



## **Developing a Deeper Insight into Prostate Cancer: review**

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### **ABSTRACT**

*There is a small sized and walnut shaped ductal gland in men named as prostate which is present below the urinary bladder. For the nourishment and transport of sperms, the production of seminal fluid occurs in prostate. Due to abnormal growth in prostate cells, an incidence of the prostate cancer may occur. It specifically arises in males as only they have the prostate gland. The prostate cancer may be due to the environmental factors such as diet, obesity, work place, smoking or surgeries etc. there may be an increase in the male androgen hormones like testosterone or dihydrotestosterone (DHT). The genes that are involved in prostate cancer are HPC2/ELAC2 genes. However mutations in breast cancer genes BRCA1, BRCA2 and other genes such as THSD7B, SPOP, ZNF595, PIK3CA, FOXA1, PTEN, TP53, MED12, CDKN1B, SCN11A and NIPA2 may also involve in the greater threat of prostate cancer. The diagnostic strategies can be different with different kind of symptoms depending upon the stage of the cancer. There are different treatment methods such as surgeries, therapies or drugs which can be used to treat the prostate cancer. Besides this ADT injections and tablets, Docetaxel, Mitoxantrone, Etoposide (VP-16) and Cabazitaxel are also used in different therapies to treat the prostate cancer. Future studies are also carried on for further development in prevention or treatment of the disease.*

**Keywords:** Prostate cancer, HPC2/ELAC2 genes, urinary bladder, Treatment, Biopsy.

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### **INTRODUCTION**

Living cells are building blocks of a human body. In a normal mechanism, the growth of body cells occurs in asystematic and an organized way. In individual's early year's life, these cells multiply more rapidly so that the growth of the person may be more. After an adult age, mostly cell division is only to substitute the dying cells to heal the injuries in repair mechanism. When the growth of these cells becomes insignificantly high, the cancer begins. There is a variety of cancers, but the main phenomenon of all types of cancers is the abnormal cells growth without any kind of halt [1]. The prostate cancer is one example found in only men because the prostate is small walnut-shaped ductal gland present below the urinary bladder in men that goods the seminal fluid for the nourishment and transport of sperms [2].The prostate gland in maturity has columnar epithelium that is enclosed by a sheet of muscle and a fibrous capsule[3]. For normal growth and differentiation of prostate, it is necessary that there is signaling interactions between epithelium and mesenchyme. But in consistent reactivation of cellular proliferation and differentiation may cause due to disturbed interactions between epithelium and mesenchyme during aging [4, 5].

The testicles present in prostate produce the male sex hormone testosterone which determines the growth of prostate cells and how the prostate gland works. Due to rise in male androgen hormones for instance testosterone and dihydrotestosterone (DHT) during puberty, there is an increase in prostate size[6]. There are several kinds of cells present in prostate but mostly the gland cells, which are involved in formation of the prostate fluid. This fluid is then added in semen later and it may be a source for prostate cancer. The development and extent of some prostate cancers is very fast, but most grow slowly. The Adenocarcinoma is the medicinal term for a gland cells cancer. Other types of cancer may include

Sarcomas rare in nature but the start is again in the prostate gland. Small cell carcinomas, neuroendocrine tumors and transitional cell carcinomas may be contained within this type[7].

### **Environmental Factors Involved in Prostate Cancer**

Prostate cancer incidence by environmental factors was studied in different populations of different countries and stated that subsequent environmental factors may cause danger of prostate cancer such as diet (such as use of beef and high fat dairy products), obesity and diabetes, smoking, workplace exposures (such as firefighters who are exposed to toxic combustion products), inflammation of the prostate, sexually transmitted infections (like gonorrhea or chlamydia) and vasectomy (minor surgeries which make men infertile) etc.[8]

### **Genetic Basis of Prostate Cancer**

Recently more than 5000 somatic mutations in prostate tumors have been identified, including periodic translocations involving the cell-adhesion molecule CADM2 or the PTEN-interacting protein MAGI2, in addition to repeated mutations of the Speckle-type POZ Protein (SPOP) [9-11]. The 12 most significantly mutated genes are THSD7B, SPOP, ZNF595, PIK3CA, FOXA1, PTEN, TP53, MED12, CDKN1B, SCN11A, NIPA2 and C14orf49. SPOP was the most frequently mutated gene in these tumors, with a frequency of 13% [10, 12].

