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Prostate Cancer: Pathophysiology, Diagnosis, and Prognosis

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Abstract:*Prostate cancer is more common in the western countries, least common in Asia, and the leading cause of cancer deaths in males worldwide. Individuals who have first-degree family members with prostate cancer have double the risk of getting disease. Risk factors for prostate cancer include familyhistory,genetics,diet, medication, infectious disease and sexual factors. Published animal research studies indicate that basal cells developed cancerous tumors, which appeared identical to human samples. Initially adenocarcinoma a condition known as carcinoma in situ or prostate intraepithelial neoplasia(PIN).Although there is no proof that PIN is a precursor, it is closely associated with cancer. Prostate cancer is associated with urinarydysfunction. Advanced cancer can spread to other parts of the body, i.e. Vertebrae, pelvic, or ribs, also compress the spinal cord, causing tingling leg weakness and urinary and fecal incontinence. Diagnosis by digital rectal examination(DRE),biopsy, Gleason score, and TNM staging(Tumor/nodes/metastasis) and by tumor markers. Management options best depends on the stage of the disease, the Gleason score and PSA level. If radiation fails then surgery may not be feasible, and radiation after surgery failure may have complications, associated with small increase in bladder and colon cancer. Prognostic indicators of disease outcome are stage, pre-therapy PSA level and Gleason score, higher the grade, and the stage poorer the prognosis.Information on the relationship of diet and prostate cancer is poor. American Urological Association(AUA) recommends screening in those of 55 to 69,no more than every two years.*

Keywords:*Prostatecancer,Riskfactors,Pathophysiology,Diagnosis.*

I. Introduction

Prostate cancer or carcinoma of prostate is the development of cancer in the prostate a gland in the male reproductive system [1].As of 2012, prostate cancer is the second most frequently diagnosed cancer, at 15% of all male cancer and the sixth leading cause of cancer deaths in males worldwide [2,3].In 2010 it resulted in 256,000 deaths up from 156,000 deaths in 1990[4].Rates of prostate cancer vary widely across the world. Although the rates vary widely between countries, it is least common in South and East Asia, and more common in Europe, North America, Australia and New Zealand[5].Prostate is least common among Asian men and most common among black men, with figures for white men in between[6].Malaysian National Cancer Registry,2007 reported 502 (6.2%) prostate cancer cases[7].The annual incidence rate of prostate cancer between 1988 and 1992 among Chinese men in U.S. was 15 times higher than Chinese living in Shanghai and Tianjin[6].Risk factors for prostate cancer include: old age, family history[8],genetic, diet,[9,10],.medication ,infectious disease[11,12],and sexual factors[13].Clinical presentations include: frequent urination,nocturia,hematuria,dysuria, and urinary dysfunction [14].Advanced prostate cancer can spread to other parts of the body e.g.,bone spine, pelvis, and ribs, causing leg weakness and urinary and fecal incontinence[14,15].Prostate cancer is diagnosed by biopsy, and medical imaging is done to determine if the cancer has spread to other parts of the body[16].Prostate cancer screening is controversial[8].Prostate specific antigen(PSA) testing increases cancer detection but does not decrease mortality[17].Treatments may include a combination of surgery, radiation therapy, hormone therapy or chemotherapy[16].Outcomes depend on a patient's age and other health problems as well as how aggressive and extensive the cancer is[16].The paper reviews the current notions on prostate cancer, diagnosis, prognosis, and the impact of prostate cancer on the quality of the life.

II. Historical Perspectives

Prostate was first described by Venetian anatomist Nicolo Massa in 1536,and illustrated by Flemish anatomist Andreas Vesalius in 1538,prostate cancer was not identified until 1853[18].Prostrate cancer was initially considered a rare disease, probably because of shorter life expectancies and poorer detection methods in 19thcentury. The first treatments of cancer were surgeries to relieve urinary obstruction[19].Removal of the entire gland(perinealprostectomy)was first performed in 1904 by Hugh H.Young at John Hopkins

Hospital[20].Surgical removal of testes(orichiectomy) to treat prostate cancer was first performed in the 1890s,but with limited success.Transurethral resection of prostate (TURP)replaced radical prostectomy for symptomatic relief of obstruction in the middle of the 20th century because it could better preserve penilefunction. Radical retro- pubicprostectomy was developed in 1983 by Patrick Walsh.This surgical approach for removal of prostate and lymph nodes with maintenance of penile function [21].

