

PROSTATE CANCER

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INTRODUCTION

The two Articles published earlier by us were number one is on general cancer & second is on breast cancer. In continuation with this, we would like to emphasis on prostate cancer here.

Anatomy, Physiology & Pathophysiology of Prostate gland^{1,1a}

The prostate gland is present only in males, although females have homologous glands (having the same embryological origin) around the urethra; these are called 'Skene's glands' or 'the female prostate'.

The prostate gland surrounds the proximal part of the urethra as it exits the base of the bladder. The size of the prostate varies with age ranging from size of a walnut, but it can be much larger in older men. It produces fluid that protects and nourishes sperm cells in semen, making the semen fluid. Semen is a gray and rather opalescent, turbid fluid having pH of 7.2 to 8.0. Life & movement of sperms depends on important properties of semen. A groove down the centre of the prostate gland divides it into left and right lobes.

Anatomists more precisely describe the prostate gland as having anterior, posterior, lateral, and median lobes, whereas pathologists sometimes describe the prostate as having zones (peripheral, central, transitional, periurethral, and fibromuscular). The peripheral zone accounts for most of the prostate gland and about 75% of prostate cancers.

Fluid secreted by the prostate forms about 30% of the volume of semen.

PSA is a protein produced by normal and cancerous prostate cells.

PSA is secreted by prostate epithelial cells into prostatic fluid, where its function is to liquefy semen and thus allow spermatozoa to move more freely. Although PSA is

secreted into prostatic fluid and semen, small amounts of PSA are present in blood. [See fig. no. 1 which depict the Anatomy of Prostate gland]

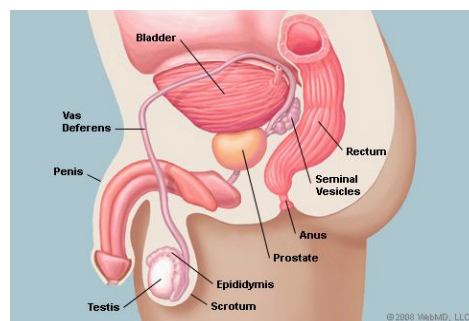


Fig. 1: Anatomy of prostate gland © 2009 WebMD, LLC.

Several types of cells are found in the prostate, but almost all prostate cancers develop from the glandular cells. Glandular cells make the prostate fluid that is added to the semen. The medical term for a cancer that starts in glandular cells is *adenocarcinoma*.

Other types of cancer can also start in the prostate gland, including sarcomas, small cell carcinomas, and transitional cell carcinomas. But these types of prostate cancer are so rare that if you have prostate cancer it is almost certain to be an adenocarcinoma.

Some prostate cancers can grow and spread quickly, but most grow slowly. In fact, autopsy studies show that many older men (and even some younger men) who died of other diseases also had prostate cancer that never affected them during their lives. In many cases neither they nor their doctors even knew they had it.

Microscopic Anatomy

Historically, the prostate has been divided into 3 zones: (1) transition zone, (2) central

zone, and (3) peripheral zone. The transition zone accounts for 10% of the prostatic glandular tissue and 20% of the adenocarcinomas. The prostate consists of approximately 70% glandular tissue and 30% fibromuscular stroma.

Transition zone

The prostatic urethra courses the length of the prostate from the level of the bladder neck to the level of the membranous urethra. The epithelium consists of transitional cells similar to bladder epithelium. This transitional zone is where benign prostatic hyperplasia occurs and can lead to bladder outlet obstruction when an adenoma grows to a significant size. When the adenoma grows large enough, it can compress the fibromuscular band surrounding this zone, creating a surgical capsule.

The transitional zone is often described as having 2 lateral lobes and a median lobe that lead to the symptoms of the lower urinary tract symptoms. A urethral crest runs along the posterior midline and disappears at the membranous urethra. On both sides of the urethral crest, there is a groove where the prostatic sinuses exist and drain all of the glandular elements.

The urethral crest widens and protrudes from the posterior wall as the seminal colliculus (verumontanum). A small midline pit, the prostatic utricle, is found at the apex of the seminal colliculus. On either side of the utricular orifice, the small slitlike openings to the ejaculatory duct can be found.

Central zone

The central zone is the area surrounding the ejaculatory ducts. This zone consists of 25% of the glandular tissue. Very few adenocarcinomas are found in this region and can represent as little as 1-5% of these tumors in the prostate.

Peripheral zone

The peripheral zone of the prostate constitutes 70% of the glandular tissue. This zone covers the posterior and lateral aspects of the prostate. The peripheral zone is the area that is palpated on digital rectal examination (DRE) and represents the area

where 70% of adenocarcinomas are found. This area is also the location most commonly affected by chronic prostatitis.

Possible pre-cancerous conditions of the prostate

Prostate cancer may start out as a following pre-cancerous condition,

Prostatic intraepithelial neoplasia (PIN)

In this condition, there are changes in how the prostate gland cells look under the microscope, but the abnormal cells don't look like they are growing into other parts of the prostate (like cancer cells would). Based on how abnormal the patterns of cells look, they are classified as:

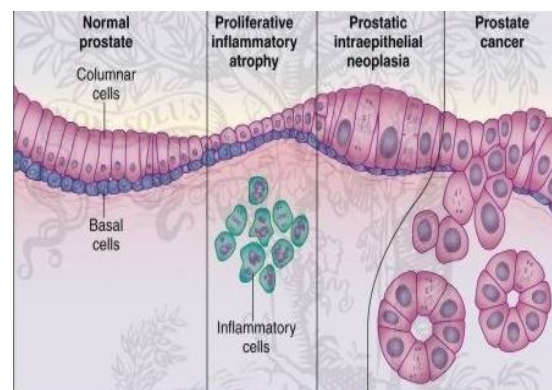
[a] Low-grade PIN: the patterns of prostate cells appear almost normal.

