REVIEW ARTICLE

Prostate Cancer

MT Rahman[1], *ATMM Chowdhury[2]

[1]*Prof. Dr. Md. Tahminur Rahman, Vice Principal & Professor of Pathology, Anwer Khan Modern Medical College*
[2]** Dr. ATM Mowladad Chowdhury, Associate Professor Urology, BIRDEM Hospital, Dhaka*

**Corresponding author*

Date of submission: 14 January 2016 *Date of acceptance: 05 May 2016*

Prostate cancer is the number one cancer by incidence in males of increasing age & second by mortality throughout the world. Many known etiological factors are associated with increased risk of prostatic carcinoma including male hormone & its active metabolites, genetic predisposition (BRCA2, inherited polymorphism of some transcription factors), racial difference, environmental factors, food habits etc, Recently an association of importance has been given to molecular level changes; inflammatory cytokines, trace elements like zinc with prostate cancer. Diagnostic modalities & treatment facilities are important for better management & giving improved quality of life to the patients. The present review article highlights some of these findings on prostate cancer namely genetic factors, Highfatty diet, Hormone, medication, sexual activity, inflammatory cytokines, trace element zinc, PSA. These will lead to in hand better understanding of the pathophysiology of prostate cancer.

Key Words: Prostate cancer, risk factors, molecular level changes, trace elements-zinc, diagnosis, treatment modalitie

Introduction

Adenocarcinoma of prostate is the most common form of cancer in men 25% by incidence and second by 10% morality throughout the World. There is one in six lifetime probability of being diagnosed with prostate cancer in men. Prostate cancer a disease of men over 50 years. In autopsy the incidence of prostate cancer is very high 20% in 50s to 70% between 70-80 years. Prostate cancer is uncommon in Asian and occurs most frequently in blacks. Androgen play on important role in prostate cancer. Growth and survival of prostate cancer cells depends on androgen which is bound to the androgen receptor (AR) and induce the expression of progrowth and prosurvival genes. The active metabolite of testosterone (Dihydroxy Testesterone) DHT constitutes about 90% of prostatic androgens[1].

Risk Factors

Understanding of the different causes of prostate cancer remains research interest. Accumulative evidence from the already done research work suggests the primary risk factors are obesity, age and family history. Prostate cancer is very uncommon in men younger than 45, but becomes more common with advancing age. The average age at the time of diagnosis is 70 years[1]. However, many men never know they have prostate cancer. Autopsy studies of Chinese's, German, Israeli, Jamaican, Swedish, and Ugandan men who died of other causes have found prostate cancer in 30% of men in their 50s, and in 80% of men in their 70s[2]. Men whom have first degree family members with prostate cancer appear to have doubled the risk of getting and disease compared to men without prostate cancer in the family[3]. This risk appears to be grater for men with an affected brother than for men with an affected father. Men with high blood pressure are more likely to develop prostate cancer. There is a small increased risk of prostate cancer associated with lack of exercise[4]. A 2010 study found that prostate basal cells were the most common site of origin for prostate cancers[6].

Genetic Factors

Genetic background is an important associated risk factor and may contribute to prostate cancer risk, as suggested by associations with race, family, and specific gene variant. Men who have a first-degree relative (father or brother) have a fivefold grater risk of developing prostate cancer compared with men with no family history[5]. In the United States, prostate cancer more commonly affects black men than white or Hispanic men, and is also more deadly in black men[6,7]. In contrast, the incidence and mortality rates for Hispanic men are one third lower than for non-Hispanic whites. Studies of twins in Scandinavia suggest that 40% of prostate cancer risk can be explained by inherited factors[8].

No single gene is responsible for prostate cancer; many different genes have been implicated. Mutations in BRCA1 and BRCA2[11], important risk factors for ovarian cancer and breast cancer in women, have also been implicated in prostate caner. Other linked genes include the Hereditary Prostate caner gene 1 (HPC1), the androgen receptor, and the vitamin D receptor. TMPRSS2-ETS gene family fusion, specifically TMPRSS2-ERG or TMPRSS2-ETV1/4 promotes cancer cell growth.