In 1941,Charles B Huggins published studies in which he used estrogen to oppose testosterone production in men with metastasisprostatecancer. This discovery of "chemical castration" won Huggins the 1966 Nobel Prize in Physiology and Medicine [22].The role of the gonadotropin-releasing hormone(GmRH) in reproduction was determined by Andrzej W Schally and Roger Guillemin,who both won the 1977 Nobel Prize in Physiology and Medicine for this work.GmRH receptor agonists, such as leuprolide and goserelin, were subsequently developed and used to treat prostate cancer[23].

Radiation therapy for prostate cancer was first developed in the 20th century and initially consisted of intra-prostatic radium implants. External radiotherapy became more popular as stronger (X-ray) radiation sources became available in the middle of the 20thcentury. Brachytherapy with implanted seeds (for prostate cancer was first described in 1983[24].Systematic chemotherapy for prostate cancer was first studied in the 1970s.The initial regimens cyclophosphamide and5-fluorouracil was quickly joined by multiple regimens using a host of other systematic chemotherapy drugs [25].

Cell studies.A series of studies published in *Science* involved introduced viruses known to cause cancerous mutation in prostate cells:AKT,ERG,and AR into isolated samples of the basal and luminal cells and grafted the treated tissue into mice. After 16 weeks, none of the luminal samples had undergone malignant mutation the basal samples had mutated into prostate-like tubules which had then developed malignancy and formed cancerous tumors, which appeared identical to human samples under magnification. This led to the conclusion that prostate basal cell may be the most likely "site of origin" of prostate cancer [26].

III. Risk Factors

A complete understanding of the causes of prostate cancer remains elusive[27].The primary risk factors are obesity, age and family history. Prostatecancer is very uncommon in men younger than 45, but becomes more common with advancing age. The average age at the time diagnosis is 70[28].However many men never know they have prostate cancer. Autopsystudies of Chinese,German,Israeli,Jamican,Swedish,and Uganda men who died of other causes have found prostate cancer in 30% of men in their 50s,and 80% of men in their 70s[29].Men who have first- degree family members with prostate cancer appear to have double the risk of getting disease compared to men without prostate cancer in the family[30].The risk appears to be greater for men with an affected brother than for men with an affected father. In the United States in 2005,there were an estimated 230,000 new cases of prostate cancer and 30,000 deaths due to prostate cancer[31].Men with high blood pressure are more likely to develop prostate cancer[32].There is a small increased risk of prostate cancer associated with lack of exercise[33]..A 2010 study found that prostate basal cells were the most common site of the origin for prostate cancers [26].

Role of genetics

Genetic background may contribute to prostate cancer risk, as suggested by associations with race,family,and specific gene variants.Men who have a first degree relative(father or brother) with prostate cancer have twice the risk of developing prostate cancer, and those with two first degree relatives affected have a fivefold greater risk compared with men with no family history[9].In the Unites States, prostate cancer more commonly affects black men than white or Hispanic men, and is also more deadly in black men[34].In contrast, the incidence and mortality rates for Hispanic men are one third lower than non-Hispanic whites. Studies of twins in Scandinavia suggest that 40% of prostate cancer risk can be explained by inherited factors [35].

No single gene is responsible for prostate cancer; many different genes have been implicated. Mutations in BRCA1 and BRCA2,important risk factors for ovarian cancer and breast cancer in women, have also been implicated in prostate cancer[36].Other linked genes include the Hereditary Prostate cancer gene 1(HPC1),the androgen receptor, and the vitamin D receptor[34,].TMPRSS2-ETS gene family fusion, specifically TMPRSS2-ERG or TMPRSS2-ETV1/4 promotes cancer growth[37].