[b] High-grade PIN: the patterns of cells look more abnormal.

Proliferative inflammatory atrophy (PIA)

This is another finding that may be noted on a prostate biopsy. In PIA, the prostate cells look smaller than normal, and there are signs of inflammation in the area. PIA is not cancer, but researchers believe that PIA may sometimes lead to high-grade PIN, or perhaps to prostate cancer directly. [See fig. no. 2]

Changes taking place during the prostate cancer are depicted in Figure 2



<http://www.elsevierimages.com/images/vt/n/000/000/027/27881-150x150.jpg>

Fig. 2: Proliferative inflammatory atrophy (PIA) as a precursor to prostatic intraepithelial neoplasia (PIN) and prostate cancer. (Adapted from Nelson WG, DeMarzo

AM, Isaacs WB: Prostate cancer. N Engl J Med 2003;349:366–381.)

Pathophysiology of prostate cancer ²

Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that begins when normal semen-secreting prostate gland cells mutate into cancer cells. The region of prostate gland where the adenocarcinoma is most common is the peripheral zone. Initially, small clumps of cancer cells remain confined to otherwise normal prostate glands, a condition known as carcinoma in situ or prostatic intraepithelial neoplasia (PIN). Although there is no proof that PIN is a cancer precursor, it is closely associated with cancer. Over time, these cancer cells begin to multiply and spread to the surrounding prostate tissue (the stroma) forming a tumor. Eventually, the tumor may grow large enough to invade nearby organs such as the seminal vesicles or the rectum, or the tumor cells may develop the ability to travel in the bloodstream and lymphatic system. Prostate cancer is considered a malignant tumor because it is a mass of cells that can invade other parts of the body. This invasion of other organs is called metastasis. Prostate cancer most commonly metastasizes to the bones, lymph nodes, rectum, and bladder. The prostate is a zinc accumulating, citrate producing organ. The protein ZIP1 is responsible for the active transport of zinc into prostate cells. One of zinc's important roles is to change the metabolism of the cell in order to produce citrate, an important component of semen. The process of zinc accumulation, alteration of metabolism, and citrate production is energy inefficient, and prostate cells sacrifice enormous amounts of energy (ATP) in order to accomplish this task. Prostate cancer cells are generally devoid of zinc. This allows prostate cancer cells to save energy not making citrate, and utilize the new abundance of energy to grow and spread. The androgen receptor helps prostate cancer cells to survive and is a target for many anti cancer research studies; so far, inhibiting the androgen receptor has only proven to be effective in mouse studies. Prostate specific membrane antigen (PSMA) stimulates the development

of prostate cancer by increasing folate levels for the cancer cells to use to survive and grow; PSMA increases available folates for use by hydrolyzing glutamated-folates.

IMPORTANCE OF AWARENESS³

Although there is growing awareness about women-affecting cancers like cervical and breast cancer, male-centric tumours are usually given step-motherly treatment. Despite the high-incidence of prostate cancer

among men in the age group of 55-60 years in united states, there is no documented data to understand its prevalence in india.

As men aged over 50 years are at high risk from the disease, it is advisable for anyone over that age to undergo check-up as the disease is easier to cure, if detected early. To spread awareness about the disease, free prostate cancer awareness camp shall be organized by government & non-government organizations.

Early diagnosis is the key to beat prostate cancer. Educational programs can increase the awareness and use of cancer screening.

PROSTATE CANCER STATISTICS IN INDIA⁴

Prostate cancer incidence is increasing in India by 1% every year. The average age adjusted incidence rates for prostate cancer in Indian registries are ranged from 4.1/100,000 for Chennai registry to 8.1/100,000 for Delhi registry, incidence rate of 6.3/100,000 at Mumbai registry and at Bangalore registry it is 5.6/100,000 in 2002-03.

Cancer Registries are under the network of National Cancer Registry Programme (NCRP) of Indian Council of Medical Research (ICMR), New Delhi. The Cancer Registry has been collecting all essential data pertaining to cancer patients, in the resident population of the respective areas. The registry collects information, analyzes it, and produces a report which is presented to the Indian Council of Medical Research. This report presents information like number of cancer cases registered, cancer rate in men, women and children, number of deaths registered due to cancer, common cancer site in men, common cancer site is women etc which in turn helps to

plan the various prevention, awareness, curative programs.

IMPORTANCE OF PROSTATE CANCER ON BASIS OF GLOBAL STATISTICS⁵

More than 241,000 men will be diagnosed with prostate cancer in 2012 and 28,170 will die from the disease, in USA according to an estimate by the National Cancer Institute.

1 in 6 men will be diagnosed with prostate cancer. 1 in 10,000 under age 40 will be diagnosed, the rate shoots up to 1 in 39 for ages 40 to 59, and 1 in 14 for ages 60 to 69. In fact, about 65% of all prostate cancers are diagnosed in men over the age of 65.