Men having BRCA mutations are at 15-25% higher risk of prostate cancer. A study reported that BRCA1, BRCA2, and HOXB13 might cause life threatening prostate cancer [13]. Till date a dozen different gene fusions have been detected in prostate cancer tumors. *TMPRSS2-ERG*, *ESRP1-RAF1*, *SLC45A3-BRAF* gene fusions are the predominant molecular subtype of prostate cancer [14].

According to a study, human prostate cancer tissue was screened to examine the presence of somatic mutations in the hormone binding domain of the AR (androgen receptor) gene. Mutation was detected in exon E on hormone binding domain of untreated stage B, organ confined prostate cancer. Sequencing showed substitution (G—A) in codon 730 which altered valine to methionine. Codon 730 is present in highly conserved region among all steroid hormones [15]. The rs10993994 single nucleotide polymorphism in MSMB (microseminoprotein-beta) gene promoter increase the risk of prostate cancer [16]. Approximately 10% of individuals acquire prostate cancer due to hereditary factors which cause early onset of disease [17]. Two familial susceptibility loci have been mapped to the X chromosome and to a region of chromosome 1q [18]. Several studies have disclosed association of breast cancer with prostate cancer [19, 20]. The allelic loss shows the loss of function or reduction of tumor suppressor genes in prostate cancer. Losses of heterozygosity were frequently reported at 8p, 10q, 13q, and 17p whereas some studies suggested losses of 6q, 7q, 16q, and 18q [21-23]. According to another study allelic loss of 10q, 13q, 16q, and 18q has been described in prostate cancer because of tumor suppressor genes in these regions. The study of 6q deletions in prostate cancer revealed that 6q14–21 may possess a tumor suppressor gene important in prostate cancer [21].

For the identification of genetic base of prostate cancer, whole genome scan of sib pairs was done and DNA markers were spaced evenly across human genome. It was demonstrated that regions on chromosome number 1, 4, 5, 7, 8, 11, 16 and 19 might possess genes which predispose individuals to prostate cancer and may influence growth rate of tumor [24]. Earlier researchers made it clear that HPC (hereditary prostate cancer) genes were on chromosome 1 whereas the second prostate cancer gene was found on X chromosome (Xq27-28) proposing X-linked pattern of HPC inheritance [18].

DNA sequence KIAA 0872 and 17- $\beta$  hydroxyl steroid dehydrogenase located within mapped region of chromosome 16 was analyzed which revealed that none of these gene carries mutations in the protein coding region and this study suggested that these are less likely to cause familial prostate cancer. The mutations of 17 $\beta$ -HSD were analyzed which described that there was one SNP (single nucleotide polymorphism) per exon 2, 5, 6, 7 and in the 5' untranslated region of exon 1. Single base substitutions on one or both strands of genomic DNA were observed on two sites i.e., 1144 and 1249 base pair. But none of the base substitutions led to a change in the amino acid coding sequence. Apparently it seemed that polymorphism at base 1249 of the mRNA sequence segregated with families [24].

Current study suggested that men with hereditary prostate cancer inherit a normal and defective copy of RNASEL gene. The normal copy of the gene generates sufficient enzyme for prostate cells to function normally and the mutant men contain once defective gene which inactivates the normal RNASEL gene and convert normal prostate cells to cancerous cell [25]. It has been observed that mutated p53 alleles are uncommon in early prostate cancers but are commonly found in 20-25% of advanced cancers indicating that mutations in tumor suppressor gene p53 plays significant role in progression of prostate cancer [26, 27].

