iii. The level of PSA is a continuous parameter: the higher the value, the more likely is the existence of PCa. PSA level of 4.0 ng/mL and lower was considered as normal, therefore, if a man had a PSA level of 4.0 ng/mL prostate biopsy is recommended to determine whether prostate cancer was present.

iv. The finding that many men may harbor PCa despite low levels of serum PSA has been underscored by recent results from a US prevention study (102).

Table 2: Risk of PCa in relation to low PSA values:

<table>
<thead>
<tr>
<th>PSA level (ng/mL)</th>
<th>Risk of PCa</th>
<th>Risk of Gleason ≥ 7 PCa</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-0.5</td>
<td>6.6%</td>
<td>0.8%</td>
</tr>
<tr>
<td>0.6-1</td>
<td>10.1%</td>
<td>1.0%</td>
</tr>
<tr>
<td>1.1-2</td>
<td>17.0%</td>
<td>2.0%</td>
</tr>
<tr>
<td>2.1-3</td>
<td>23.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td>3.1-4</td>
<td>26.9%</td>
<td>6.7%</td>
</tr>
</tbody>
</table>

v. Various factors can cause a man’s PSA level to fluctuate .

- The PSA level can increases by a number of factors other than prostate cancer such as (103,104-108):
  - Benign prostate hyperplasia.
  - Older age.
  - Prostatitis.
  - Ejaculation.
  - Riding a bicycle.
• DRE.
• Certain medicines (testosterone).
• UTI.
• Prostate surgery & biopsy.

• Factors that might cause PSA level to go down(109,110):
  • 5 α reducates inhibitors such as finasteride.
  • Herbal mixtures mask high PSA level.
  • Obesity.
  • Aspirin.
  • Statin (Cholesterol lowering drugs).
  • Thiazide diuretics.

Several modifications of serum PSA value have been described, which may improve the specificity of PSA in the early detection of PCa. They include: PSA density, PSA density of the transition zone, age-specific reference ranges, race specific reference ranges and PSA molecular form. However, these derivatives and PSA isoforms (cPSA [complex PSA], proPSA [precursor isoforms of PSA], BPSA [benign PSA] and iPSA [intact PSA]) have limited usefulness in the routine clinical setting.

* Free/total PSA ratio (f/t PSA)(111):

The free/total PSA ratio (f/t PSA) is the concept most extensively investigated and most widely used in clinical practice to discriminate BPH from PCa. The ratio is used to stratify the risk of PCa for men who have total PSA levels between 4 and 10 ng/mL and a negative DRE.

The concept must be used with caution as several pre-analytical and clinical factors may influence the f/t PSA, e.g. instability of free PSA, variable assay characteristics and very large prostate size. In addition, assay characteristics may vary and concomitant BPH in large prostates may result in a dilution effect. Furthermore f/t PSA is of no clinical use in total serum PSA values higher than 10 ng/mL or during follow-up of patients with known PCa.

* PSA velocity (PSAV), PSA doubling time (PSADT)(112-118):

There are two methods of measuring PSA over time: (1) PSAV which is defined as an absolute annual increase is serum PSA (ng/mL/year) (112) and (2) PSADT which measures the exponential increase of serum PSA over time reflecting a
relative change(113). These two concepts may have a prognostic role in patients with treated PCa (114) but they have limited use in the diagnosis of PCa because of background noise (total volume of prostate, BPH), the variations in interval between PSA determination, and acceleration/deceleration of PSAV and PSADT over time. Prospective studies have shown that these measurements do not provide additional information compared to PSA alone (115-118).

* PSA density:

PSA density compares the PSA concentration and the volume of the prostate (as measured by ultrasound).

* Complexed PSA

Another strategy to improve PSA specificity has been to measure complexed PSA (cPSA). Most circulating PSA is bound to alpha-1-antichymotripsin. A study using archival serum found that at 95 percent sensitivity cPSA had a specificity of 26.7 percent compared with 15.6 percent for the free-to-total PSA ratio and 21.8 percent for total PSA (119).

A prospective study in 831 men undergoing prostate biopsy found that cPSA was more specific than total PSA (120).

* ProPSA:-

ProPSA (also known as p2PSA) is a specific isoform of the PSA proenzyme proPSA. It has been used to increase the detection of prostate cancer for men with PSA values between 2.0 to 10.0 ng/mL. One prospective observational study estimated that using the p2PSA assay could reduce the number of unnecessary biopsies by 7.6 percent while maintaining a sensitivity of 95 percent for detecting prostate cancer (121). Another prospective study of 268 subjects using the ratio of p2PSA over free PSA estimated about a 35 percent reduction in the number of unnecessary biopsies while maintaining 95 percent sensitivity (122).

*Age-specific reference range

Age-specific reference ranges have been developed from normal population to improve the discriminating power of PSA(238).

- 40 to 49 years – 0 to 2.5 ng/mL
- 50 to 59 years – 0 to 3.5 ng/mL
- 60 to 69 years – 0 to 4.5 ng/mL
- 70 to 79 years – 0 to 6.5 ng/mL
Raising the PSA biopsy threshold in older men improves specificity thus reducing the number of unnecessary biopsies. Conversely, lowering the threshold in younger men improves sensitivity and increases detection of early-stage tumors.

*Race-specific reference ranges*

Black men in the United States have the world's highest incidence of prostate cancer and are the most likely to present with advanced stage disease (123). PSA levels in blacks are higher compared with whites even after adjusting for age, clinical stage and histology (124). Race-specific PSA reference ranges have been established in the hope of achieving earlier diagnosis (125):

- 40 to 49 years – 0 to 2.5 ng/mL (whites); 0 to 2.0 ng/mL (blacks)
- 50 to 59 years – 0 to 3.5 ng/mL (whites); 0 to 4.0 ng/mL (blacks)
- 60 to 69 years – 0 to 4.5 ng/mL (whites); 0 to 4.5 ng/mL (blacks)
- 70 to 79 years – 0 to 6.5 ng/mL (whites); 0 to 5.5 ng/mL (blacks)

However, a study of 651 men undergoing radical prostatectomy found that the race-specific reference ranges which raise the cutoff for blacks 50 years and older compared with whites would be associated with similar or worse outcomes (126).

*PCA3 score*

Prostate cancer antigen3 (PCA3) also referred to as DD3 is a gene that expresses anon coding RNA. It is only expressed in human prostate tissue and the gene is highly overexpressed in prostate cancer (127,128). Because of its restricted expression profile, the PCA3 RNA is useful as tumor marker (129). Compared to serum PSA, PCA3 has a lower sensitivity but a higher specificity and better positive and negative predictive value. It should be measured in the first portion of urine after prostate massage with digital rectal examination. PCA3 score was calculated as the ratio of PCA3 and PSA mRNA (PCA3 m RNA / PSA m RNA X 1000) and the cut-off PCA3 score was set at 35.
Table 3: PCA3 Score(130)

<table>
<thead>
<tr>
<th>PCA3 Score</th>
<th>Probability of prostate cancer on biopsy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 5</td>
<td>14%</td>
</tr>
<tr>
<td>5 – 19</td>
<td>26</td>
</tr>
<tr>
<td>20 – 34</td>
<td>37%</td>
</tr>
<tr>
<td>35 – 49</td>
<td>47%</td>
</tr>
<tr>
<td>50 – 100</td>
<td>55%</td>
</tr>
<tr>
<td>More than 100</td>
<td>78%</td>
</tr>
</tbody>
</table>

PCA3, unlike PSA level is not affected by the size of the prostate but it increases with prostate cancer volume. It is also less affected by urinary infection. It is possible that reduced level of testosterone or dihydrotestosterone that can occur with age or on drugs (LHRH agonist) might influence the results.

The main current indication of PCA3 urine test may be to determine whether a man needs a repeat biopsy after an initially negative biopsy outcome or not(131).

1-3-4-3: TRUS and prostate biopsy(132,133):

TRUS, also called prostate ultrasound, provides images of the prostate and surrounding tissues and allows examination of the Gland for abnormalities.

- TRUS and prostate biopsy can be used to diagnose prostate cancer in patients with abnormal DRE and/or elevated PSA level.
- Prostate biopsy remains the gold standard investigation for diagnosing prostate cancer. First described by Astradli in 1937, it allows for tissue samples of the prostate to be obtained for histological analysis.
- All patients need to have a history and assessment prior to the procedure and they should be informed about the procedure and its purpose and they also should be aware of the main potential complications and the risks of a false negative test result and the potential need for a repeat biopsy.
- Patients should be instructed to discontinue blood thinning medication for a week to 10 days prior to undergoing TRUS and prostate biopsy. An antibiotic (ciprofloxacin) is to be prescribed prior to and for a couple of days following
the procedure to help prevent infection. An enema is administered to cleanse the bowel.

- It is important that the environment is suitably prepared and all the required equipment is available and checked to be in working order before commencing the procedure. All staff should be familiar with their expected roles and emergency procedures, the location of any emergency equipment and the ability to contact a senior clinician should the need arise.

- The patient is positioned in the left lateral position ensuring that the knees are bent up toward the chest or in the lithotomy position(132).

- Immediately before the rectal probe is inserted a DRE is undertaken and attention should be taken to exclude anal and rectal pathology. The prostate should be examined for symmetry, size, presence of nodules or tenderness and pain.

- Ultrasound guided periprostatic block is state of the art(134).

- On the first biopsy (baseline biopsy) the sample sites should be as far posterior and lateral in the peripheral zone as possible. Traditional sextant biopsies are no longer considered adequate. At volume 30-40 ml at least 8cores should be taken(137). More than twelve cores have not been shown to be significantly more conclusive. The British Prostate Testing for Cancer and Treatment Study recommends a 10 core biopsy. In prostate > 50 ml up to 18 cores can be considered(135,136).