Two large genome-wide association studies linking single nucleotide polymorphism (SNPs) to prostate cancer were published in 2008[38].These studies identified several SNPs which substantially affect the risk of prostate cancer. For example, individuals with TT allele pair at SNP rs10993994 were reported to be at 1,6 times higher risk of prostate cancer than those with CC allele pair. This SNP explains part of the increased prostate cancer risk of Africans men compared to American men of European descent, since C allele is much more prevalent in the latter, this SNP is located in the promoter region of the MSMB gene, thus affects the amount of MSMB protein synthesized and secreted by epithelial cells of the prostate[39].

Diet and prostate cancer

Some dietary factors have been associated with prostate cancer the evidence is still tentative. Evidence support little role for dietary fruits and vegetables in prostate canceroccurrence [40.41].Red meat and processed meat also to have little effect in human studies. Higher meat consumption has been associated with a higher risk in some studies [42,43].Lower blood levels of vitamin D may increase the risk of developing prostate cancer. Folic acid supplements have no effect on the risk of developing prostate cancer [44,45].

Medication and Infection

There are some links between prostate cancer and medications, medical procedures, and medical conditions. Use of the cholesterol-lowering drugs known as the statins may decrease prostate cancer risk [46,47].Infection or inflammation of the prostate(prostatitis) may increase the chance for prostate cancer while another study shows infection may help prevent prostate cancer by increasing blood to the area. In particular infection with sexually transmitted infections chlamydia, gonorrhea, or syphilis seems increase risk[48].An association with gonorrhea has been found, but a mechanism for which for this relationship has not been identified[49].Finally, obesity and elevated blood levels of testosterone may increase the risk for prostate cancer [50,51].There is an association between vasectomy and prostate cancer, however, research is needed to determine if this is a causative relationship[52].

In 2006,a previously unknown retrovirus,XenotropicMuL.V-related virus or XMRV,was associated with human prostate tumors[53],but subsequent reports on the virus were contradictory[54], and the original 2006 finding was instead due to a previously undetected contamination[55].The Journals *Science* and *PLosONE* both retracted XMRV related articles[56].Research released in May 2007,found that US war veterans who had been exposed to Agent Orange had a 48% increased risk of prostate cancer recurrence following surgery[57].

Prostate cancer and Sexual activity

Sexual case-control studies have shown that having many lifetime sexual partners or staring sexual activity early in life substantially increases the risk of prostate cancer[58].While the available evidence is weak, tentative results suggest that frequent ejaculation may decrease the risk of prostate cancer[59,60].A study over eight years, showed that those that ejaculated most frequently (over 21 times per month on average) were less likely to get prostate cancer[61].The results were broadly similar to the findings of a smaller Australian study[62].

IV. Pathophysiology

The prostate gland is a part of the male reproductive system that helps to make and store seminal fluid. In adult men, a typical prostate is 3 centimeters long and weighs about 20 grams[63].Because of its location, prostate disease often affect urination,ejaculation, and rarely defecation. The prostate contains many small glands which make 20 percent of the fluid constituting semen [64].In prostate cancer, the cells of these prostate glands mutate into cancer cells.The prostate glands require male hormones, known as androgens,to work properly.Androgens include testosterone, which is made in the testes, dehydroepiandrosterone,made in the adrenal glands; and dihydrotestosterone,which is converted from testosterone within the prostate itself. Androgens are also responsible for secondary sex characteristics such as facial hair and increased muscle mass.Prostate cancer is classified as an adenocarcinoma, or glandular cancer, that begins when normal semen-screening 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 prostate intraepithelial neoplasia(PIN).Although there is no proof that PIN is a precursor, it is closely associated with cancer. Overtime, 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 blood stream and lymphatic system. The invasion of other organs is called metastasis. Prostate cancer most commonly metastasizes to the bones, lymph nodes, and may invade rectum, bladder and lower ureters after local progression. The route of metastasis to bone is thought to be venous as the prostatic venous plexus draining the prostate connects with the vertebral veins [65].

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 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 absence of zinc is thought to occur via a silencing of the gene that producing the transporter proteinZIP1..ZIP1 is now

called a tumor suppressor gene product for the gene SLC39A1.The cause of epigenetic silencing is unknown. Strategies which transport zinc into transformed prostate cells effectively eliminate these cells in animals. Zinc inhibits BF-kBpathways, Is anti- proliferative,and induces apoptosis in abnormal cells. Unfortunately, oral ingestion of zinc is ineffective since high concentrations of zinc into prostate cells is not possible without the active transporter ZIP1[66].