Though, chromosome gains are comparatively less frequent than chromosome losses but gains at 8q and 7 are reasonably common [28, 29]. Regardless of the importance of allelic loss for prostate cancer, not a single candidate tumor suppressor gene has assigned a role in cancer progression. Many candidate genes

e.g., RB, p53, PTEN, NKX3.1 have been involved depended on their localization to allelic loss regions but none of these genes exhibited mutations in large percentage of prostate cancer specimens. In 80% of prostate tumors specific region of chromosome 8p is lost and this indicates the most common event of early prostate carcinogenesis [30, 31]. In case of prostate cancer losses occur at two and three regions of 8p, corresponding to 8p22 and 8p12-21 [32]. Many studies indicate that loss of 8p12-21 is an early event of prostate carcinogenesis and loss of 10q is considered to be later event in cancer progression than loss of 8p. NKX3.1 homeobox gene maps lies in the critical region of 8p12-21 lost in human prostate cancers. Amid potential candidate genes PTEN/MMAC1 maps to 10q23, in a region that is lost in prostate carcinomas as well as several other carcinomas, including breast, glioblastoma and endometrial cancers [33]. A second candidate gene mapping to 10q25 is MXI1 encoding Myc-binding protein [34] which play an important part in prostate cancer as it maps to commonly amplified region of chromosome 8q [35, 36]. Another study suggested that loss of homozygous deletion of the *MSR* locus and heterozygosity at 8p22 of chromosome 8p lead to development of prostate cancer as these regions contain tumor suppressor genes [37]. Loss of 13q chromosome containing Rb (retinoblastoma) gene occurs in atleast 50% of prostate tumors. The expression of RB (retinoblastoma) gene was analyzed in three human prostate carcinoma and the results showed that inactivation of mutated RB gene suppressed human prostate carcinoma cells [38]. Among cell cycle regulatory genes loss of function of CDK4 inhibitor p27<sup>kip1</sup> is frequently occurring in prostate tumors [39]. p27<sup>kip1</sup> maps to 12p12-13.1 [40], a region of repeated deletion in advanced prostate cancer [41]. p53 mutations appears to be lower in prostate cancer than in other cancers because a study described that Li-Fraumeni patients with germline p53 mutations exhibited lower incidence of prostate cancer [36, 42].

Prostate cancer risk loci have been identified on several chromosomes especially chromosome number 1. The targeted candidate genes are *PCAP* on chromosome 1q42-43, *HPC2* on chromosome 17p, *HPC20* on chromosome 20q13, *HPC1* on chromosome 1q23-25, *HPCX* on chromosome Xq27-28, *CAPB* on chromosome 1p36 and linkage to chromosome 8p22-23. These linkage studies lead to mutation screening and mapping of powerful candidate genes including *RNASEL*, *ELAC2* and *MSR1* [43]. The recurrent and rare germline mutation G84E in *HOXB13* has been associated with increased risk of familial prostate cancer [44]. It has been studied that men carrying both polymorphisms in the *HPC2/ELAC2* gene experience considerable increase in prostate cancer [45].

A study suggested that E2F1 gene knockdown inhibited prostate tumor growth in vitro and in vivo via sensitizing tumor cells to ICAM-1 mediated anti-immunity by NF- $\kappa$ B modulation emphasizing the ability of E2F1 as through sensitizing tumor cells to ICAM-1 mediated anti-immunity by NF- $\kappa$ B modulation, highlighting the potential of E2F1 as a therapeutic target [46].

### **Risk Factors of Prostate Cancer**

A risk factor is anything that influences your possibility of getting an illness, for example, disease. Diverse diseases have distinctive risk factor. Some risk factor, such as smoking, can be changed. Others, similar to a man's age or family history, can't be changed [44]. Be that as it may, risk factors don't let us know everything. Numerous individuals with one or more risk factors never get disease, while other people who get growth may have had few or no known risk factor. We don't yet totally comprehend the reasons for prostate tumor, yet specialists have found a few components that may influence a man's risk of getting it [1].

#### **1. Family History and Genetic Conditions: Overall**

5 to 9% of prostate cancers were clarified by acquired elements [47]. Most likely a blend of hereditary or organic components and expanded symptomatic action in influenced families may underline the familial danger. Hereditary connection speculation underpins that Prostate growth danger is not connected with prostate disease in a new parent [48]. But expanded symptomatic movement theory bolsters that it is higher within the near future after analysis in a relative [49] (associate studies have uncovered).

#### **2. Age**

Prostate tumor is exceptionally uncommon in men more youthful than 40, however the possibility of having prostate growth rises quickly after age 50. Around 6 in 10 instances of prostate cancer are found in men beyond 65 [1].