RISKFACTORS⁶

Age-Although men of any age can get prostate cancer, age is the strongest risk factor. Over 80% of prostate cancer diagnoses occurring in men older than age 65 years. The degree to which the incidence of prostate cancer increases exponentially with age is greater than with any other cancer. Autopsy studies found that as many as 75% of men older than age 85 years have prostate cancer at the time of death.

Family history- Having a first-degree relative with a history of prostate cancer increases the risk two- to three-fold. However; the exact genes responsible for the development of prostate cancer are not known.

Ethnic/racial background- African-American men are 1.6 times more likely to develop prostate cancer compared with Caucasian men, and are nearly 2.4 times as likely to die from the disease. It is rare among the Chinese.

Other potential risk factors- The endogenous levels of androgens and other hormones (vitamin D levels, insulin-like growth factors), inflammation, and vasectomy status may also be associated with prostate cancer risk.

Genes- Scientists have found few inherited gene changes that seem to raise prostate cancer risk, but they account for a very small percentage of prostate cancer cases.

Recently, some common gene variations have been linked to a higher risk of prostate cancer.

Diet-There appears to be a link with people living in urban areas exposed to pollution and those consuming large quantities of dietary fat. Lower blood levels of vitamin D may increase the risk of developing prostate cancer.

Obesity- Some studies have found that obese men have a lower risk of getting a low-grade (less dangerous) form of the disease, but a higher risk of getting more aggressive prostate cancer.

Inflammation of the prostate- Some studies have suggested that *prostatitis* (inflammation of the prostate gland) may be linked to an increased risk of prostate cancer; Inflammation is often seen in samples of prostate tissue that also contain cancer. The link between the two is not yet clear, but this is an active area of research.

Sexually transmitted infections- Researchers have looked to see if sexually transmitted infections (like gonorrhea, orchlamydia) might increase the risk of prostate cancer, possibly by leading to inflammation of the prostate.

Vasectomy- Some earlier studies had suggested that men who have had a vasectomy (minor surgery to make men infertile) – especially those younger than 35 at the time of the procedure – may have a slightly increased risk for prostate cancer. But most recent studies have not found any increased risk among men who have had this operation.

PROGNOSIS⁷

Prostate cancer rates are higher in developed countries than in the rest of the world. Many of the risk factors for prostate cancer are more prevalent in the developed world, including longer life expectancy and diets high in red meat. Also, where there is more access to screening programs, there is a higher detection rate. Prostate cancer is the ninth-most-common cancer in the world, but is the number-one non-skin

cancer in men from the United States. In India in the 1990s, half of the people with prostate cancer confined to the prostate died within ten years. African-American men have 50–60 times more prostate cancer and prostate cancer deaths than men in Shanghai, China & Nigeria. In patients who undergo treatment, the most important clinical prognostic indicators of disease outcome are stage, pre-therapy PSA level, and Gleason score. In general, the higher the grade and the stage, the poorer the prognosis.

DETECTION AND DIAGNOSIS^{8,8a}

There is no single test to diagnose prostate cancer. The main tests include:

- A urine test to rule out a urine infection
- Digital rectal exam (DRE) -- in this test, the doctor inserts a gloved, lubricated finger into the rectum in order to feel the prostate for bumps or other abnormalities. Many malignant tumors begin in the outer part of the prostate and may be found with this exam. Some men find this test embarrassing, but it is quick, relatively painless, and helps find many prostate cancers.
- PSA test -- a blood test measuring the level of prostate-specific antigen (PSA). Prostate cancer cells produce higher amounts of PSA, so measuring PSA levels may help find cancer while it is still microscopic. However, finding elevated levels of PSA does not always mean that a man has cancer. Benign conditions such as an enlarged prostate can also elevate PSA levels. If either the DRE or PSA test suggests that cancer might be present, doctor may recommend the following tests:
 - Transrectal ultrasound -- using a small probe inserted into the rectum, sound waves help get a visual image of the prostate.
 - Biopsy of the prostate -- a tissue sample is obtained through the rectum and examined for cancerous cells.

Gleason score

The samples of tissue from the biopsy are then studied in microscopically. If cancerous cells are found, they can be

studied further to see how quickly the cancer will spread.

This measure is known as the Gleason score. The lower the score, the less likely the cancer will spread.

- A Gleason score of 6 or less means the cancer is unlikely to spread.
- A Gleason score of 7 means that there is a moderate chance of the cancer spreading. If the biopsy shows the presence of cancer, patient may need more tests to see if the cancer has spread.
- Imaging tests -- computerized tomography (CT) or magnetic resonance imaging (MRI) scans may pinpoint the location of cancer that has spread beyond the prostate.
- Bone scans and x-rays -- these tests look for spread of cancer to the bones.
- Lymph node biopsy -- a surgical procedure to find out if the cancer has spread to the lymphatic system.