- Additional biopsy cores can be taken towards suspicious findings on DRE or TRUS(137).
Table 4: Complication of Prostate biopsy (99)

<table>
<thead>
<tr>
<th>Complications</th>
<th>% of biopsies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematospermia</td>
<td>37.4</td>
</tr>
<tr>
<td>Haematuria &gt; 1 day</td>
<td>14.5</td>
</tr>
<tr>
<td>Rectal bleeding 2 day</td>
<td>2.2</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>1.0</td>
</tr>
<tr>
<td>Fever 38.5C (101.3F)</td>
<td>0.8</td>
</tr>
<tr>
<td>Epididymitis</td>
<td>0.7</td>
</tr>
<tr>
<td>Rectal bleeding &gt; 2 day+ requiring surgical intervention</td>
<td>0.7</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>0.2</td>
</tr>
<tr>
<td>Other complications requiring hospitalization</td>
<td>0.3</td>
</tr>
</tbody>
</table>

Magnetic resonance imaging (MR1) guided targeted biopsy

Since the mid-1980s, TRUS biopsy has been used to diagnose prostate cancer in essentially a blind fashion because prostate cancer cannot be seen on ultrasound due to poor soft tissue resolution. However, multiparametric MR1 has been used to better identify and characterize prostate cancer from the mid-2000s (138). A study correlating MR1 and surgical pathology specimens demonstrated a sensitivity of 59% and specificity of 84% in identifying cancer when T2-weighted dynamic contrast enhanced and diffusion weighted imaging together (139). Many prostate cancers missed by conventional biopsy are detectable by MR1 guided targeted biopsy (140).

Two methods of MR1 guided or targeted prostate biopsy are available; 1\ direct "in bore biopsy within the MR1 tube and 2\ fusion biopsy using a device that fuses stored MR1 with real-time ultrasound *(MR1-US). Visual or cognitive MR1-US fusion has been described (141).

In the fusion MR1-US prostate biopsy, a prostate MR1 is performed before biopsy and then at the time of biopsy the MR1 images are fused to the ultrasound images to guide the urologist to the suspicious targets.

MR1-guided prostate biopsy appears to be superior to standard TRUS-biopsy in prostate cancer detection. Several groups in the U.S. (142,143) and Europe (144,145), have demonstrated that targeted biopsies obtained with fusion imaging are several times more likely to reveal cancer than blind systematic biopsies The more suspicious the MR1 the greater the likelihood of cancer on targeted biopsy.
Grossing and processing of prostate needle biopsies:

Prostate core biopsies taken from different sites are usually sent to the pathology laboratory in separate vials and should be processed in separate cassettes. Before processing, number of core per vial and length of each core should be recorded. There is a significant correlation between the length of prostate biopsy tissue on the histological slide and the detection rate of PCa. To achieve optimal flattening and alignment of individual cores, one should embed a maximum of three cores per cassette and use sponges or paper to keep the cores stretched and flat to optimize the detection of small lesions. Blocks should be cut at three level.

1-3-4-3-2 Gleason grading score:

This scoring system is named after Donald Gleason, a pathologist at the Minneapolis Veterans Affairs Hospital who developed it with other colleagues at the facility in the 1960s. In 2005 the Gleason system was altered by the international society of urological pathology. The criteria were refined and the attribution of certain pattern changed. It has been shown that this modified Gleason score has higher performance than the original one and is currently assumed standard in urological pathology.

The results from a prostate biopsy are usually given in the form of Gleason score. This scoring system describes the histological appearance of PCa under low magnification (architectural as opposed to cytological grading). The Gleason score is the sum of two numbers. The first number is the score of most common tumor pattern, the second number is the score of the second most common pattern. If there is only one pattern the grade is doubled. If there are three patterns the first number is the most common and the second is the one with the highest grade.

It assigns a number from 2 to 10 to describe how abnormal the cells under a microscope. A score of 2 to 4 means the cells still look very much like normal cells and pose little danger of spreading quickly. A score of 8-10 indicates that the cell have very few features of a normal cell and are likely to be aggressive. A score of 5 to 7 indicates intermediate risk.
The Gleason grading system is used to help evaluate the prognosis of men with prostate cancer. Together with other parameters it is incorporate into strategy of prostate cancer staging which predicts prognosis and helps guide therapy. 

Gleason patterns are associated with the following features:

- **Pattern 1** - The cancerous prostate closely resembles normal prostate tissue. The glands are small, well-formed and closely packed. This corresponds to well differentiated carcinoma.

- **Pattern 2** - The tissue still has well-formed glands but they are larger and have more tissue between them implying that the stroma has increased. This also corresponds to a moderately differentiated carcinoma.

- **Pattern 3** - The tissue still has recognizable glands but the cells are darker. At high magnification, some of these cells have left the glands and are beginning to invade the surrounding tissue or having an infiltrative pattern. This corresponds to a moderately differentiated carcinoma.

- **Pattern 4** – The tissue has few recognizable glands. Many cells are invading the surrounding tissue in neoplastic clumps. This corresponds to a poorly differentiated carcinoma.

- **Pattern 5** – The tissue does not have any or only a few recognizable glands. There are often just sheets of cells throughout the surrounding tissue. This corresponds to an anaplastic carcinoma.

Although the Gleason system is now internationally accepted, there are several issues concerning it as a grading system. Most notably Gleason grading is observer dependent and may vary depending on the level of experience. Another limitation is that the majority of patients diagnosed today fall into the Gleason 6-7 category, an intermediate prognostic range limiting the potential usefulness of a 10-point scale.

Recently, a new system based on the quantification of intratumoral reactive stroma, also named "stromogenic cancer" has been introduced as another way to grade PCa. Stromogenic cancer is the phenomenon of differentiation of smooth muscle cells into myofibroblasts that have the capability of promoting PCa growth (153,154). Based on the percentage of the prostatic tissue showing reactive stromal response, it was classified into four groups grade o, up to 5% RS grade 1, 6-15% RS grade 2, 16-50% grade3, 75% RS grade 4.
Quantification of stromal response grade 3 has a significant correlation with poor prognosis and is also a significantly predictive factor of prostate carcinoma specific death.

1-3-4-3-3 Pathology of prostate cancer (155):

- By far the most common (90%) prostatic malignancy is acinar adenocarcinoma. Most (75%) adenocarcinomas are located in the peripheral zone and most (85%) are multifocal. 15–20% of adenocarcinomas arise in the central zone and 10–15% arise in the transitional zone. Histological variants of prostatic carcinoma have been variably defined. One approach is to consider two groups of variants. The first group comprises histological variant of acinar adenocarcinoma and the second group non acinar carcinomas variants. Variants of usual acinar adenocarcinoma defined in 2004 by World health organization include atrophic, pseudohyperplastic, foamy/, colloid, signet ring, oncocytic and lymphoepithelioma like carcinoma.

- The second group of non acinar carcinomas account for 5-10% of carcinomas that originate in the prostate. These include:
  i. Ductal adenocarcinoma.
     This type of prostate cancer starts is the cell that line the ducts of the prostate gland. It tends to grow and spread more quickly than acinar adenocarcinoma.
  ii. Transitional cell (urothelial) cancer:
     This type starts in the cell that line the urethra. More commonly this type of cancer may start in the bladder and spread into the prostate.
  iii. Squamous cell cancer:
     This is a non glandular cancer that starts from the flat cells covering the prostate gland. Squamous cell cancer tends to grow and spread more quickly than adenocarcinoma of the prostate. In this type there is no increase in PSA level.
  iv. Adenosquamous:
  v. Carcinoid of the prostate
     Carcinoid tumors start from cells of the neuroendocrine system which is made up of specialized nerves and gland cells. These tumors are very rare and seem to be slowly growing.
vi. Small cell cancer:
This is a type of neuroendocrine tumor and is made up of small round cells. It is very aggressive and it does not lead to increase PSA level.

vii. Sarcoma and sarcomatoid cancer.
Sarcomas start from muscle cells and often grow quite quickly. The most common type of prostate cancer in adults is leiomyosarcoma. It tends to occur in men between the age of 35 and 60.
Sarcomatoid cancers have a mixture of sarcoma and adenocarcinoma cells.

viii. Large cell prostate cancer:
It is a type of neuroendocrine prostate cancer.

ix. Basal cell prostate cancer:

x. Microcytic adenocarcinoma.

xi. Prostatic intraepithelial neoplasia – like adenocarcinoma.

1-3-4-3.4: Local spread and metastases(156)

When these cancer are locally invasive, the transitional zone tumors spread to the bladder neck while the peripheral zone tumors extend into the ejaculatory duct and seminal vesicles. Penetration through the prostate capsule and along the perineural or vascular spaces occurs relatively late.

The mechanism for distant metastasis is poorly understood. The cancer spread to bone early often without significant lymphadenopaty. Currently predominant theories have been proposed for spread, the mechanical theory and the seed and soil theory.

The mechanical theory attributes metastasis to direct spread though the lymphatics and venous spaces into the lower lumbar spine.

A dovcates of the seed and soil theory however believe that tissue factors that allow for preferential growth in certain tissue such as bone must be present. Lung, liver and adrenal metastasis have also been documented.