#### **3. Family History**

Meta examination have demonstrated that Prostate cancer is 2.1-2.4 times higher in men whose father, 2.9-3.3 times higher in men whose sibling has/had the malady while 1.9 times higher in men with a second-degree relative (granddad, uncle, nephew, or half-kin) who has/had the illness [50].

Familial prostate malignancy danger is higher in men matured under 65 contrasted and more seasoned men, and in men with more than one influenced first-degree relative or with an influenced relative analyzed matured more youthful than 60 [51]. Cohort studies have uncovered that prostate tumor danger

is 19-24% higher in men whose mother has/had breast cancer. Prostate cancer danger is not connected with breast cancer in a sister [52].

#### **4. Race/ethnicity**

Prostate cancer happens all the more frequently in African-American men and in Caribbean men of African family line than in men of different races. African-American men are additionally more than twice as prone to kick the bucket of prostate disease as white men. Prostate disease happens less frequently in Asian-American and Hispanic/Latino men than in non-Hispanic whites. The purposes behind these racial and ethnic contrasts are not clear[1].

#### **5. Genetic Conditions**

##### **BRCA2 Mutation**

A cohort study demonstrated that Prostate cancer danger is up to 5 times higher in men with BRCA2 transformation contrasted and the all-inclusive community likewise the Prostate growth hazard among men under 65 years of age is more than 7 times higher in those with BRCA2 change contrasted and the overall public [41]. Prostate tumor danger might be higher in men with BRCA1 change, yet confirm stays vague [6]. Prostate malignancy danger might be expanded with a few other hereditary variations; examination is progressing [53].

##### **Lynch Syndrome**

Prostate tumor danger is 2.1-4.9 times higher in men with Lynch disorder, contrasted and the overall public, a meta-investigation and partner cohort study demonstrated [42].

#### **6. Endogenous Hormones**

##### **Insulin like Growth Factor-1 (IGF-1)**

Prostate tumor danger is 38-83% higher in men with the most abnormal amounts of insulin-like development element 1 (IGF-1), meta-and pooled investigations have demonstrated [54]. Prostate tumor danger is not connected with insulin-like development component 2 (IGF-2) levels, meta-and pooled investigations have indicated [55]. Prostate disease danger is by and large not connected with insulin-like development variable tying protein (IGFBP) levels, meta-and pooled investigations have demonstrated; this may change between IGFBPs [56].

##### **Testosterone**

Androgenic (anabolic) steroids – which have comparable impacts to testosterone in the body – are ordered by the International Agency for Research on Cancer (IARC) as a reasonable justification of prostate tumor, taking into account restricted proof. Prostate growth treatment can include utilization of solutions or surgery to lessen testosterone levels, as prostate tumors depend on testosterone to develop [57].

#### **7. Ionizing Radiations**

Thorium-232 and its decay items, X radiation, and gamma radiation are arranged by the International Agency for Research on Cancer (IARC) as likely explanations of prostate cancer, in light of restricted proof [57]. Prostate malignancy danger is higher in nuclear bomb survivors contrasted and the all-inclusive community, an accomplice study has demonstrated [8].

#### **Symptoms of Early Prostate Cancer**

There are no particular indications of early prostate malignancy, Following symptoms may happen once prostate organ swells or when disease spreads past the prostate.

- A continuous need to urinate, particularly during the evening
- Difficulty beginning or ceasing a flood of urinate
- A frail or interfered with urinary stream
- Leaking of urinate when chuckling or hacking
- Inability to urinate holding up
- A difficult or smoldering sensation amid urinate or discharge
- Blood in urinate or semen

These are not indications of the tumor itself; rather, they are brought on by the blockage from the malignancy development in the prostate. They can likewise be created by an amplified, noncancerous prostate or by urinary tract disease.