Two large genome-wide association studies lining single nucleotide polymorphisms (SNPs) to prostate cancer were published in 2008. These studies identified several SNPs which substantially affect the risk of prostate cancer [9]. 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 the CC allele pair. This SNP explains part of the increased prostate cancer risk of African American men as compared to American men of European descent, since the 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.[10,11]

Loss of cancer suppressor genes localized to chromosome 8p,10q,13q, 16q are sen in early prostatic carcinogenesis.p53 mutation in primary prostate cancer is low and more frequently seen in metastatic carcinoma hence p53 mutation is a late event in prostate cancer. Loss of PTEN gene and KAI gene are also important in prostatic cancer.About 70% of men with prostate cancer lost PTEN gene at the time of diagnosis.Loss of ecadherin and CD44 have also being observed[15]. RUNX2 is a transcription factor that prevents cancer cells undergoing apoptosis and also contribute to development of Prostate carcinoma. PSMA is associated with increase supply of folate for the cancer cells to survive and grow by hydrolyzing glutamated folate.[12]

ERK5 is a protein that is present in abnormally high levels of prostate cancer including invasive cancer which has spread to other parts of the body.[17]

Dietary Factors

While some dietary factors have been associated with prostate cancer the evidence is still tentative. Evidence supports little role for dietary fruits and vegetables in prostate cancer occurrence[14]. Red meat and processed meat also appear to have little effect in human studies. Higher meat consumption has been associated with a higher risk in some studies. Lower blood levels of vitamin D may increase the risk of developing prostate cancer[15]. Folic acid supplements have no effect on the risk of developing prostate cancer[16]. The role of High fatty Diet(HFD) is discussed in later part under separate heading.

Medication Exposure

There are also some links between prostate cancer and medications, medical procedures, and medical conditions. Use of the cholesterol-lowering drugs known as the satins may also decrease prostate cancer risk[17,18].

Sexual factors: Many case control study have shown that many lifetime sexual partners and starting sexual activity in early life substantially increases the risk of prostate cancer.There is weak tentative result which suggests that frequent ejaculation may decrease the risk of prostate cancer.A study of eight years and a study in Australia showed that most frequent ejaculation over 21 times per month were less likely to get prostate cancer[19,20,21,22].

Inflammation & Cytokines

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are the most common urological diseases in elderly men. Although studies suggest the cytokine family might be associated with BPH and PCa, there has been no systemic comparisons of expression of IL-17A, E.F and their receptors,

Genetic Factors

Genetic background is an important associated risk factor and may contribute to prostate cancer risk, as suggested by associations with race, family, and specific gene variant. Men who have a first-degree relative (father or brother) have a fivefold grater risk of developing prostate cancer compared with men with no family history[5]. In the United States, prostate cancer more commonly affects black men than white or Hispanic men, and is also more deadly in black men[6,7]. In contrast, the incidence and mortality rates for Hispanic men are one third lower than for non-Hispanic whites. Studies of twins in Scandinavia suggest that 40% of prostate cancer risk can be explained by inherited factors[8].

No single gene is responsible for prostate cancer; many different genes have been implicated. Mutations in BRCA1 and BRCA2[11], important risk factors for ovarian cancer and breast cancer in women, have also been implicated in prostate caner. Other linked genes include the Hereditary Prostate caner gene 1 (HPC1), the androgen receptor, and the vitamin D receptor. TMPRSS2-ETS gene family fusion, specifically TMPRSS2-ERG or TMPRSS2-ETV1/4 promotes cancer cell growth.

Two large genome-wide association studies lining single nucleotide polymorphisms (SNPs) to prostate cancer were published in 2008. These studies identified several SNPs which substantially affect the risk of prostate cancer [9]. 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 the CC allele pair. This SNP explains part of the increased prostate cancer risk of African American men as compared to American men of European descent, since the 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.[10,11]

Loss of cancer suppressor genes localized to chromosome 8p,10q,13q, 16q are sen in early prostatic carcinogenesis.p53 mutation in primary prostate cancer is low and more frequently seen in metastatic carcinoma hence p53 mutation is a late event in prostate cancer. Loss of PTEN gene and KAI gene are also important in prostatic cancer.About 70% of men with prostate cancer lost PTEN gene at the time of diagnosis.Loss of ecadherin and CD44 have also being observed[15]. RUNX2 is a transcription factor that prevents cancer cells undergoing apoptosis and also contribute to development of Prostate carcinoma. PSMA is associated with increase supply of folate for the cancer cells to survive and grow by hydrolyzing glutamated folate.[12]

ERK5 is a protein that is present in abnormally high levels of prostate cancer including invasive cancer which has spread to other parts of the body.[17]

Dietary Factors

While some dietary factors have been associated with prostate cancer the evidence is still tentative. Evidence supports little role for dietary fruits and vegetables in prostate cancer occurrence[14]. Red meat and processed meat also appear to have little effect in human studies. Higher meat consumption has been associated with a higher risk in some studies. Lower blood levels of vitamin D may increase the risk of developing prostate cancer[15]. Folic acid supplements have no effect on the risk of developing prostate cancer[16]. The role of High fatty Diet(HFD) is discussed in later part under separate heading.