After prostate cancer have been diagnosed, tests need to find out if cancer cells have spread within the prostate or to other parts of the body. These are:

i. Bone scan.

ii. magnetic resonance imaging(MRI).
CT scan.

pelvic lymphadenectomy.

seminal vesicle biopsy

1-3-5: Prostate cancer staging

The stage (extent) of a cancer is one of the most important factors in choosing treatment options and predicting a man's outlook. The most common is promulgated by the American Joint Committee on Cancer and is known as the TNM system which evaluates the size of the tumor, the extent of involved lymph nodes, and any metastasis (distant spread) and also takes into account cancer grade. As with many other cancers, these are often grouped into four stages (I-IV).

1-3-5-1 TNM staging (158)

Evaluation of the primary tumor ('T')

TX: cannot evaluate the primary tumor.

T0: no evidence of tumor.

T1 tumor present, but not detectable clinically or with imaging

T1a: tumor was incidentally found in less than 5% of prostate tissue resected.

T1b: tumor was incidentally found in greater than 5% of prostate tissue resected.

T1c: tumor was found in a needle biopsy performed due to an elevated serum PSA.

T2: the tumor can be felt (palpated) on examination but has not spread outside the prostate

T2a: the tumor is in half or less than half of one of the prostate gland's two lobes

• T2b: the tumor is in more than half of one lobe, but not both.

• T2c: the tumor is in both lobes but within the prostatic capsule.

*T3: the tumor has spread through the prostatic capsule (if is only part-way through, it is still T2)

* T3a: the tumor has spread through the capsule on one or both sides.

* T3b: the tumor has invaded one or both seminal vesicles.

*T4: the tumor has invaded other nearby structures.
It should be stressed that the designation "T2c" implies a tumor which is palpable in both lobes of the prostate. Tumors which are found to be bilateral on biopsy only but which are not palpable bilaterally should not be staged as T2c.

Evaluating the regional lymph nodes ('N')
- **Nx**: cannot evaluate the regional lymph nodes
- **No**: there has been no spread to the regional lymph nodes
- **N1**: there has been spread to the regional lymph nodes.

Evaluating distant metastasis ('M')
- **MX**: cannot evaluate distant metastasis.
- **Mo**: there is no distant metastasis.
- **M1**: there is distant metastasis.
  - **M1a**: the cancer has spread to lymph nodes beyond the regional ones.
  - **M1b**: the cancer has spread to bone.
  - **M1c**: the cancer has spread to other sites (regardless of bone involvement).

Evaluating the histologic grade ('G')

Usually the grade of the cancer (how different the tissue is from normal tissue) is evaluated separately from the stage. However for prostate cancer grade information is used in conjunction with TNM status to group cases into four overall stages.
- **GX**: cannot assess grade
- **G1**: the tumor closely resembles normal tissue (Gleason 2-4) well differentiated.
- **G2**: the tumor somewhat resembles normal tissue (Gleason 5-6) moderately differentiated.
- **G3-4**: The tumor resembles normal tissue barely or not at all (Gleason 7-10) poorly differentiated.

### 1.3.5.2: Overall staging

- The tumor lymph node metastasis and grade status can be combined into four stages of worsening severity

<table>
<thead>
<tr>
<th>Stage</th>
<th>Tumor</th>
<th>Nodes</th>
<th>Metastasis</th>
<th>Grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>G1</td>
</tr>
<tr>
<td></td>
<td>T1a</td>
<td>N0</td>
<td>M0</td>
<td>G2-4</td>
</tr>
<tr>
<td>Stage</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>--------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
<td>-------</td>
</tr>
<tr>
<td>Stage I</td>
<td>T1b</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>Stage III</td>
<td>T3</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>N0</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td>Stage IV</td>
<td>Any T</td>
<td>N1</td>
<td>M0</td>
<td>Any G</td>
</tr>
<tr>
<td></td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
<td>Any G</td>
</tr>
</tbody>
</table>

1-3-5-3: Whitmore-Jewett staging (159)

The Whitmore-Jewett system is similar to the TNM system with approximately equivalent stages. Roman numerals are sometimes used instead of Latin letters for the overall stages (for example. Stage I for stage A, stage II for Stage B, and so on).

- **A**: tumor is present but not detectable clinically found incidentally
  - A1: tissue resembles normal cells: found in a few chips from one lobe.
  - A2: more extensive involvement
- **B**: the tumor can be felt on physical examination but has not spread outside the prostate capsule.
  - B1N: the tumor can be felt it does not occupy a whole lobe and is surrounded by normal tissue.
  - B1: the tumor can be felt and it does not occupy a whole lobe.
  - B2: the tumor can be felt and it occupies a whole lobe or both lobes
- **C**: the tumor has extended through the capsule.
  - C1: the tumor has extended through the capsule but does not involve the seminal vesicles
  - C2: the tumor involves the seminal vesicles
- **D**: the tumor has spread to other organs

**Localized prostate cancer (T1, T2a)**

Localized prostate cancer is cancer that is contained within the prostate gland. It is also called early or organ-confined prostate cancer.
Locally advanced prostate cancer (T2b, T3, T4)

Locally advanced prostate cancer is cancer that is breaking through the capsule of the prostate or has spread to the area just outside the prostate. This can include the seminal vesicles, lymph nodes, neck of the bladder or back passage.

Advanced prostate cancer (M1)

Advanced prostate cancer is cancer that has spread from the prostate gland to other parts of the body. It is also called metastatic prostate cancer. It develops when the prostate cancer cells move from the prostate to other parts of the body through the blood stream or lymphatic system.

Prostate cancer can spread to any part of the body but it most commonly spreads to the bones and the lymph nodes.

1-3-6: Prostate Cancer treatment (160, 161)

Treatment Decision Making

Factors to Consider

While the stage and grade of the cancer as well as the serum PSA level are key factors in choosing the treatment that is right for patient that choice is also influenced by other factors such as:

- Patient age and life expectancy.
- Patient general health and specific medical conditions.
- Cost and practical considerations.
- Attitudes about cure and/or living with cancer.
- Patient needs concerns, values and social relationships.
- Patient feelings about specific side effects.

Treatment option for stage 1 prostate cancer may include

- watchful waiting.
- Radical prostatectomy.
- Radiation therapy.
- Cryosurgery.
- HIFU.

Treatment options for stage 2 prostate cancer may include:

- Hormone therapy.
- Radical prostatectomy.
- Brachytherapy (radiation therapy).
• Cryosurgery (surgery that freezes diseased tissue).
• HIFU.

Treatment option for stage 3 may include:
• Watchful waiting (for men of advanced age with no symptoms or men with a non-related but serious illness).
• Hormone therapy only.
• External beam radiation in combination with hormone therapy.
• Radical prostatectomy.
• HIFU.

Treatment option for stage 4 may include:
• Watchful waiting (for men of advanced age with no symptoms or men with a non-related but serious illness).
• Hormone therapy only.
• External beam radiation in combination with hormone therapy.
• HIFU.

1-3-7: Risk Categories(162-169):

• A straightforward and logical way for clinicians to estimate risk of disease recurrence after treatment is to stratify patients into distinct risk categories. In the pretreatment setting, this approach is attractive for many physicians as they can easily categorize patients based on a few ubiquitous clinical parameters. The most widely used risk grouping system was developed by D’Amico and colleagues(163-165) where men with localized prostate cancer are grouped into categories according to whether their risk of biochemical recurrence (BCR) after definitive treatment was low, intermediate or high. Patients are primarily stratified according to their biopsy Gleason score, serum PSA level, and clinical stage, and defined as: (1) low risk, clinical stage T1c and T2a, PSA level ≤ 10 ng/mL, and biopsy Gleason score ≤ 6; (2) intermediate risk, clinical stage T2b or biopsy Gleason score of 7 or PSA level > 10 and ≤ 20 ng/mL; (3) high risk, clinical stage ≥ T2c or PSA level > 20 ng/mL or biopsy Gleason score ≥ 8. Note that a patient must meet all 3 criteria to be included in the low-risk group, but any 1 criterion can move him to a higher risk group. The American Urological Association (AUA) has incorporated D’Amico’s risk groups into their most recent prostate cancer clinical guidelines(166).
Another example of pretreatment risk categorization is described by Zelefsky and colleagues. Patients are divided into favorable, intermediate, and unfavorable prognostic groups based on whether PSA is \( \leq 10 \) ng/mL, clinical stage \( \leq T2 \), and Gleason sum \( \leq 6 \)(167). If all 3 conditions are met, the patient is considered to have a favorable prognosis. If 1 of the conditions is not met, then the patient falls into the intermediate group, and if 2 or 3 are unmet, then an unfavorable prognosis is assigned. The National Comprehensive Cancer Network (NCCN) adopted a modified version of Zelefsky’s and D’Amico’s risk grouping systems for their prostate cancer clinical practice guidelines(168). The NCCN guidelines panel recommends risk stratification incorporating “available predictive features included in the guidelines, risk tables and nomograms when discussing options for the treatment of clinically localized prostate cancer(168).”

The enthusiasm for risk groupings is primarily due to their ease of application but this enthusiasm should be tempered by the loss of predictive power associated with collapsing variables into broad categories. For example, when 2 newly diagnosed prostate cancer patients are classified as intermediate risk according to D’Amico’s grouping strategy, one assumes they are at equal risk of disease recurrence after treatment. In fact, patients within each of the 3 risk groups are a heterogeneous group and the individual risk may vary widely(169). Additionally, the clinical variables used to assign risk groups are weighted equally in their potential to result in a given outcome, when 1 variable (eg, grade) may have a much greater effect on prognosis than another (eg, stage). Inappropriate weighting results in a mixture of patients with very different individualized risks of recurrence all lumped into a broad category. Despite their limitations, many clinicians continue to rely on these methods of risk characterization when advising newly diagnosed prostate cancer patients.