#### **Symptoms of Advanced Prostate Cancer**

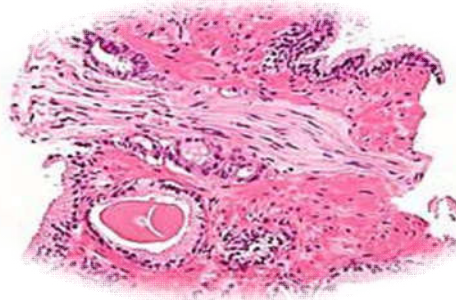
- Dull, profound agony or firmness in the pelvis, lower back, ribs, or upper thighs; torment in the bones of those regions
- Loss of weight and voracity, exhaustion, sickness or retching
- Swelling of the lower furthest points
- Weakness or loss of motion in the lower appendages, regularly with clogging

## Diagnosis

Prostate cancer screening is controversial. Prostate specific antigen (PSA) testing increases cancer detection but does not decrease mortality [58]. While 5 $\alpha$ -reductase inhibitors appear to decrease low grade cancer risk they do not affect high grade cancer risk and thus are not recommended for prevention [47]. Supplementation with vitamins or minerals does not appear to affect the risk [59].

### Formal Diagnosis (Biopsy)

The only test can fully confirm the diagnosis prostate cancer is Biopsy. Making a formal diagnosis of prostate cancer requires a needle biopsy. A biopsy gun is inserting and removes special hollow core needles (usually three to six on each side of the prostate) in less than a second. Fifty five percent of men report discomfort during prostate biopsy [60]. Usually a little bleeding occurs and takes less than half an hour. An antibiotic is usually given prior to and following the procedure to reduce the risk of infection. This discussion is restricted to core prostate biopsies obtained by either Transrectaltransperineal sampling under ultrasound guidance (TRUS). The cancer detection rates of perineal prostate biopsies are comparable with those obtained for Transrectal biopsies. [61, 62].



**Fig: Micrograph showing a prostate cancer with Perineural invasion H & E stain**

### Gleason score

The tissues samples are then examined under a microscope to determine whether cancer cells are present, and to evaluate the microscopic features (or Gleason Score) of any cancer found. Prostate specific membrane antigen is a transmembrane carboxypeptidase and exhibits folate hydrolase activity. [63] The protein is associated with a higher Gleason score.

**Transrectal ultrasound (TRUS) guided biopsy-** A TRUS uses sound waves produced by a small probe placed in the rectum to create an image of the prostate on a video screen. It informs whether the cancer has reached the edge of or broken through the capsule of the prostate gland and the size of the prostate. While the image reveals the suspicious areas that should be sampled, multiple other areas of the prostate should be sampled for tumors that don't show on ultrasound. The decision on whether to proceed with prostate biopsy is made after considering patient preferences, patient age, life expectancy, co-morbidity, abnormality on rectal examination, suspicion of malignancy on diagnostic imaging and abnormalities of serum PSA. **Color Doppler Ultrasound-** this is a refinement of the standard Transrectal ultrasound, which produces only black and white images of the prostate gland and immediate adjoining tissues according to the density of blood vessels.

### Prostate imaging

Ultrasound (US) and magnetic resonance imaging (MRI) are two main imaging methods used for prostate cancer detection. Urologists use Transrectal ultrasound during prostate biopsy and can sometimes see a hypoechoic area (tissues or structures that reflect relatively less of the ultrasound waves). Ultrasound has poor tissue resolution and thus, is generally not critically used. Prostate MRI is like a CT scan except that magnetic fields are used instead of X-rays to create detailed images of selected areas of the body and has better soft tissue resolution than ultrasound [64]. MRI in those who are at low risk might help people choose active surveillance, in those who are at intermediate risk it may help with determining the stage of disease, while in those who are at high risk it might help find bone disease [65]. Currently (2011), MRI is used to identify targets for prostate biopsy using fusion MRI with ultrasound (US). Biopsy detected 33% of cancers compared to 7% with standard ultrasound guided biopsy [66]. Prostate MRI is also used for surgical planning for men undergoing robotic prostatectomy [67]. Cystoscopy shows the urinary tract from inside the bladder, using a thin, flexible camera tube inserted down the urethra. **Magnetic Resonance Spectroscopy Imaging (MRSI)** - is a refinement of MRI. It detects the levels of certain compounds in benign and cancerous prostate tissues. This method can produce findings for the prostate glands, but doesn't image the lymph nodes. Currently, it remains investigational.

**Bone Scan-** It shows whether the cancer has spread from the prostate to the bones. Some low level radioactive material is injected into the body and will be taken up by diseased bone cells. These areas may

suggest that metastatic cancer I present, but arthritis and other bone diseases could create similar pattern. Very small metastasis may not be detected by this scan.