RUNX2 is a transcription factor that prevents the cancer cells from undergoing apoptosis thereby contributing to the development of prostate cancer[67].The androgen receptor helps prostate cancer cells to survive and is a target for many anticancer research studies; so far, inhibiting androgen receptor has only proven to be effective in mouse studies[68].Prostate specific membrane antigen(PSMA) stimulates the development of prostate cancer by increasing folate levels for cancer cells to use to survive and grow. PSMA increases available folates for use by hydrolyzing glutamate folate [69].

V. Clinical Manifestations

Early prostate cancer usually has no clear symptoms. Sometimes, however, prostate cancer does cause symptoms, often similar to those of disease such as benign prostatic hyperplasia. These include frequent urination,nocturia(increased urination at night),difficulty starting and maintaining a steady stream of urine, hematuria, anddysuria. Astudy based on the 1998 Patient Care Evaluation in the US found that about a one third of patients diagnosed with prostate cancer had one or more such symptoms, while two third had no symptoms [14].

Prostate cancer is associated with urinary dysfunction as the prostate gland surrounds the prostatic urethra. Changes within the gland, therefore, directly affect urinary function. Because the *vas deferens* deposits seminal fluid into the prostatic urethra and secretion from prostate gland itself are included in semen content, prostate cancer may also cause problems with sexual function and performance, such as difficulty achieving erection or painful ejaculation [14].

Advanced prostate cancer can spread to other parts of the body, possibly causing additional symptoms. The most common symptom is bone pain, often in the vertebrae, pelvic, or ribs. Spread of cancer into bones such as the femur is usually to the proximal or nearby part of the bone. Prostate cancer in the spine can also compress the spinal cord, causing tingling leg weakness and urinary and fecal incontinence [15].Other late symptoms may include feeling tired due to low levels of red blood cells[70].

VI. Diagnosis

The American Cancer Society believes that men should not be tested without learning about what we know and don't know about the risks and possible benefits of testing and treatment. Starting at age 50(45 if African American or brother or father suffered from condition before age 65) talk to your doctor about pros and cons of testing so you can decide if testing is the right choice for you[71].Frequently used tests to diagnose prostate and urinary tract abnormalities include:

Digital Rectal Examination andProstate Imaging

Digital rectal examination (DRE) may detect the prostate abnormalities. Cystoscopy shows the urinary tract from inside the bladder, using a thin, flexible camera tube inserted down the urethra.Transrectal ultrasonography creates a picture of the prostate using sound waves from a probe in the rectum[71].Prostate MRI has better soft tissue resolution than ultrasounds[72].Currently(2011) MRI is used to identify targets for prostate biopsy using fusion MRI with ultrasound(US) or MRI-guidance alone. In men who are candidates for active surveillance, fusion MR/US guided prostate biopsy detected 33% of the cancers compared to 7% with standard ultrasound guided biopsy [73].

Biopsy,GleasonScore And Staging

During a biopsy a urologist or a radiologist obtains tissue samples from the prostate via the rectum. Biopsy gun inserts and removes special hollow-core needles (usually three to six on each side of the prostate) in less than a second. Antibiotics should be used to prevent complications like fever, urinary tract infections and sepsis[74].Fifty-five percent of men feel discomfort during prostate biopsy[75].Tissue samples are then examined to determine whether cancer cells are present, and to evaluate the microscopic features(Gleason score) of any cancer found. Prostate specific membrane antigen is a transmembranecarboxypeptidase and exhibits folate hydrolase activity[76].This protein is over- expressed in prostate cancer tissues and is associated with a higher Gleason score[76].

The common staging system is four–stage TNM system(abbreviated from Tumor/ Nodes/ Metastasis).Its components include the size of the tumor, number of involved lymph nodes, and the presence of any metastasis[77].In the TNM system, clinical T1 and T2 cancers are found only in the prostate, while T3 and

T4 cancers are have spread elsewhere[78].In the Gleason system is used to grade prostate tumors from 2 to 10,and Gleason score of 10 indicates most abnormalities[78].