Stages of Prostate Cancer

The clinical stage of cancer is important in choosing a treatment. The clinical stage tells how much the cancer may have grown within the prostate and whether it has spread to other tissues or organs. In case of surgery, lymph nodes, and seminal vesicles nearby prostate will be removed and samples of them studied under a microscope. This exam gives the pathologist the information to find out the pathological stage of one's cancer. Based on this doctor may do one or more of the following tests or exams to help figure out the stage of cancer:

- DRE
- Prostate biopsy
- Bone scan
- MRI
- CT scan
- Biopsy of the lymph nodes in the pelvis
- Biopsy of the seminal vesicles

Tumor Stages

Prostate cancer is typically staged according to the American Joint Committee on Cancer's tumour, node, metastasis (TNM) system, in which the tumour stage (T) is based on the extent of penetration or invasion beyond the prostatic capsule into adjacent structures (**Table 1**). Localized

prostate cancer is classified as stages T1 (non-palpable) and T2 (palpable) and is confined within the prostatic capsule. The likelihood of progression to invasive cancer

is associated with the presence of more poorly differentiated cells and other histopathologic features.

Table 1: Showing Prostate Cancer Tumor Staging*

Tumor Stage	Description
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically unapparent tumor not palpable or visible by imaging T1a: Tumor incidental histologic finding in ≤5% of tissue resected T1b: Tumor incidental histologic finding in >5% of tissue resected T1c: Tumor identified by needle biopsy (e.g., because of elevated PSA levels)
T2	Tumor confined within prostate T2a: Tumor involves 50% of one lobe or less T2b: Tumor involves >50% of one lobe but not both lobes T2c: Tumor involves both lobes
T3	Tumor extends through the prostate capsule T3a: Extracapsular extension (unilateral or bilateral) T3b: Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall

* From the American Joint Committee on Cancer.

According to the National Institute of cancer, T1 means that the cancer is so small it can't be felt during a DRE. T1a and T1b cancer is most often found by accident, when men have surgery to relieve symptoms of BPH (benign prostatic hyperplasia).

T1c is most often found when a prostate biopsy is done because of a PSA test result that showed a high PSA blood level. This is the most commonly diagnosed stage of prostate cancer.

A stage of T2 means that prostate cancer can be felt during a DRE, but is still only in the prostate. The stage may be a, b, or c, depending on the cancer's size and whether it is in 1 or more lobes of the prostate.

IN-VITRO DETECTION

Prostate cancer cell lines^{9,9a}

Cell lines are widely used in many aspects of laboratory research and particularly as in vitro models in cancer research. They have number of advantages; for example, they are easy to handle and represent an unlimited self-replicating source that can be grown in almost infinite quantities. They represent a relatively high degree of homogeneity and are easily replaced from frozen stock if lost through contamination. However cell lines that have been deposited for long period in banks may prone to genotypic and phenotypic drift during their continual culture.

Information flows in a cell from DNA → RNA → Protein. A rearrangement or translocation of chromosomes results in two abnormally fused genes whose abnormal RNA and protein products put cells on the path to cancer. Such gene fusions are commonly found in human cancers such as prostate and leukemia. Researchers have identified abnormal RNA fusions that were generated without any changes to their corresponding genomic DNA by a mechanism they've dubbed "cis-splicing of adjacent genes," or cis-SAGe, for short.

When analyzing the prostate cancer cell lines, Dr.Hui Li and his team found fusions in the RNA products of the SLC45A3 and ELK4 genes located adjacent to each other on chromosome 1. They showed that this SLC45A3-ELK4 RNA fusion transcript was generated by an aberrant read-through of the two genes, when the message should have stopped transcribing after the first gene. This aberrant read-through was termed cis-SAGe.Li and his team observed that SLC45A3-ELK4 fusion RNA promoted cancer cell growth in vitro and that the levels of SLC45A3-ELK4 fusion RNA in human prostate samples correlated with disease progression—non-cancerous prostate tissue had the lowest levels of SLC45A3-ELK4 fusion RNA; men with metastatic prostate cancer had the highest. The new cell lines are the first available derived from a bone metastasis of an

androgen-independent prostatic adenocarcinoma that grow both in vivo and in vitro and have retained PSA expression and androgen sensitivity. Scientists developed a novel cell line which mimics the stages of resistance to androgen therapy for study of the molecular mechanisms by which androgen therapy sensitive prostate cancer cells differentiate to androgen resistant cancer cells. This technology will allow the generation of entirely novel methods for screening, treatment and prevention of androgen resistant prostate cancer. These cell lines are available in

market and UNeMed currently offers a variety of licensing options and collaborative development opportunities with the University of Nebraska Medical Center.

Cell lines are marketed by --- American Type Culture Collection [ATCC], Life technologies& others.

SIGNS AND SYMPTOM¹⁰

Many men with prostate cancer often have no symptoms. If symptoms appear, they include:

Table 2: Describes signs & symptoms

Blood in the urine
The need to urinate frequently, especially at night
Weak or interrupted urine flow
Pain or burning feeling while urinating
The inability to urinate
Constant pain in the lower back, pelvis, or upper thighs
Painful ejaculation.

CENTRES FOR DETECTION & DIAGNOSIS IN INDIA

- Dharamshila Hospital -----
Delhi
- Indian Cancer Society-----
Mumbai
- BGS Global Hospital -----
Bangalore
- DeenanathMangeshkar Hospital & Res.
Centre ----- Pune

TYPES OF TREATMENT^{11,11a}

Different types of treatment are available for patients with prostate cancer. Some treatments are standard (the currently used treatment), and some are being tested in clinical trials.

Six types of standard treatment are used.

Watchful waiting or active surveillance

Watchful waiting is closely monitoring a patient's condition without giving any treatment until symptoms appear or change.