**Computed Tomography (CT scan or CAT scan)** - uses a rotating X-ray beam to reveal abnormally enlarged pelvic lymph nodes, or spread of the cancer to the internal organs. A CT scan usually isn't ordered unless there is an elevated PSA (>20ng/ml), a high Gleason score or primary Gleason grade of 4, or evidence of a large tumor.

**ProstaScint™** - this method uses a special antibody is chemically attached to a radioactive tracer, and then injected into bloodstream. It can locate microscopic amounts of prostate cancer cell in soft tissues in the body. The test is not commonly used due to high likelihood of both "false positive" and "false negative" results.

#### Other imaging techniques

Under unusual circumstances other imaging studies may be indicated such as PET/CT, Combindex (not FDA approved), Sentinel node imaging and use of Tumor marker for checking the existence of PSA(organ-specific but not cancer-specific), EN2, BCA-3, BCL-2, Ki-67, ERK5, EPCA2 and Prostatomes other tumor markers in order to verify the source of malignant cells that have metastasized. [68]. Probable methods include chromatographic separation methods by mass spectrometry, or protein capturing by immunoassays or immunized antibodies. The test method will involve quantifying the amount of the biomarker PCI, with reference to the Gleason Score. Not only is this test quick, it is also sensitive. It can detect patients in the diagnostic grey zone, particularly those with a serum free to total Prostate Specific Antigen ratio of 10-20%.

Currently, a dynamic area of research and non-clinically practical investigations involve non-invasive methods of prostate tumor detection. Adenoviruses customized to transfect tumor cells with undisruptive yet different genes (such as luciferase) have proven capable of early detection. Until now, on the other hand, this area of research has been tested only in animal and LNCaP cell models [54].

#### Digital rectal examination

Most prostate cancers are located in the peripheral zone of the prostate and some may be detected by DRE. Prostate cancer may present as a hard discrete nodule or with asymmetry of the gland. In about 18% of all patients, prostate cancer is detected by a suspect DRE alone, irrespective of the PSA level. [69]. A suspect DRE in patients with a PSA level of up to 2 ng /mL has a positive predictive value of 5–30% [70]. A suspect DRE is a strong indication for prostate biopsy as it is predictive for more aggressive prostate cancer.[52, 71].

#### Stages of Prostate Cancer

Staging means selecting different kinds of treatments & diagnosis according to spread of disease. Such as TMN system: T (Tumor), M (absence or presence of metastasis), N (near by lymph nodes) [72, 73]. T type is classified as: Clinical stage, it involves Digital rectal examination & imaging results. Pathological state: the lymph nodes, seminal vesicles & prostate glands are completely detached.

#### Further Stages of TMN Classification

<b>T1</b> (Tumor not felt during Digital Rectal examination).	<b>T1a</b>	If the area of prostate is less than 5% involved in tumor formation.
	<b>T1b</b>	Cancer (>5% tumor) diagnosed during Transurethral resection of prostate ( <b>TRUS</b> ).
	<b>T1c</b>	Biopsy shows elevated levels of <b>PSA</b> .
<b>T2</b> (Tumor felt during Digital Rectal examination & imaging results).	<b>T2a</b>	Less than one half of only one side of prostate.
	<b>T2b</b>	More than one half of only one side of prostate.
	<b>T2c</b>	Cancer spread to both side of prostate.
<b>T3</b> (Cancer extends to the capsule of prostate or to the seminal vesicles).	<b>T3a</b>	Cancer extends outside the prostate on one side but not to the Seminal Vesicles.
	<b>T3b</b>	Cancer spread to Seminal vesicles.
<b>T4</b> (Organs beside prostate are affected).	<b>T4</b>	Such as Bladder's external sphincter, Rectum, pelvis walls. Imaging testing is required.
<b>N</b> Categories:	<b>N<sub>0</sub></b>	Cancer has not spread to lymph nodes.
	<b>N<sub>1</sub></b>	Cancer spread to one or more local pelvic lymph nodes.