1-3-8:Prostate cancer prognosis(170,171)

The 5 year relative survival rate compares the number of people who are still alive 5 years after their cancer was found to the survival of the others the same age who don't have cancer.
Survival rate by stage

Table (5): Survival rate by stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>5 year relative survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local</td>
<td>100%</td>
</tr>
<tr>
<td>Regional</td>
<td>100%</td>
</tr>
<tr>
<td>Distant</td>
<td>28%</td>
</tr>
</tbody>
</table>

Including all stage of prostate cancer;

- The relative 5 year survive rate is almost 100%
- The relative 10 years survive rate is 99%
- The relative 15 years survival rate is almost 94%

By age:

Five- year relative survival for prostate cancer is slightly lower in men under 50. In men aged over 80, five year relative survival is considerably lower than men in their fifties and sixties at 60%. The reason for high survival rate seen in men aged fifties and sixties is likely to be due to PSA testing in this age group.

1-3-9: Prostate cancer screening:

Although screening for prostate cancer with PSA can reduce mortality from prostate cancer, the absolute risk reduction is very small. Given limitations in the design and reporting of the randomized trials, there remain important concerns about whether the benefits of screening outweigh the potential harms to quality of life, including the substantial risks for overdiagnosis and treatment complications. Men who are willing to accept a substantial risk of morbidity associated with treatment in return for a small reduction in mortality might reasonably choose to be screened. Men who are at increased risk of prostate cancer because of race or family history may be more likely to benefit from screening.

Screening should be discussed with men beginning at age 50, though not with men who have a co-morbidity that limits their life expectancy to less than 10 years (172, 173).

Suggestion is that black men, men with a family history of prostate cancer particularly in relatives younger than age 65 and men who are known or likely to have the BRCA1 or BRCA2 mutations should first discuss screening at age 40-45 (173-175).
When a decision is made to screen for prostate cancer, the recommended strategy has been to perform a digital rectal examination and measure a PSA level\(^{(172,173)}\). However the randomized ERSPC found that PSA screening alone, measured at an average interval of four years (range two to four years), resulted in a significant, though small, reduction in prostate cancer mortality\(^{(176)}\). The PLCO, study which screened with annual PSA and DRE, found no reduction in mortality\(^{(176)}\).

No controlled studies have shown a reduction in the morbidity or mortality of prostate cancer when detected by DRE at any age\(^{(177)}\). The majority of cancers detected by digital examination alone are clinically or pathologically advanced\(^{(178)}\).

**Recommendations for screening:**

The American Cancer Society (ACS) emphasizes the need for involving men in the decision whether to screen for prostate cancer. Men need to have sufficient information regarding the risks and benefits of screening and treatment to make an informed and shared decision, providing them with a decision aid may facilitate the decision-making process\(^{(173)}\). For men who decide to be screened, the ACS recommends PSA testing with or without DRE for average-risk men beginning at 50 years of age. Screening should not be offered to men with a life expectancy less than 10 years. Men whose initial PSA level is greater than or equal to 2.5 ng/mL should undergo annual testing, men with a lower initial level can be tested every two years. The guidelines also recommend beginning screening discussion at age 40 to 45 in patients at high-risk of developing prostate cancer (eg. Black men and men with a first-degree relative with prostate cancer diagnosed before age 65).

The guideline also recommends keeping the biopsy referral threshold at 4.0 ng/mL. However for men with PSA levels from 2.5 to 4.0 ng/mL, the guideline encourages individualized decision making and assessment which can include age, race, family history, digital rectal examination findings, previous biopsy results, and use of five alpha-reductase inhibitors.

The American Urological Association (AUA) recommends against screening men younger than 40, and also does not recommend routine screening for average-risk men ages 40 to 54, men older than 70, or men with a life expectancy of less than 10 to 15 years. Decisions should be individualized for higher-risk men ages 40 to 54, and the AUA noted that some men over age 70 in excellent health might benefit from screening. The AUA strongly recommends shared decision making in deciding on
PSA screening in men ages 55 to 69. The guideline panel could find no evidence to support the continued use of DRE as a first-line method of screening. The AUA stated that a screening interval of two years for men who choose screening may be preferred to annual screening and that screening intervals can be individualized based on baseline PSA level. The guideline noted the lack of evidence for using any tests (eg. PSA derivatives, PSA kinetics, PSA molecular markers, urinary markers, imaging, or risk calculators) other than PSA for triggering a biopsy referral. However, the AUA did not recommend a specific threshold for biopsy referral.

The United States Preventive Services Task Force (USPSTF) updated its recommendations in 2012 to recommend that men not be screened for prostate cancer concluding that there is moderate certainty that the benefits of such screening do not outweigh the harms (179). The USPSTF did advise that men requesting screening be supported in making an informed decision.

The Canadian Task Force on Preventive Health Care recommends against screening for prostate cancer, with PSA or TRUS and states that there is insufficient evidence to recommend for or against screening with DRE(180).

The United Kingdom National Screening Committee does not recommend screening for prostate cancer(181).

The Australian Cancer Council states that the evidence does not support population-based screening and recommends a patient-centered approach that individualizes the decision(182).

The European Society for medical Oncology (ESMO) recommends against population based screening and in favor of an individualized approach using shared decision making(183). ESMO further states that there is inconsistent evidence on screening men younger that 50 and between 70 and 75 years, of age and evidence that the harms of screening outweigh the benefits for men over age 75.

The Clinical Guidelines Committee of the American College of Physicians (ACP) produced a "guidance statement" in 2013 based on their rigorous review of guidelines developed by other United States organizations, including the American College of Preventive Medicine, The American caner Society, the American Urological Association, and the US Preventive Services Task Force(184s). The ACP guidance statement recommends that clinicians inform men ages 50 to 69 about the limited potential benefits and substantial harms of prostate cancer screening and only screen men who express a clear preference for being screened. The guidance
statement also recommends against screening for prostate cancer in average-risk men under the age of 50 and against screening in men over the age for 69 or with a life expectancy less than 10 to 15 years.

1-3-10: Prostate Cancer Prevention (185-204)

Cancer prevention is action taken to lower the chance of getting cancer. by preventing cancer the number of new cases of cancer in a group or population is lowered. Hopefully, this will lower the number of deaths caused by cancer.

To prevent new cancers from starting, scientists look at risk factors and protective factors.

Some risk factors for cancer can be avoided but many cannot. There's no sure way to prevent prostate cancer. Study results often conflict with each other, and no clear ways to prevent prostate cancer have emerged. In general, the recommendation is that men with an average risk of prostate cancer make choices that benefit their overall health if they're interested in prostate cancer prevention and that by making healthy choices such as exercising and eating healthy diet. Strategies for Preventing Prostate Cancer

Eat your G-Bombs

G-BOMBS (green, beans, onions, mushrooms, berries and seeds) have powerful anti-cancer effects. For example cruciferous vegetables (green like broccoli, Kale, bok Choy, arugula, Brussels sprouts, and cabbage plus cauliflower, radish and more) contain phytochemicals that stimulate the body to detoxify carcinogens, and higher cruciferous vegetable intake is associated with lower prostate cancer risk (185).

Men who consumed three or more half-cup servings of cruciferous vegetables per week were 41 percent less likely to develop prostate cancer (186). Also the onion family (onion, garlic, leeks, shallots, scallions, and chives) have organosulfur compounds with anti-cancer effects and are associated with reduced prostate cancer risk (187, 188).

Reduce consumption of animal protein:

It is widely recognized that a high consumption of animal protein has been linked to a greater risk of prostate cancer (189). Greater consumption of meat, poultry and fish is associated with higher blood level of IGF1 (insulin-like growth factor-1) which is positively correlated with an increased risk of prostate cancer (190).
Similarly, greater intake of choline (abundant in meat dairy and eggs) is associated with increased prostate cancer risk(191). For prostate health, limit or avoid animal products to two or fewer servings per week. Plant protein, however is protective – legumes and minimally processed soy products are associated with decreased risk of prostate cancer(192,193).

**Eat lots of tomatoes, especially cooked:**

A review of several studies revealed that those who consumed the most tomato-based foods reduced their total risk of prostate cancer by 35 percent and their risk of advanced prostate cancer by 50 percent(194). Lycopene which is abundant especially in cooked tomatoes is believed to be primarily responsible for this benefit(195). Tomatoes are extremely nutrient-dense, containing lycopene as well as a variety of other protective phytochemicals.

**Eat plenty of yellow and orange vegetables:**

Consumption of carotenoid-risk yellow and orange vegetables including carrots, pumpkin, sweet potatoes, winter squash and corn was also found to be inversely related to prostate cancer(192).

**Confirm adequate vitamin D levels with a blood test:**

Accumulating research shows that insufficient vitamin D levels are associated with an increased risk of several cancer, including prostate cancer(196,197).

**Avoid supplemental folic acid:**

Folic acid is the synthetic form of folate (one of the B vitamins) and is included in most multivitamins. Similar to breast cancer, folic acid supplementation has been associated with increased risk of prostate cancer, whereas food folate is associated with decreased risk(198). Get natural folate from green vegetables and beans instead of synthetic folic acid from supplements.

**Avoid dairy products:**

There is substantial evidence indicating that men who avoid dairy products are at a lower risk for prostate cancer(199,200). One study that spanned 41 countries reported a strong correlation between per capita milk consumption and prostate cancer deaths(201).
Supplement with a conservative amount of zinc:

Zinc has been shown in scientific studies to suppress tumor growth and induce prostate cancer cell death (202). There is evidence that adequate levels of zinc are protective while deficiency and excess may promote prostate cancer (203).