Active surveillance is closely following a patient's condition without giving any treatment unless there are changes in test results. It is used to find early signs that the condition is getting worse. In active surveillance, patients are

given certain exams and tests, including biopsies, on a regular schedule.

Chemotherapy

Chemotherapy is a cancer treatment that uses drugs to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. When chemotherapy is taken by mouth or injected into a vein or muscle, the drugs enter the bloodstream and can reach cancer cells throughout the body (systemic chemotherapy). When chemotherapy is placed directly into the cerebrospinal fluid, an organ, or a body cavity such as the abdomen, the drugs mainly affect cancer cells in those areas (regional chemotherapy).

Biologic therapy

Biologic therapy is a treatment that uses the patient's immune system to fight cancer. Substances made by the body or made in a laboratory are used to boost, direct, or restore the body's natural defenses against cancer. This type of cancer treatment is also called biotherapy or immunotherapy. Sipuleucel-T is

a type of biologic therapy used to treat prostate cancer that has metastasized (spread to other parts of the body).

Hormone Therapy

Male sex hormones, such as testosterone, can help prostate cancer grow. Hormone therapy slows prostate cancer's growth by reducing the body's ability to make testosterone or by blocking testosterone's action in prostate cancer cells.

Hormone therapy used in the treatment of prostate cancer may include the following :

- Luteinizing hormone-releasing hormone agonists can prevent the testicles from making testosterone. Examples are leuprolide, goserelin, and buserelin.
- Antiandrogens can block the action of androgens (hormones that promote male sex characteristics). Examples are enzalutamide, flutamide, and nilutamide.
- Drugs that can prevent the adrenal glands from making androgens include ketoconazole and aminoglutethimide.
- Orchiectomy is a surgical procedure to remove one or both testicles, the main source of male hormones, to decrease the amount of hormone being made.
- Estrogens (hormones that promote female sex characteristics) can prevent the testicles from making testosterone. However, estrogens are seldom used today in the treatment of prostate cancer because of the risk of serious side effects.

Radiation Therapy

This type of treatment uses high doses of radiation energy to treat cancer. Radiation therapy is a good choice with early-stage prostate cancer. It is also the best treatment for older men or those who have other health problems. There are different types of radiation therapy:

- **External beam radiation-** In this type of radiation therapy, a machine aims radiation at cancer. The machine moves around body, sending radiation from many directions. The treatment once a day, 5 days a week, for 6 to 9 weeks may be given. Each treatment session usually

lasts about 15 minutes. 3-D conformal radiation therapy is a type of external beam radiation that is often used to treat prostate cancer. It allows doctors to carefully plan the shape of the radiation beam so it targets the cancer more precisely, while avoiding healthy tissues nearby.

- **Brachytherapy-** is a type of internal radiation therapy in which a doctor places radioactive material inside the prostate. Brachytherapy is a choice for men with low-risk prostate cancer. There are two main types of brachytherapy used for prostate cancer, low-dose rate (also called LDR) and high-dose rate (also called HDR).
- **LDR brachytherapy-** In this type of brachytherapy, a doctor will place low-dose sources of radiation, or seed implants, throughout your prostate. Each seed implant is smaller than a grain of rice. The number of seeds will depend on the size of your prostate. The radiation will get weaker each day and run out in 2 to 10 months.
- **HDR brachytherapy-** Before treatment starts, a doctor will place tiny catheters (hollow tubes) throughout prostate. For each treatment, the doctor will place 1 or more sources of high-dose radiation in the prostate through the catheters. Then, radioactive material will be removed after a few minutes. The catheters will remain in place for the entire course of treatment. The catheters will be removed, once treatment is over. External beam radiation therapy and brachytherapy can be used together.

Surgery

Surgery is a treatment choice for men with early-stage prostate cancer who are in good health. Surgery to remove the prostate is called prostatectomy. There are different types of surgery for prostate cancer. They include:

- **Open prostatectomy.** Also called retropubic prostatectomy. In this surgery, the prostate is removed through a single long cut made in abdomen from a point below navel to just above the pubic bone. This type of surgery can be used for nerve-sparing

surgery. Nerve-sparing surgery lessens the chances that the nerves near your prostate will be harmed. These important nerves control erections and normal bladder function.

- **Laparoscopic surgery.** In this type of surgery, uses a laparoscope to see and remove the prostate. This surgery is done through 4 to 6 small cuts in the navel and the abdomen.
- **Perineal prostatectomy.** In this type the prostate is removed through an incision between scrotum and anus. This type of surgery is not used very often.

New types of treatment are being tested in clinical trials.

Cryosurgery

Cryosurgery is a treatment that uses an instrument to freeze and destroy prostate cancer cells. This type of treatment is also called cryotherapy.

High-intensity focused ultrasound

High-intensity focused ultrasound is a treatment that uses ultrasound (high-energy sound waves) to destroy cancer cells. To treat prostate cancer, an endorectal probe is used to make the sound waves.

Proton beam radiation therapy

Proton beam radiation therapy is a type of high-energy, external radiation therapy that targets tumors with streams of protons (small, positively charged particles). This type of radiation therapy is being studied in the treatment of prostate cancer.

Medication

List of medicines used to treat prostate cancer and approved by FDA.