	<b>N<sub>x</sub></b>	Local lymph nodes have not been assessed.
<b>M</b> Categories: ( <b>M<sub>0</sub></b> : Cancer has not been metastasized away from lymph nodes)	<b>M1a</b>	Metastasis is present nearby lymph nodes.
	<b>M1b</b>	Cancer has spread to bones.
	<b>M1c</b>	Cancer has spread to distant organs: lungs, liver, brain.
	<b>M<sub>x</sub></b>	Distant metastasis has not been assessed.

Usually Clinical Models are used for staging more complex diseases. 1. Many men who have received local therapy such radical prostatectomy or radiation may increase a rising PSA without any evidence of metastatic disease. 2. For patients with metastatic disease, there is significant difference between the forms of the disease that is responsive to hormonal therapy. As a result, determining as best as possible in which “Clinical state” the cancer is non- metastatic or metastatic; hormone responsive or hormone independent (important for guiding the treatment of patients with advanced disease).

### Treatment

Different treatment options are available (discussed below) to treat cancer.

#### Active surveillance

To check the state of cancer digital rectal exams (DREs), prostate specific antigen (PSA) blood tests and ultrasounds are performed at regular intervals in active surveillances. High PSA level indicated that the cancer has widely spread and faster growth of cancer is showed by high Gleason level, in these cases the active surveillance is not measured a better option [74].

#### Surgery

Radical prostatectomy is considered a main type of surgery. In this the tissues surrounding the prostate gland consisting of seminal vesicles and sometimes the whole prostate gland is removed. A patient is not dispossessed of surgery on the matter of his age. [75]. Sometimes the patient develop one or more additional disorders not relevant to prostate cancer, may result the cause of death [76] and a doctor should properly guide a patient about sugery to estimate life expectations [77]. There are different ways in which radical prostatectomy can be performed.

#### Radiation therapy

Radiation therapy has two important types known external beam radiation and internal beam radiation.

##### External beam radiation therapy (EBRT)

The prostate cancer in its early stage should be treated by EBRT, in this approach the prostate gland is targeted by radiation beams emitting from machine present exterior to the body. Each treatment session usually lasts about 15 minutes [78].

##### Brachytherapy (internal radiation therapy)

**Permanent (low dose rate) brachytherapy** Thin needles are used to place pellets of radioactive material, into the prostate. The needles are removed while the pellets are left there; for weeks and months low level of radiation beams are supplied. The reported data showed in Canada, that using this approach low and intermediate-risk patients were spending better quality of life [79]. Patients showed considerably elevated biochemical control rate (PSA < 1.0 ng/mL) receiving a D90 (dose covering 90% of the prostate volume) of > 140 Gy as compared to the patients who received less than 140 Gy (92% vs 68%) [57].

**Temporary (high dose rate) brachytherapy** The radiation beams of high doses are used for a small instance in this technique. The prostate gland is treated by hollow needles. These needles contain the catheters composed of flexible tubes of nylon. Later the needles are detached while the catheters remain at their place. This approach is considered safe and feasible as suggested by a statement from the Memorial Sloan-Kettering Cancer Center [80].

##### Hormone (androgen deprivation) therapy for prostate cancer

Male hormones, called androgens including testosterone and dihydrotestosterone (DHT) is decreased by this therapy. Consequently, for some period the growth of the prostate cancer will be slow down. [81]reported that a patient could spend a better and healthy life by periodic androgen control therapy. [82]reported that for the treatment of patients, AR is considered to be a main target.

##### Chemotherapy for prostate cancer

Anti-cancer drugs are also used for the treatment of prostate cancer that might be ingested or injectable. Here is following drugs use for the treatment include: Docetaxel (Taxotere®), Estramustine (Emcyt®), Etoposide (VP-16), Mitoxantrone (Novantrone®), Cabazitaxel (Jevtana®), and Doxorubicin (Adriamycin®). A taxane that is semisynthetic known as Cabazitaxel approved in 2010 by FDA, is now

use for the treatment of patients with metastatic castration resistant prostate cancer (CRPC), who were previously failed in treatment by docetaxel [83].