Eat fish:

Fatty fish – such as salmon, sardines, tuna and trout contain a fatty acid called omega-3 that has been linked to a reduced risk of prostate cancer.

Drink green tea:

Studies of men who drink green tea or take green tea extract as a supplement have found a reduced risk of prostate cancer.

Maintain a healthy weight:

Men with a body mass index (BMI) of 30 or higher are considered obese. Being obese increases the risk of prostate cancer.

Exercise at least 3 hours a week:

Exercise particularly endurance-type exercise such as walking, running, cycling and swimming is an effective form of disease protection. In one study, men who reported vigorous activity for at least three hours per week had a 61% lower risk of death from prostate cancer suggesting that not only does exercise help to prevent prostate cancer it may also slow its progression (204).

Drink alcohol in moderation if at all:

If you choose to drink alcohol, limit yourself to no more than a drink or two each day.

There's no clear evidence that drinking alcohol can affect your risk of prostate cancer but one study found men who drank several drinks each day over many years had an increased risk.
1.4.: Justification and Objectives:

During my training in Gezira Hospital for Renal Diseases and Surgery and attending the weekly prostate clinic many cases were diagnosed as prostatic carcinoma. I've never heard any one in my surrounding community talk about the prevalence of prostate cancer. I was surprised to find out that it's getting more.

So it is problem which needs to be studied to determine its incidence in our community and its possible risk factors and which group of the community have the higher risk, so as to find out a way to protect them or at least reduce its incidence and try to evade its risk factors.

General Objectives:

To determine the clinical pattern of prostate cancer among patients managed at Gezira NCI.

Specific Objectives:

1. To determine age distribution and possible risk factors
2. To determine the commonest symptoms of presentation
3. To assess the sensitivity of the diagnostic tools.
4. To determine the stage of the disease on presentation.
5. To determine the most common site of metastases in patients with metastatic disease.
6. To determine the relation of PSA level to the stage and metastases and prognosis.
CHAPTER 2

Patients and Methods

2-1: Study design:

The design of the study was a descriptive retrospective hospital based study which was conducted on 424 patients in National Cancer Institute from January 2009 to December 2013. Most of the descriptive data of the patients with prostate cancer were provided by the national cancer institute registry and patients’ medical records.

Most of these patients were diagnosed at Gezira Hospital For Renal Diseases and Surgery and then referred to Gezira NCI for further evaluation and discussion of the most appropriate treatment option for the patients in the combined clinic. Few number of the patients were referred to Gezira NCI from other centers to complete their treatment and for follow up.

2-2: Study area:

Wad Medani city is the capital of Gezira State. According to the 1993 census, the area of Gezira State is 8901 square kilometer with population of 2,706,941. Wad Medani is one of the highly populated cities in Sudan.

Health services are provided through health centers with limitations at the level of doctors giving almost only the outpatient consultation and refer most of the cases for further management.

2-2-1. Gezira National Cancer Institute:

The National Cancer Institute (NCI) was established in 1994 as the second center in Sudan for nuclear medicine and molecular biology. In 1999 An oncology department has been added to the institute. NCI is the first oncology center outside the capital of Sudan, Khartoum.

All patients with surgical malignancies referred to NCI go through a weekly combined clinic by surgeons, oncologists, pathologists and radiologists where detailed evaluation and design of treatment plan is made. The options of management available in NCI include radiotherapy, chemotherapy, hormonal therapy and palliative care and in the future asurgical oncology department.
2-3: Criteria of the study:

All Patients who were referred to Gezira NCI, either from Gezira Hospital for renal diseases and surgery or other hospitals and centers outside this state as cases of prostate cancer were included in this study even those with some insufficient data, we trying to use the available data in every case.

This is a retrospective study on 424 patients representing the total number of patients with prostate cancer presented to Gezira NCI in the period of Jan2009-Dec2013. The data for this study was collected using a questionnaire designed to obtain information about: age, BMI, education level, occupation, residence, marital status, presenting symptoms, family history, concomitant diseases, social habits, finding on digital rectal examination, PSA level, histopathology result including Gleason score and stage of the disease including the sites of distant metastases in case of metastatic disease.

These data were analyzed using statistical package for social science (SPSS) version16.0. Percentage and descriptive statistics were used to summarize the data. Chi-square ($\chi^2$) test was used to test for associations between variables. The data was presented in percentage and table forms.

Ethically we got the permission of the hospital directory before we conducted this study and also the research ethical committee of Gezira university approval.

One limitation of the study is the non-inclusion of a control. Another limitation is the insufficient data in some cases.
CHAPTER 3

3.1: Results and Analysis

The total number of patients included in this study was 424. Those were all the patients seen and treated in Gezira NC1 as cases of prostate cancer in the period from January 2009 up to December 2013. Table 6 shows the distribution of patients by their socioeconomic characteristics. About 65% of the patients were from the Gezira state and the majority were married (91.3%). Regarding age group, the majority of the patients were in the age group '71-80' years (36.1%) and the age group '61-70' years (35.6%) while less than 1% with age less than 50 years. The mean age was 72 with a standard deviation 9.45. For education level, most of the patients were illiterate (37.3%), 50% were either khalwa graduates (26.7%) or with primary education (23.3%). Very few had university degree and higher education (4.4%). For occupation half of the patients were farmers and about 30% worked in the private sector and only 10.6% were government employees. Regarding body mass index (BMI), about one third of the data for this variable was missed. The majority of the patients had either normal weight (32.8%) or underweight (24.5%). Those who were obese were 3.3% of the total number of the available data. The mean BMI was 21.8 with standard deviation 4.06.

Table 7 depicts the mode of presentation. While some patients presented with only one symptom others have more than one at the time of presentation. Characteristically LUTs and urine retention represented the dominant presenting symptoms among the other presenting symptoms. 359 patients (84.7%) presented with LUTs and 216 patients (50.9%) presented with urine retention while 61 patients (14.4%) presented with backache, 38 patients (9%) presented with haematuria, 29 patients (6.8%) presented with neurological symptoms, 19 patients (4.5%) presented with renal impairment while only one patient presented with incontinence. No patient presented with sexual dysfunction.
### Table (6): Patients characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>less than 50</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>50-60</td>
<td>49 (11.6%)</td>
</tr>
<tr>
<td>61-70</td>
<td>151 (35.6%)</td>
</tr>
<tr>
<td>71-80</td>
<td>153 (36.1%)</td>
</tr>
<tr>
<td>81-90</td>
<td>63 (14.9%)</td>
</tr>
<tr>
<td>91-100</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
</tr>
<tr>
<td>missed</td>
<td>141 (33.3%)</td>
</tr>
<tr>
<td>less than 20</td>
<td>104 (24.5%)</td>
</tr>
<tr>
<td>20-25</td>
<td>139 (32.8%)</td>
</tr>
<tr>
<td>26-29</td>
<td>26 (6.1%)</td>
</tr>
<tr>
<td>30-34</td>
<td>13 (3.1%)</td>
</tr>
<tr>
<td>35-49</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td><strong>Education</strong></td>
<td></td>
</tr>
<tr>
<td>Illiterate</td>
<td>158 (37.3%)</td>
</tr>
<tr>
<td>Khalwa</td>
<td>113 (26.6%)</td>
</tr>
<tr>
<td>Primary</td>
<td>99 (23.3%)</td>
</tr>
<tr>
<td>intermediate</td>
<td>5 (1.2%)</td>
</tr>
<tr>
<td>high school</td>
<td>30 (7.1%)</td>
</tr>
<tr>
<td>University</td>
<td>15 (3.5%)</td>
</tr>
<tr>
<td>Above university</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td><strong>Occupation</strong></td>
<td></td>
</tr>
<tr>
<td>Farmer</td>
<td>215 (50.7%)</td>
</tr>
<tr>
<td>Driver</td>
<td>32 (7.5%)</td>
</tr>
<tr>
<td>free work</td>
<td>132 (31.1%)</td>
</tr>
<tr>
<td>Employee</td>
<td>45 (10.6%)</td>
</tr>
<tr>
<td><strong>Residence</strong></td>
<td></td>
</tr>
<tr>
<td>missed</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>in state</td>
<td>277 (65.3%)</td>
</tr>
<tr>
<td>out state</td>
<td>143 (33.7%)</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>387 (91.3%)</td>
</tr>
<tr>
<td>Unmarried</td>
<td>37 (8.7%)</td>
</tr>
</tbody>
</table>
Figure (1)

Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>71.80</td>
<td>36.1</td>
</tr>
<tr>
<td>61.70</td>
<td>35.6</td>
</tr>
<tr>
<td>51.90</td>
<td>14.9</td>
</tr>
<tr>
<td>41.60</td>
<td>11.6</td>
</tr>
<tr>
<td>31.40</td>
<td>1.2</td>
</tr>
<tr>
<td>21.30</td>
<td>0.7</td>
</tr>
<tr>
<td>less than 50</td>
<td></td>
</tr>
</tbody>
</table>

Figure (2)

BMI

<table>
<thead>
<tr>
<th>BMI</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.01</td>
<td>33.3</td>
</tr>
<tr>
<td>0.02</td>
<td>32.8</td>
</tr>
<tr>
<td>less than 20</td>
<td>24.5</td>
</tr>
<tr>
<td>20.29</td>
<td>6.1</td>
</tr>
<tr>
<td>30.34</td>
<td>3.1</td>
</tr>
<tr>
<td>35.49</td>
<td>0.2</td>
</tr>
</tbody>
</table>
Figure (5)

![Education Graph](image)

Figure (6)

![Marital Status Graph](image)
Table 7: Presentation of prostate cancer:

<table>
<thead>
<tr>
<th>Presentation</th>
<th>LUTS</th>
<th>Urine retention</th>
<th>Haematuria</th>
<th>Backache</th>
<th>Sexual dysfunction</th>
<th>Incontinence</th>
<th>Neurological impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>359</td>
<td>216</td>
<td>38</td>
<td>61</td>
<td>0</td>
<td>1</td>
<td>29</td>
</tr>
<tr>
<td>Pts</td>
<td>424</td>
<td>424</td>
<td>424</td>
<td>424</td>
<td>424</td>
<td>424</td>
<td>424</td>
</tr>
<tr>
<td>Percent%</td>
<td>84.7%</td>
<td>50.9%</td>
<td>9%</td>
<td>14.4%</td>
<td>0.2%</td>
<td>6.8%</td>
<td>4.5%</td>
</tr>
</tbody>
</table>

Figures (7)

Table 8 displays family history of the disease, comitant diseases and social habits. Concerning comitant diseases (HTN/DM), 13.4% of the patients have HTN, 4% have DM, 2.4% have both HTN and DM but the majority of the patients hadn't any of these diseases. Regarding smoking and alcohol consumption, the majority (55%) were neither alcohol consumers nor cigarette smokers. About quarter of the patients were smokers, 3.3% were alcohol consumers and 14.9 were both. The majority of the patients showed no family history for the disease (80.9%).
Table (8). family history, concomitant diseases and social history

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Family History</strong></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>63 (14.9%)</td>
</tr>
<tr>
<td>Positive</td>
<td>18 (4.2%)</td>
</tr>
<tr>
<td>Negative</td>
<td>343 (80.9%)</td>
</tr>
<tr>
<td><strong>Concomitant Disease</strong></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (1.9%)</td>
</tr>
<tr>
<td>HTN</td>
<td>57 (13.4%)</td>
</tr>
<tr>
<td>DM</td>
<td>17 (4%)</td>
</tr>
<tr>
<td>HTN+DM</td>
<td>10 (2.4%)</td>
</tr>
<tr>
<td>None</td>
<td>332 (78.3%)</td>
</tr>
<tr>
<td><strong>Social History</strong></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7 (1.7%)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>14 (3.3%)</td>
</tr>
<tr>
<td>tobacco</td>
<td>107 (25.2%)</td>
</tr>
<tr>
<td>alcohol+ tobacco</td>
<td>63 (14.9%)</td>
</tr>
<tr>
<td>none</td>
<td>233 (55%)</td>
</tr>
</tbody>
</table>
Figure (8)

![Bar chart showing frequency of family history with values: 80.9% negative, 14.9% positive, and 4.2% other.]

Figure (9)
Figure (10)

Social habits
Table 9. presents results for digital rectal examination (DRE). Although 67.6% had hard prostate, nodularity was found on DRE of 62.3%. Asymmetry and obliteration of the median sulcus were found in 10.1% and 12% respectively. In the majority of cases these findings presented in combination.

**Table (9): Result of DRE**

<table>
<thead>
<tr>
<th>DRE</th>
<th>Hard prostate</th>
<th>Nodular prostate</th>
<th>Asymmetrical</th>
<th>Obliterated median sulcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>288%</td>
<td>264%</td>
<td>43%</td>
<td>51%</td>
</tr>
<tr>
<td>Pts</td>
<td>424%</td>
<td>424%</td>
<td>424%</td>
<td>424%</td>
</tr>
<tr>
<td>percent%</td>
<td>67.6%</td>
<td>62.3%</td>
<td>10.1%</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Figure (11)**
Table 10 shows PSA testing results for the patients. This testing revolutionized prostate cancer screening. The traditional cut-off point for an abnormal PSA level in major screening studies is 4.0 ng/ml. In this study 411 patients had PSA level above 4.0 ng/ml while 7 patients had PSA level less 4.0 ng/ml.

Table (10): PSA Level

<table>
<thead>
<tr>
<th>PSA level</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 4</td>
<td>7 (1.7%)</td>
</tr>
<tr>
<td>4-10</td>
<td>27 (6.4%)</td>
</tr>
<tr>
<td>11-20</td>
<td>21 (5%)</td>
</tr>
<tr>
<td>21-100</td>
<td>129 (30.4%)</td>
</tr>
<tr>
<td>more than 100</td>
<td>234 (55.2%)</td>
</tr>
</tbody>
</table>

Figure (12)
Table 11 presents results of biopsy which is the gold standard for diagnosis of prostate cancer. It showed that all patients (100%) in this study had adenocarcinoma. The majority of the patients (63.2%) had Gleason score above 7, 18.4% had score less than 7 and 15.8% with a score of 7.

Table (11) : Result of Biopsy

<table>
<thead>
<tr>
<th>Biopsy</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adenocarcinoma</td>
<td>424 100%</td>
</tr>
<tr>
<td><strong>Gleason Score</strong></td>
<td></td>
</tr>
<tr>
<td>less than 7</td>
<td>78 18.4%</td>
</tr>
<tr>
<td>7</td>
<td>67 15.8%</td>
</tr>
<tr>
<td>more than 7</td>
<td>268 63.2%</td>
</tr>
</tbody>
</table>

Figure (13)
Figure (14)

Table 12 shows stages of the disease on presentation. 1.7% of the patients were found to have organ confined disease, 40.3% had locally advanced disease while 58% had metastatic disease. Bone metastases were found in 46.7% of the patients, 1.4% had liver metastases, 0.2% had lung metastases and 0.2% had para-aortic lymph nodes metastases while 41.7% showed no distant metastasis. Very few showed combinations of metastasis. This ranges from 2.6% for 'bone + lung' and 'bone + liver' to 0.2% for 'bone + Para Ln + lung'.

Tables 13 and 14 showed the results of the association between PSA, bone metastases and stages of the disease. Chi square test showed a significant association between PSA level and bone metastases (P = 0.001). The test showed that most of the patients (99%) with metastasis to the bones were above the cut-off point. Also a
significant association was detected between PSA and stage of the disease ($p = 0.001$). Most of the patients had either locally advanced (63.7%) or metastatic stage (62.6%).

Table (12): Stage of Prostate carcinoma and distant metastasis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>organ confined</td>
<td>7 (1.7%)</td>
</tr>
<tr>
<td>locally advance</td>
<td>171 (40.3%)</td>
</tr>
<tr>
<td>metastatic</td>
<td>246 (58%)</td>
</tr>
<tr>
<td>MET(distant)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>177 (41.7%)</td>
</tr>
<tr>
<td>Bone</td>
<td>198 (46.7%)</td>
</tr>
<tr>
<td>Liver</td>
<td>6 (1.4%)</td>
</tr>
<tr>
<td>Lung</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Para LN</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Bone +lung</td>
<td>11 (2.6%)</td>
</tr>
<tr>
<td>Bone +liver</td>
<td>11 (2.6%)</td>
</tr>
<tr>
<td>Bone +Para LN</td>
<td>10 (2.4%)</td>
</tr>
<tr>
<td>Liver +lung</td>
<td>4 (0.9%)</td>
</tr>
<tr>
<td>Bone +liver +lung</td>
<td>3 (0.7%)</td>
</tr>
<tr>
<td>Bone +lung +brain</td>
<td>1 (0.2%)</td>
</tr>
<tr>
<td>Bone +Para LN+ lung</td>
<td>1 (0.2%)</td>
</tr>
</tbody>
</table>
Figure (15)

![Figure 15: Bar chart showing frequency of metastatic, locally advanced, and organ confined stages.](image)

Figure (16)

![Figure 16: Bar chart showing frequency of Met in bone, liver, lung, para LN, and brain.](image)
### Table (13): Relation of PSA to bone metastasis

<table>
<thead>
<tr>
<th>PSA</th>
<th>Met bone</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>less than 4</td>
<td>2 (33)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>4-10</td>
<td>1 (14.3)</td>
<td>6 (85.7)</td>
</tr>
<tr>
<td>11-20</td>
<td>4 (14.8)</td>
<td>23 (85.2)</td>
</tr>
<tr>
<td>21-100</td>
<td>6 (28.6)</td>
<td>15 (71.4)</td>
</tr>
<tr>
<td>more than 100</td>
<td>44 (34.1)</td>
<td>85 (65.9)</td>
</tr>
</tbody>
</table>

### Table (14): Relation of PSA to stage of PCa

<table>
<thead>
<tr>
<th>PSA</th>
<th>Stage</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>organ confined</td>
<td>locally advance</td>
</tr>
<tr>
<td>less than 4</td>
<td>0</td>
<td>4 (67)</td>
</tr>
<tr>
<td>4-10</td>
<td>1 (14.3)</td>
<td>5 (71.3)</td>
</tr>
<tr>
<td>11-20</td>
<td>3 (11.1)</td>
<td>20 (74.1)</td>
</tr>
<tr>
<td>21-100</td>
<td>2 (9.5)</td>
<td>12 (57.1)</td>
</tr>
<tr>
<td>more than 100</td>
<td>1 (0.08)</td>
<td>80 (62.0)</td>
</tr>
</tbody>
</table>
### Table (15): Family History * Age Crosstabulation

<table>
<thead>
<tr>
<th>Family History</th>
<th>Age</th>
<th>Count</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>less than 50</td>
<td>1</td>
<td>0.724</td>
</tr>
<tr>
<td>positive</td>
<td>7</td>
<td>23</td>
<td>10</td>
</tr>
<tr>
<td>negative</td>
<td>22</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