Finasteride

Degarelix

Jevtana (Cabazitaxel)

Lupron (Leuprolide Acetate)

Xtandi (Enzalutamide)

Zytiga (Abiraterone Acetate)

Prednisone

Provenge (Sipuleucel-T)

Taxotere (Docetaxel)

Viadur (Leuprolide Acetate)

DRUG DISCOVERY RESEARCH &RECENTLY DISCOVERED TREATMENTS

^{12,12a,12b,12c}

Discovery and development of anti-canceragents are the key focus of several pharmaceutical companies as well as non-profitgovernment and non-government organizations, like the National Cancer Institute (NCI) in the United States, the European Organization for Researchand Treatment of Cancer (EORTC), and the British Cancer Research Campaign(CRC).

The pharmaceutical industry is increasingly looking for ways to speed development of new drugs.

The Institute of Cancer Research, London, and its partner hospital The Royal Marsden NHS Foundation Trust jointly led the new Phase III trial of enzalutamide and the Phase III trials of two other drugs, cabazitaxel and abiraterone. Drug enzalutamide can significantly extend life and improve quality of life in men with advanced prostate cancer. The drug, Xtandi (enzalutamide) made by pharmaceutical companies Medivation and Astellas, could be licensed for use by British patients early next year,2013.The US Food and Drug Administration (FDA) announced that Xtandi has been approved for men with metastatic castration-resistant prostate cancer that has recurred or spread, regardless of whether patients received medical or surgical therapy to reduce testosterone levels.

Progenics Pharmaceuticals Inc. has opened enrollment in a Phase 2 study in prostate cancer patients of its PSMA ADC compound. PSMA ADC is a targeted anti-cancer therapeutic that uses a monoclonal antibody to deliver a cell-killing drug to malignant cells.

According to a report issued by PhRMA (formerly known as the Pharmaceutical Research and Manufacturers Association), there are approximately 80 drugs currently in clinical development for the treatment of prostate cancer.

Gamma-Tocotrienol Kills Prostate Cancer Stem Cells. A study reveals that gamma-tocotrienol is effective in targeting prostate cancer stem cells, offering a potential means to prevent cancer growth and disease relapse.

Scientists from Singapore, Australia and Hong Kong have found that gamma-tocotrienol is potent in killing prostate cancer stem cells. This small group of cells is responsible for the initiation of prostate cancer and is resistant to conventional chemotherapy drugs. It causes relapses in the cancer by producing new chemo-resistant cancer cells. Gamma-tocotrienol is a member of the Vitamin E family and is derived naturally from palm oil. This study aimed to find a way to eradicate prostate cancer stem cells. It follows an earlier report that demonstrated the effectiveness of gamma-tocotrienol in targeting the bulk of the prostate tumour mass. This latest finding highlights the considerable potential of gamma-tocotrienol as a natural remedy to prevent and treat prostate cancer. The scientists found that low doses of gamma-tocotrienol cause apoptosis in the prostate cancer stem cells and suppress

their colony formation capability. This results in a lower prostate cancer stem cell population (as defined by the protein markers CD133 and CD44). Further tests in mice models were conducted, where mice implanted with hormonal refractory prostate cancer cells were given gamma-tocotrienol orally. The results showed that gamma-tocotrienol not only reduced tumour size formed, but also decreased the incidence rate of tumour formation by 75%, as compared to the control group of mice, which had 100% tumour formation. These results strongly suggest that gamma-tocotrienol could be developed for prostate cancer prevention and treatment. "Current chemotherapy drugs, such as Docetaxel, have limited effect on prostate cancer stem cells, although they are currently the first-line drug given to patients with advanced hormonal refractory prostate cancer.

Table 3: illustrates products under development by leading pharma companies

Pharmaceutical company	New molecule	Use
Centocor Ortho Biotech	Siltuximab	hormone-refractory prostate cancer
Novartis Pharmaceuticals	Imatinib	prostate cancer
Bristol-Myers Squibb	Ipilimumab	prostate cancer
NewLink Genetics	Prostate cancer vaccine	hormone-refractory prostate cancer
Johnson & Johnson	JNJ-26854165	prostate cancer
Abbot pharmaceuticals	leuprorelin depot (6-month formulation)	prostate cancer
IncuronBuffalo	mepacrine	hormone-refractory prostate cancer
Molecular Insight	MIP1095 and radiolabelled diagnostic	diagnosis of prostate cancer
PolyphenonPharma	polyphenonE	prostatic intraepithelialneoplasia
DendreonSeattle	Sipuleucel-T	androgen-dependent recurrent prostate cancer
Amgen	Rilotumumab	early stage prostate cancer
Genta	Tesetaxel	advanced prostate cancer
OncoGenex Pharmaceuticals	custiren	prostate cancer
AstraZeneca	Zibotentan	castration-resistant prostate cancer

New Dosage Forms

Magnetic nanoparticles (MNPs) and polymer magnetic nanoparticles (PMNPs) have been attracting a great amount of attention because of their numerous applications including contrast agents in magnetic resonance imaging (MRI), magnetic targeted drug carriers, and hyperthermia treatments for cancer. Researcher have developed the polymer magnetic nanoparticles (PMNPs) using a silane coupling agent and a novel thermo-sensitive polymer, N-isopropylacrylamide-acrylamide-allylamine (NIPA-AAm-AH). The temperature-sensitive polymers were chosen as a shell for the purpose of creating a controlled drug delivery system. In this

system, the temperature induced by the magnetic core would be used to release therapeutic agents from the polymer shell at a specific location. The chemical and physical properties of these PMNPs were determined using Fourier transformed infrared spectroscopy, nuclear magnetic resonance, x-ray photoelectron spectroscopy, and a superconducting quantum interference device.