#### **Future medications**

Tumor cell itself or the malignancy cell–host connection are potential helpful focuses for future medications of prostate growth. Careful comprehension of the atomic acceptance of targets is key before some of these are talked about in more detail. This envelops both phenotypic acceptance (i.e., the objective is over communicated in the larger part of malignancies) and utilitarian approval (i.e., the pathway focused on is urgent for disease cell survival or forcefulness) pathway in which any potential target assumes a part is obligatory [84]. Another concern is the part of prostate immature microorganisms. A few proofs backing the theory that prostate tumor emerges from threatening change of halfway immature microorganisms [14]. On the off chance that disease undifferentiated cells for sure end up being urgent in prostate tumor, elements crucial for their upkeep or recharging would be future's potential targets.

#### **Tumor cell targets**

Still a dynamic territory in exploration is the androgen receptor pivot in disease cells that has been a center of consideration truly [78] Another center is towards focusing on the development variables (e.g., receptor inhibitors) In which component of activity depends on the change from paracrine to autocrine regulation that can happen in prostate growth cells. Quality therapy is additionally being effectively sought after [20] and is an alluring expectation because of various potential targets and the straightforward entry to the prostate.

#### **Growth cell–host connections**

##### **Stromal–epithelial associations**

These are key to all parts of prostate regulation, from the development of the prostate in utero through to prostate disease, metastasis and hormone-freedom. Such cooperations are multifactorial, including extracellular grid associations, direct correspondence and paracrine regulation. Specialists, for example, the particular androgen receptor modulators (sARMs) and an adenoviral-osteocalcin promoter vector could be utilized to target both disease cells and the stromal–epithelial association, with focusing of both components at the same time speaking to an exceptional way to deal with restricted and metastatic malignancy treatment [74].

##### **Cadherins**

They are a class of cell bond particle that keeps up epithelial tissue separation and auxiliary uprightness. A study led by Umbas *et al.*, demonstrated that patients with variant E-cadherin recoloring of prostate malignancy tumors had a quite bring down survival rate than patients with ordinary recoloring ( $P < 0.001$ ) at a mean follow-up of 36 months [77] this distinction was likewise obvious after longer-term follow-up [85]. A 'cadherin switch' has been seen in tumor cells, in which the capacity of E-cadherin is supplanted or overruled by mesenchymal cadherins, for example, N-cadherin [16]. The impact of this switch is that cells be able to wind up motile and intrusive. Cadherins show incredible guarantee as a remedial focus, with the test being to turn around the switch in sorts [84].

##### **Angiogenesis**

The capacity of a tumor to become bigger than 2 mm in distance across is reliant on both tumor cell multiplication and impelling of new host-determined veins (ie angiogenesis). Specialists that hinder angiogenesis will diminish the consequent size of the tumor, and by diminishing the quantity of vessels it can get to may even deflect metastasis. Angiogenesis includes release of components, for example, vascular endothelial development variable (VEGF) [86]. A killing hostile to VEGF immune response was appeared to totally stifle prostate cancer impelled angiogenesis and avert tumor development past the underlying prevascular development stage [86]. Integrin receptor alpha v and beta 3 additionally assumes a basic part in angiogenesis [87].

##### **Immune system targets**

Supporting the insusceptible framework, either through inoculation or the utilization of antibodies is another center of potential treatment mode [87]. Immunization can empower an antitumor reaction by selecting various diverse arms of the invulnerable framework (eg cytotoxic T-lymphocytes (CTLs) and T-aided reactions). The achievability of hostile to PSA inoculation has been explored utilizing a few strategies, for example, dendritic cells beat with PSA, human leucocyte antigen-limited PSA peptides, PSA-communicating recombinant infections and cytokines [18]. HuJ591 is a mouse monoclonal counter acting agent against prostate-particular layer antigen, in which murine immunoglobulin arrangements have been supplanted with human counterparts. A Phase I examine demonstrated that HuJ591 is all around endured, does not instigate a host safe reaction and successfully targets spread prostate tumor destinations [80].



## CONCLUSION

Prostate cancer is the disease of male's reproductive system and specifically the cancer of prostate gland. So many environmental factors and gene mutations are involved in progression of abnormal prostate cells growth which in turn leads to the formation of cancerous cells. These cancerous cells can be diagnosed at each level of the disease and different treatments with effective drugs are also available to cure the disease. However advancement in each treatment technology and prevention strategy is still in progress.

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