### Table (16): Family History * Stage Cross tabulation

<table>
<thead>
<tr>
<th>Family History</th>
<th>Stage</th>
<th>Count</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>organ confined</td>
<td>2</td>
<td>0.613</td>
</tr>
<tr>
<td>positive</td>
<td>25</td>
<td>36</td>
<td>13</td>
</tr>
<tr>
<td>negative</td>
<td>5</td>
<td>141</td>
<td>197</td>
</tr>
</tbody>
</table>

### Table (17): Gleason Score * Stage Cross tabulation

<table>
<thead>
<tr>
<th>Gleason Score</th>
<th>Stage</th>
<th>Count</th>
<th>P.value</th>
</tr>
</thead>
<tbody>
<tr>
<td>less than 7</td>
<td>organ confined</td>
<td>0</td>
<td>0.000</td>
</tr>
<tr>
<td></td>
<td>locally advance</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>metastatic</td>
<td>42</td>
<td>29</td>
</tr>
<tr>
<td>7</td>
<td>organ confined</td>
<td>7</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>locally advance</td>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td></td>
<td>metastatic</td>
<td>39</td>
<td>180</td>
</tr>
<tr>
<td>more than 7</td>
<td>organ confined</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>locally advance</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>metastatic</td>
<td>88</td>
<td></td>
</tr>
</tbody>
</table>
3.2: Discussion

Prostate cancer is one of the major medical problems facing the male population. It is estimated to be a major cancer for men in sub-Saharan African countries. African American have higher rate of prostate cancer incidence and mortality compared to other ancestries (217). This study showed that the number of patients diagnosed with prostate cancer increased from 64 patients in 2009 to 112 in 2013. The percentage increase was 75%. This is probably because of the increasing use of PSA testing and using of prostate biopsy protocol. But because prostate cancer is diagnosed at an old age, a substantial proportion of men may die before they were diagnosed with prostate cancer and many more of a live men may have prostate cancer but not know about it, so this percentage of increase in the number of patients diagnosed with prostate cancer does not reflect the true one And is just the tip of the ice berg.

Previous researches demonstrated that age is one of the major risk factors in prostate cancer(215,216). The results in this study showed that the bulk of patients (71.7%) diagnosed with prostate cancer were in the age groups '61-70' and '71-80' years while only 0.17% of the patients had an age less than 50 years. The mean age was 72.10 with standard deviation 9.45. This result is in line with what is stated by Kirby et. al. and Parkin et.al.(148-149) and it is also in agreement with the study carried out by F.Hamad and Dr.D. AbuIdris when they studied the risk factors for prostate cancer in Gezira state Sudan(2006-2009) they found that more than 70% of the patients with the prostate cancer were over 66 years.

The finding on overall obesity is mixed but recent data suggest that obesity is more consistently related to aggressive prostate tumour(61,62). This study showed that those who were obese were 3.3%. The mean BMI was 21.82 with standard deviation 4.06. We could not draw any conclusion from our data as 33% of the data for this variable were missed.

Educational level may influence the risk of cancer in many ways. Education is an important attribute guiding the selection of occupation. This in turn is a predictive factor for disposable income and many socioeconomic aspect of life including residential and lifestyle factor. Health contentious behaviour, seeking and affordability of healthy food, access to and use of health care services which are related to education and
socioeconomic factors help to identity and remove tumours at an early stage. Also education helps in acceptance of aggressive forms of treatment (231).

In this study most of the patients had low education level. 37.3% were illiterate, 50% were either khalwa graduates (26.7%) or had primary education (23.3%). The low level of education among patients studied explains why they presented late and the advanced stage they presented with and the refusal of some of them to accept some options of treatment (orchiectomy).

Researches on occupational causes of prostate cancer has produced inconsistent results. There is some evidence though currently inconclusive, that supports the association of prostate cancer incidence with certain occupations. It appears that men who are exposed to high level of pesticides through farming may be at higher risk for developing prostate cancer (67). In this study more than 50% of our patients were farmers but because Gezira state is the house of farmers in Sudan as the bulk of its residences are either farmers or have jobs related to farming, this number consider to be small compared to the big number of farmers exposed to pesticides. So pesticides need more investigations to say that it is a definite cause for development of prostatic carcinoma.

Prior researches had indicated that being married was an independent factor for prostate cancer research. Ayal among others reported that married patients were less likely to present with metastatic disease (234). In this study 91.3% were married, the majority of them have either locally advanced or metastatic disease. This can be explained in part by low level of education and low socioeconomic status of these patients.

A considerable percentage of the patients (35%) were from outside the Gezira state. Most of them if not all had advanced disease at presentation. This is most probably due to the unavailability of the standard diagnostic tools for prostate cancer where they live, low socioeconomic state, low education level, decrease suspicious level in treating doctors at the periphery for the prostate cancer especially that prostate cancer in early stage presents with symptoms (LUTs) commonly seen in patients with BPH and urinary tract infection. These factors collectively resulted in delay of presentation and diagnosis of prostate cancer.

Family history represents a complex mix of genetics and environmental factors. It is considered as one of the major risk factors for prostate cancer. The aggregation of prostate cancer cases in a family that does not fulfil the criteria for hereditary prostate cancer (nuclear families with three cases of prostate cancer, families with prostate cancer
in each of three generation in the paternal or maternal lineage and families with two men diagnosed with the disease before age of 55 years) (206) is called familial prostate cancer. Numerous studies have consistently reported familial aggregation of prostate cancer showing 2 to 3 fold increase risk of prostate cancer among men who have a first degree male relative with a history of prostate cancer (208) and the risk of prostate cancer increase with increasing number of affected family members, thus the lifetime absolute risk of clinical prostate cancer has been estimated to be 35-45% for men with three or more affected male relatives compared with 8% absolute risk in men without family history of the disease(207). F. Hamad and Dr. D. Abu Idris in their study of risk factors for prostate cancer found that family history was positive in 6.7% which is in agreement with previous studies that showed approximately 9% of all prostate cancers may result from heritable susceptibility genes(218). Our results revealed that 4.2% have positive family history. This percentage is lower than that reported in the literature. This maybe explained in part by decrease awareness and ignorance of a big number of Sudanese patients about their family history as an important parameter in the process of surveillance and early detection of hereditable and familial diseases and besides that approximately 80% of our patients had education level less than secondary school. Concerning age on presentation for our group with familial disease which is suspected to be earlier as many epidemiological studies stated (95,96), the majority of them 77%(14 out of 18) presented with age above 60 years which is the common as in those with sporadic disease. The remaining 23% were included in the age group 50-60. Concerning stage of the disease for this group with familial disease,72.2% presented with metastatic disease and the remaining 27.8% presented with locally advanced disease.

Smoking and use of alcohol have been evaluated as risk factors for prostate cancer but their roles in prostate cancer are weak or unclear (209-211). Numerous studies have found that cigarette smoking may be a risk factor for the development of prostate cancer (219). Hsing and colleagues demonstrated relative risk of 1.8 and 2.1 for cigarette smoking and chewing tobacco respectively. Also Bagnardi et. al. found significant increased risk for men drinking more than 50g/day of alcohol with slightly higher risk for consuming more than 100 g/day(230). In our study surely we cannot comment about the effect of smoking and alcohol consuming as a single risk factor for prostate cancer as most of our patients have another strong risk factor (age) but probably this may increase the risk of prostate cancer as it is a multifactorial disease.
The evidence of diabetes as risk factor for prostate cancer is inconsistent. In a population based cohort study conducted in Sweden, men hospitalized for diabetes had a 9% low risk of prostate cancer and those hospitalized for a diabetic complication had an 18% low risk than in other population based registers(92,93). Most studies which investigated the association between Diabetes Mellitus and prostate cancer stated that there is inverse relationship between diabetes and prostate cancer(220,221). Some investigators limited this low risk of prostate cancer in diabetics to white men(156). In our study we can't comment about the effect of Diabetes Mellitus on prostate cancer as our study didn't include control group.

Concerning hypertension as a risk factor for prostate cancer, no association between hypertension and prostate cancer was found(227). A study about effect effect of metabolic factors on prostate cancer resulted in that non of the metabolic risk factor including high blood pressure and high blood sugar were associated with the risk of developing prostate cancer but the study stated that high BM1 and blood pressure were associated with high risk of dying from prostate cancer(228,229).

The principal diagnostic tools for evaluating patients for prostate cancer include a combination of digital rectal examination and prostate specific antigen prompting a decision to perform TRUS guided prostate biopsy.

DRE has long been used to diagnose prostate cancer. A meta-analysis of DRE estimated a sensitivity for detecting prostate cancer of 59% and a specificity of 94%(232). A suspicious DRE is a strong indicator for prostate biopsy as it is a predictor for more aggressive PCa. Some cases of prostate cancer are detected by a suspicious DRE alone irrespective of PSA level.

The traditional cut off point for an abnormal PSA level in the major screening studies has been 4.0 ng/ml(223,224). In this study 97% of the patients have PSA level above 4 ng/ml, which agrees with major screening studies. Some investigators have suggested using a lower PSA cut off point because some men with PSA level below 4 ng/ml were found to have prostate cancer(225,226). In our study 1.7% of patients diagnosed with prostate cancer had PSA level less than 4. This study revealed that most of the patients had advanced disease. This is a reflection of educational level, low socioeconomic state and decreased awareness.

TRUS has become an extension of the urologist finger in the early detection of prostate cancer. The impact of TRUS in detection of prostate cancer was studied at Gezira NCI by Dr. Abu idris D., prof.EL Imam M., and Mr Omran M. They stated that
introduction of TRUS in diagnosing prostate cancer leads to an increase in the number of patients diagnosed with prostate cancer. Prostate biopsy remains the gold standard investigation for diagnosing prostate cancer. In our study, all patients with prostate cancer were found to have adenocarcinoma which is the most common type worldwide.