COMPLEMENTARY AND ALTERNATIVE THERAPIES¹³

These treatment methods are not practiced by conventional western medicine. They can include herbal, animal derived, and mind-body approaches to treating

cancer. The scientific evidence about the efficacy of these treatments either refutes cancer fighting claims or is inconclusive at the present time.

Nutrition and Dietary Supplements

A comprehensive treatment plan to support the health of men living with prostate cancer may include a range of complementary and alternative therapies. Preliminary studies suggest that some nutritional supplements may reduce the symptoms of some prostate cancers or reduce risk of developing it.

Tips to reduce risk of developing prostate cancer:

- Eat antioxidant foods, including fruits (such as berries, watermelon, and tomatoes) and vegetables (such as squash and bell peppers).
- Include more cruciferous vegetables (such as broccoli, cauliflower, cabbage, and Brussels sprouts) in diet. One preliminary study suggested men who eat three or more servings a week reduced their chance of developing prostate cancer. Another study found that men who ate 28 or more servings of all kinds of vegetables per week were 35% less likely to develop prostate cancer than those who had fewer than 14 servings per week. These foods also appear to have anticancer properties in test tube studies.
- Some studies show men who regularly eat fish have a lower risk of prostate cancer than those who don't eat as much fish.
- High-fat diets may raise risk of prostate cancer.
- Stay at a proper weight, and exercise regularly.

Following nutrients may have cancer-fighting properties

- Lycopene, 15 mg two times per day, is an antioxidant found in tomatoes and watermelon. In one preliminary study, men with prostate cancer either received a lycopene supplement or placebo for 3 weeks before undergoing prostate surgery. Those who received the supplement had less aggressive growth of cancer cells than those who received placebo. Lab studies have also

found that lycopene inhibits the growth of prostate cancer cells in test tubes. Lycopene also appears to reduce the risk of developing prostate cancer.

- Vitamin E -- in one lab test, a specific form of vitamin E blocked the growth of prostate cancer cells. Vitamin E may also lower the risk of developing prostate cancer in men who smoke. Overall, studies on vitamin E and prostate cancer have been mixed. More research is needed to know whether vitamin E is helpful for men who already have prostate cancer.

Herbs

Herbs are generally a safe way to strengthen and tone the body's systems. Individuals may use herbs as dried extracts (such as capsules, powders, and teas), glycerites (glycerine extracts), or tinctures (alcohol extracts). Unless otherwise indicated, one should make teas with 1 tsp. herb per cup of hot water. Steep covered 5 - 10 minutes for leaf or flowers, and 10 - 20 minutes for roots. Drink 2 - 4 cups per day.

- Green tea (*Camellia sinensis*) standardized extract, 250 - 500 mg daily, is an antioxidant that may decrease risk of cancer and heart disease. In one study, green tea extract seemed to have a slight benefit in treating some forms of prostate cancer. Use caffeine-free products.
- Saw palmetto (*Serenoa repens*) standardized extract, 160 mg two times daily, has been shown in some studies to help with symptoms of benign prostatic hyperplasia. It seems to have anti-androgenic effects. However, it's not clear whether saw palmetto has any effect on prostate cancer. And researchers have been concerned that saw palmetto could mask prostate cancer by lowering prostate-specific antigen (PSA) levels. However, a randomized study of more than 1,000 patients did not show this effect on PSA levels.
- Milk thistle (*Silybum marianum*) -- In one lab test, milk thistle stopped prostate cancer cells from growing. However, there is no evidence yet that it works in humans.

- Pomegranate (*Punicagranatum*) -- In one study, men who had surgery or radiation to treat prostate cancer that had not spread and who drank 8 oz. of pomegranate juice every day slowed down the time it took their PSA levels to double. Researchers think that meant that their tumors may have not grown as fast, either. More research needs to be done.
- Garlic (*Allium sativum*), standardized extract, 400 mg two to three times daily, may help fight cancer cells, but more research is needed to know whether it's effective against prostate cancer. Garlic can interact with many medications. It may increase the risk of bleeding, particularly if you also take blood thinners such as warfarin (Coumadin) or aspirin.

Acupuncture

Acupuncture may provide relief from side effects of orchiectomy, removal of the testes. Studies also support using acupuncture to relieve pain that often occurs when cancer has spread beyond the prostate, particularly to the bones. A National Institutes of Health statement released in 1997 also supports the use of acupuncture to reduce nausea from chemotherapy.

Evidence suggests acupuncture can be a valuable therapy for cancer-related symptoms, particularly nausea and vomiting that often accompanies chemotherapy treatment. Studies have also found that acupuncture may help reduce pain and shortness of breath. Acupressure, or pressing on rather than needling acupuncture points, may also help control breathlessness and is a technique that patients can learn and then use to treat themselves.

Massage and Physical Therapy

Studies suggest that massage reduces stress and boosts immune function, so it may help relieve anxiety for men being treated for prostate cancer.

Pelvic floor exercises -- tightening and releasing muscles that start and stop the flow of urine -- may help with incontinence

caused by prostatectomy (removal of the prostate).