For tumor markers tissue samples can be stained for the presence of PSA and other tumor markers in order to determine the origin of malignant cells that have metastasized [79].Small cell carcinoma is very rare(1%) type of prostate cancer that cannot be diagnosed using the PSA[80].

VII. Management And Prognosis

The first decision to be made in managing prostate cancer is whether treatment is needed. Prostate cancer, especially low- grade found in elderly men, often grows so slowly that no treatment is required [81].Which option is best depends on the stage of the disease, the Gleason score and PSA level. Other important factor is age,health general, and a person's views about potential treatments and their potential side effects. A combination of treatment options is often recommended for managing prostate cancer[82]. Guidelines for treatment for specific clinical situations requires a good estimation of a person's long term life expectancy[83].If radiation therapy is done first, and fails, then radical prostectomy becomes a very technically challenging surgery may not be feasible. On the hand, radiation done after surgical failure may have many complications [84].It is associated with a small increase in bladder and colon cancer [85].

Treatment of aggressive prostate cancer may involve surgery (i.e. Radical prostectomy), radiation therapy, including brachytherapy, and external beam radiation therapy, high-intensity focused ultrasound(HIFU),chemotherapy, oral chemotherapeutic drugs (Temozolomide/TMZ),cryosurgery, hormonal therapy, or some combination[86].Palliative care which focuses on treatment of symptoms from serious illness, like cancer, and improving quality of life[87].

Prognosis

Prostate cancer rates are higher and prognosis is poorer in developed countries than in the rest of the world. Many of the risk factors are more prevalent in the developed world, including longer life expectancy and diets high in red meat, and less consumption of fruits and vegetables. It is not clear whether both these factors or just one of them, contribute to the occurrence of prostate cancer[88].In the United States, prostate cancers that are local or regional at the time of diagnosis have a 5-year survival rate of 100%,while those with distant metastasis have a 5-survival rate of 28%[89].In Japan, death from prostate cancer was one-fifth to one- half the rates in the United States and Europe in the 1990s[90].In India in the 1990s,half of the people with prostate cancer confined to the prostate died within ten years[91].African-American men have 50-60 times more prostate cancer and prostate cancer deaths than men in Shanghai,China.In Nigeria two percent of men develop prostate cancer, and 64% of them are dead after two years[92,93].

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 higher the grade, and the stage, the poorer the prognosis Nomograms can be used to calculate the estimated risk of the individual patient. The predictors are based on the experience of large groups of patients suffering from cancers at various stages [94].

VIII. Prevention

The data on the relationship of diet and prostate cancer is poor [95].In the light of this the rate of prostate cancer in linked to the consumption of the western diet[95].There is little if any evidence to support as association between trans-fat and carbohydrate intake and risk of prostate cancer[95].Evidence regarding the role of omega-3 fatty acids in preventing prostate cancer does not suggest that they reduce the risk of prostate cancer, although addition research is needed[95].Vitamin supplements appear to have no effect and some even may increase the risk[95].High calcium intake has been linked to advanced prostate cancer[96].Consuming fish may lower prostate cancer deaths but does not appear to affect it occurrence[97].Vegetarian diet, and foods containing lycopene and selenium have lower rates of prostate cancer[98,99].Diet rich in cruciferous vegetables,legumes,soy,bean and vigorous exercise may be associated with lower risk of advanced prostate cancer[95].

Prostate cancer screening options include the digital rectal examination(DRE) and the prostate specific antigen(PSA) blood test.Such screening is controversial, may lead to unnecessary, possibly harmful, consequences. Routine screening with either a DRE or PSA is not supported by evidence as there is no mortality benefit from screening[94,17].American Urological Association (AUA,2013) recommends screening decisions in those 55 to 69 be based on shared decision making, and no more often than every two years[100].

IX. Conclusion

Prostate cancer is an age related male problem, high incidence and mortality in the USA, Europe and low prevalence in Asia. Early diagnosis and treatment has better prognosis. Guidelines by American Urologist Association (AUA) are useful.

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