The Gleason grading system is found to help in evaluating the prognosis of patients with prostate cancer. It is indicative of aggressiveness of the disease and it is essential for treatment planning and decision making.

The positive relationship between PSA level and bone metastases indicated that the risk of positive bone scan increases with PSA level. Thus serum PSA could be considered as a good tool for the prediction of bone metastases in the group of patients with PSA reference value of more than 100 ng/ml, which is higher than that predicted in Jordanian patients with bone metastases in a study carried out at prince Hussein urology centre and which resulted in that PSA level above 20 is a predictive value for bone metastases(233).
CHAPTER 4

4.1: Conclusion

1. Prostate cancer is increasing in Sudan. This is most probably due to the increasing use of serum PSA testing, use of prostate biopsy protocol and increase public concern about prostate cancer.

2. Prostate cancer is multi-factorial disease but age, race and family history still are the main risk factors for the disease while smoking, snuffing, alcohol, hypertension, Diabetes M. and obesity have inconsistent evidence.

3. The bulk of patients diagnosed with prostate cancer were in the age group 61 – 80 year with the mean age 72 with standard deviation 9.45.

4. Education may affect prostate cancer in different ways e.g. Selection of occupation and its effect in socioeconomic state, lifestyle of the patients, stage of the disease and acceptance to treatment.

5. High incidence of prostate cancer among farmers may reflect the effect of herbicides and pesticides and may recommend a study to confirm this hypothesis.

6. Prostate Cancer can present with different symptoms according to the stage of the disease. Patients in early stage of the disease have similar presenting symptoms as BPH and UTI but with advance stage, patients may present with symptoms that indicate local or distant metastases.

7. DRE, PSA testing and TRUS and biopsy constitute the triple for catching patients with prostate cancer and prostate biopsy remains the gold standard investigation for diagnosing prostate cancer.

8. Among all types of prostate cancer adenocarcinoma is the most common cancer type.

9. Education level, low socioeconomic status, decrease in awareness about prostate cancer and non availability of diagnostic tools at many part of the county stand behind patient's advanced stage at presentation.

10. PSA can be considered as a good tool for the prediction of bone metastases and stage of the disease in patients with prostate cancer.

11. Prostate cancer can spread to other parts of the body through the blood, lymph and direct local invasion but bones are the most common site for distant metastases.
4.2: Recommendation

1. Prostate cancer is a deadly disease, so increasing the awareness and education of the Community about it is the first step towards its early detection and Acceptance of any screening test and treatment described.

2. Creation of a screening program for the surveillance and early detection of the disease for the groups most likely to develop it.

3. Establishment of more centres for cancers at peripheral state level and availability of investigation required for detection of the disease help patients to present early in the course of their disease.

4. Availability of investigation as free help the process of detection and follow up of the patients during the course of the disease and treatment.

5. Education of the community that healthy choices such as exercising, eating healthy diet and stopping smoking, snuffing and alcohol drinking will reduce the risk of prostate cancer.

6. DRE should be done to any patient above 60 years with UTI symptoms.

7. Hospital administration should give more concern to the patients' file. Those files are an invaluable asset to the hospital as well as to researchers seeking information.
References

1. Adams J (1853). "The case of scirrhous of the prostate gland with corresponding
   affliction of the lymphatic glands in the lumbar region and in the pelvis". Lancet 1
2. E. David Crawford, epidemiology of prostate cancer, j.urology 2003.10.013
   30: 281-95
4. McCaul KA, LuKe CG, Roder DM. Trends in prostate cancer incidence and
5. Sarma AV, Schottenfeld D. prostate cancer incidence, mortality, and survival
6. Qunin M, Babb P. pattern and trends in prostate cancer incidence, survival,
   prevelance and mortality. Part 1; international comparisons. int 2002; 90
   (2):162-173
7. Potosky AL, Miller BA, Albersten PCet al. the role of increasing detection in the
   rising incidence of prostate cancer. JAMA 1995; 273(7):548-552
8. Legler JM, Feuer EJ, Potosky AL, et al. the role of prostate specific antigen (PSA)
   testing patterns in the recent prostate cancer incidence decline in the United
   States, cancer causes control 1998; 9 (5) 519-527
   seven areas. The international Agency for research on cancer , Lyon, France. Int J
   cancer 1997; 20 (5) 680-688
10. Sakr WA, Grignon DJ, Crissman JD, Heibrun LK, Cassin BJ, Pontes JJ et al. High
    grade prostatic intraepithelial neoplasia (HGPIN) and prostatic adenocarcinoma
11. Haas GP, Delongchamps N, Brawley OW, et al. the worldwide epidemiology of
    3871
    6(2): 87-95
    carcinoma presentation, diagnosis, and staging: an update form the National
    Cancer Data Base". Cancer 98 (6): 1169–78
14. van der Cruijsen-Koeter IW, Vis AN, Roobol MJ, Wildhagen MF, de Koning HJ,
    van der Kwast TH, Schröder FH (July 2005). "Comparison of screen detected and
clinically diagnosed prostate cancer in the European randomized study of screening for prostate cancer, section rotterdam Urol 174 (1) 121-5


17. Polascik TJ, Oesterling JE, Partin AW. Prostate specific antigen: a decade of discovery-what we have learned and where we are going. J Urol 1999;162:293-306


25. Tom J Walton, Prostate Embryology, Anatomy and Physiology January 2010 Available at http://surg.online.net/wp-content/uploads/2012/12/1


52. Terry, P. D., T. E. Rohan & A. Wolk: Intakes of fish and marine fatty acids and the risks of cancers of the breast and prostate and of other hormone-


85. Fernandez, L., Y. Galan, R. Jimenez, A. Gutierrez, M. Guerra, C. Pereda, C. Alonso, E. Riboli, A. Agudo & C. Gonzalez: Sexual behaviour, history of


prostate specific antigen combined with prostate specific antigen and free prostate
specific antigen for prostate cancer detection in the 2.0 to 10.0 ng/ml prostate
isofom p2PSA significantly improves the prediction of prostate cancer at initial
extended prostate biopsies in patients with total PSA between 2.0 and 10 ng/ml:
1973-1995, Publication no. 99-4543, SEER Program, National Cancer Institute,
Bethesda, MD 1999.
124. Moul JW, Sesterhenn IA, Connelly RR, et al. Prostate-specific antigen values
at the time of prostate cancer diagnosis in African-American men. JAMA 1995;
274:1277.
126. Powell JI, Banerjee M, Novallo M, et al. Should the age specific prostate
specific antigen cutoff for prostate biopsy be higher for black than for white men
DD3:a new prostate-specific gene, highly overexpressed in prostate cancer "Cancer Res
59 (23):5975-9 PMID 10606244.
128. Neves AF Arajuo TG Biase WK et at.(July 2008) Combined analysis of
multipic mRNA markers by RT-PCR assay for prostate cancer diagnosis" Clin.
Biochem 41(14-15):1191.s
129. Loeb S (July 2008 )Does PCA3 hep identifly Clinically Signifleant prostate
Cancer . EUR Urol 54 (5) 980
130. PCA3 score: Windsor Urology: Available at: http://www. Windsor
Urology.co.UK/clinical information/PCA3score.
review: prostate cancer antigen 3 testing for the diagnosis and management of


146. Iczkowski KA Casella G. Seppala RJ. Et al.; Needle core length in sextant biopsy influences prostate cancer detection rate. Urology 2002 May. 59(5) 698-703.


149. Pelzer AE. Bektic J. Berger AP. Et al; Are transsuction zone biopsies still necessary to improve prostate cancer detection? Results from the Tyrol screening project. EUR Urol 2005 Dec. 48(6) 916-21 discussion 921.


229. Chales Barkhead, Robert Jasmer; BMI,BP Dort U[ prostate cancer risk; published on Dec.22/2012.
233. Dr. Ali Alasmar, PSA as a predictive tool for detecting bone metastases in bone scan, middle east journal Medicine volume,12 issue2 March 2014.


Questionnaire

A/ Personal Data:
1. File number: .................................................................
2. Age: ..............................................................................
3. BMI: ..............................................................................
4. Education: .......................................................................  
5. Occupation: ......................................................................
6. Residence: Gezira ( )  Outside Gezira ( )
7. Marital Status: ..................................................................

B/ Presentation:
1. LUTs: ................................................................................
2. Urine retention: .................................................................
3. Haematuria: ......................................................................
4. Sexual dysfunction: .........................................................
5. Backache: .........................................................................
6. Incontinence: ....................................................................
7. Neurological: .....................................................................
8. Renal impairment: ...........................................................
9. Others: ................................................................................

C/ Family History: 1/ positive ( )  2/ Negative ( )

D/ Concomitant Disease: 1/ HTN ( )  2/ DM ( ) 3/ non ( )

E/ Social History: Alco ( )  Snuff ( )  None ( )

F/ Examination: DRE:
1. Size small ( ) Moderate ( ) Huge ( ) 2. Hard prostate ( )
3. Nodular prostate ( ) 4. Asymmetrical ( ) 5. Obliterated median sulcus ( )

G/ Diagnosis:
1. PSA level: ........................................................................
2. U/S size of the prostate: ....................................................
3. Biopsy (H/P): ....................................................................
4. Post prostatectomy: 1/ TVP ( ) 2/ TURP ( )
5. Gleason score: ..................................................................
6. Bone scan: ........................................................................
7. Stage: 1/ organ confined ( ) 2/ Locally advance ( ) 3/ Metastatic ( )