Mind-Body Medicine

Meditation

Meditation may reduce stress, ease anxiety, and allow men with prostate cancer to regain a sense of self-control.

RESEARCH IN INDIA^{14,14a}

The Advanced Centre for Treatment, Research and Education in Cancer (ACTREC) is actively involved in cancer research.

ACTREC designed to compare Helical Tomotherapy (HT) based IMRT and conventional sliding window (SW IMRT) in patients with high risk prostate cancer. Complementary plans with HT and SWIMRT were compared using DVH parameters. The PTV Prostate was prescribed 74 Gy in 37 fractions and the nodal PTV received 55 Gy in 37 fractions by simultaneous integrated boost. Conformity Index, Homogeneity Index and dose-volume parameters were compared.

A population based case-control study on prostate cases was carried out in Delhi to identify potential risk factors. Cases were each matched with two controls. Past smoking and current alcohol consumption significantly increased the risk of prostate cancer. No statistically significant association was found with family history of cancer or prostate cancer. The risk of prostate cancer declined with increasing dietary consumption of tea, citrus fruits and melon. A statistically significant marginal increase in the odds ratio was observed with the consumption of eggs, fish and sunflower oil. Though an increased risk of prostate cancer was evident among vasectomised men, the association was not statistically significant.

COMMERCIAL ASPECTS OF PROSTATE CANCER DRUGS^{15,15a}

Four new product launches in prostate cancer over the next 10 years, including Medivation's androgen receptor inhibitor MDV3100 and Takeda's 17, 20 lyase inhibitor TAK-700 will counter generic erosion. In addition Increasing use of Zytiga (abiraterone; Johnson&Johnson) and

Jevtana (cabazitaxel; Sanofi) will boost market value from \$1.7bn in 2011 to \$4.3bn by 2020.

The report on prostate drug market from 2005 to 2020 covering 21 major drugs categorized into four therapies; namely hormonal therapy, chemotherapy, immunotherapy, and targeted therapy. Out of 21 drugs, 13 are currently commercially available in the market and 8 are in pipeline. Growing prostate cancer population (25% increase in the incidence of prostate cancer in mature countries and 40% increase in emerging countries, from 2010 to 2020) is an impetus for the growth of the market. In 2010, among the mature markets, U.S. was the major contributor; accounting for 35% of the total sales of prostate cancer drugs and amongst the emerging countries, China contributed to the share of about 2% of the overall prostate cancer therapeutics market.

As far as drugs are concerned, Taxotere accounted for 23% of the total sales of prostate cancer drugs in 2010. Astrazeneca PLC is a leading market player with the share of 30% in the total prostate cancer therapeutics market, in 2010. However, by 2020, Astrazeneca will lose its market share by 19%, due to entry of new players such as Active Biotech, Bristol Myers-Squibb, Teva Pharmaceuticals Industries Ltd, and Johnson & Johnson (entered the market in 2011, with its key drug Zytiga).

Players are implementing various growth strategies in the market to gain a competitive edge. New products launch, product pipelines, agreements and collaborations, clinical trials, and acquisitions were certain major strategies adopted by the players from January 2006 to September 2011.

Scope of the report

This research report evaluates the prostate cancer drugs market with respect to the current and pipeline drugs. The report analyzes geography; forecasting revenue, and trends in each of the following submarkets:

Global prostate cancer hormonal therapy drugs market -

- LHRH antagonists - Firmagon

- LHRH analogs - Zoladex, Lupron, Eligard, Vantas, and Decapeptyl
- Antiandrogens - Casodex
- Pipeline drugs for hormonal therapy - Zytiga, MDV3100, and TAK700

Global prostate cancer chemotherapy drugs market -

- Off patent drugs - Taxotere, mitoxantrone, and Emcyt
- Patented drugs - Jevtana.

Global prostate cancer immunotherapy drugs market-

- Patented drug - Provenge
- Pipeline drug - ipilimumab

Global prostate cancer targeted therapy drugs market-

- Angiogenesis inhibitor - lanreotide, TASQ, Zaltrap
- Apoptosis inducing - custirsen sodium
- Signal transduction inhibitor - Sprycel

SUMMARY AND CONCLUSION

The article covers the following

- a] Anatomy, Physiology & Pathophysiology of Prostate gland
- b] Types & Pathophysiology of prostate cancer
- c] Awareness & Statistics of prostate cancer
- d] Risk factors, Prognosis, Detection and Diagnosis, Signs & Symptoms & Treatment of prostate cancer
- e] Drug discovery research & Recently discovered treatments, New dosage forms, CAM therapy, & Commercial aspects of prostate cancer.

Based on the article the following silent conclusions can be drawn :

Prostate cancer survival tends to be poorer in developing countries, most likely because of a combination of late diagnosis and limited access to standard treatment. A substantial proportion of cancer burden can be prevented by implementing programs, early detection and treatment, and majorly public health check-up camps promoting investigations. Clinicians, health professionals, and policy makers can play an active role in the application of such interventions on a pan-India level.

Identifying risk factors for advanced disease may help to decrease the rate of poor

prostate cancer outcomes and associated mortality worldwide.

It is recommended that every man beginning at age 50 should perform yearly PSA screening and men who are at higher risk of prostate cancer, including African American men and men whose father or brother had prostate cancer, begin screening at age 40 or 45.

Researcher can take their research ahead through In-Vitro evaluation using cell lines.

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