Medication Exposure

There are also some links between prostate cancer and medications, medical procedures, and medical conditions. Use of the cholesterol-lowering drugs known as the satins may also decrease prostate cancer risk[17,18].

Sexual factors: Many case control study have shown that many lifetime sexual partners and starting sexual activity in early life substantially increases the risk of prostate cancer.There is weak tentative result which suggests that frequent ejaculation may decrease the risk of prostate cancer.A study of eight years and a study in Australia showed that most frequent ejaculation over 21 times per month were less likely to get prostate cancer[19,20,21,22].

Inflammation & Cytokines

Benign prostatic hyperplasia (BPH) and prostate cancer (PCa) are the most common urological diseases in elderly men. Although studies suggest the cytokine family might be associated with BPH and PCa, there has been no systemic comparisons of expression of IL-17A, E.F and their receptors,

infiltration of inflammatory cells and changes in structural cells in PCa and BPH. Immunoreactivity for IL-17A, E.F and their receptors IL-17RA, IL-17BR, and IL-17CR, infiltration of inflammatory cells, and changes in structural cells including endothelial cells fibroblast and smooth muscle cells in prostate tissue from subjects with PCa or BPH as well as controls. Immunostaining showed that expression of immunoreactivtiy for IL-17A, IL-17RA, IL-17E and IL-17F was significantly elevated in prostatic tissue form BPH and PCa compared with that in controls, which was accompanied by increased numbers of infiltrating inflammatory cells and CD31(+) blood vessels. Compared with BPH. PCa was characterized by reduced immunocreativity for IL-17BR and reduced numbers of CD68(+) macrophages, Fibroblast and smooth muscle cells, although there was a trend for these changes to co-relate with diseases severity in both PCa and BPH. Their data are compatible with hypothesis that IL-17A acting through IL-17A, but not IL-17CR contribute to the pathogenesis of BPH and PCa. In contrast IL-17E interacting with the IL-17BR might have an anti tumor effect[23].

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 the sexually transmitted infections Chlamydia, gonorrhea, or syphilis seems to increase risk. Finally, obesity and elevated blood levels of testosterone may increase the risk for prostate cancer. There is an association between vasectomy and prostate cancer; however, more research is needed to determine if this is a causative relationship[24,25,26,27].

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[28].

Precursor Lesion

Prostate containing cancer have a higher frequency and greater extent of PIN, which is allow often seen in proximity to cancer, studies have shown that many of the molecular changes found in invasive cancer are present in PIN such as rearrangement of ETS gene found in a subset of PIN[29].

Cancer Antigen

A molecular test that detects the presence of cell-associated PCA3 mRNA in fluid massaged from the prostate by the doctor and first-void urinated out has also been under investigation. PCA3 mRNA is expressed almost exclusively by prostate cells and has been shown to be highly over-expressed in prostate cancer cells. The test result is currently reported as a specimen ratio of PCA3 mRNA to PSA mRNA. Although not a replacement for serum PSA level, the PCA3 test is an additional tool to help decide whether, in men suspected of having prostate cancer (especially if an initial biopsy fails to explain the elevated serum PSA), a biopsy/rebiopsy is really needed. The higher the expression of PCA3 in the sample the greater the likelihood of a positive biopsy; i.e., the presence of cancer cells in the prostate. The PCA3 test for the detection of prostate cancer is highly specific and more precise than all other available screening tests for prostate cancer. The PCA3 test is a molecular biology assay that measures the expression of PCA3 (prostate cancer gene 3) mRNA in urine samples. PCA3 is specific to the prostate and is significantly up-regulated in prostatic cancerous cells. The test quantitatively measures PCA3 mRNA as well as PSA mRNA and determines their ratio. High ratios have been shown to be indicative of prostate cancer.[30]

Trace Element Zinc

The prostate is a zinc accumulating citrate producing organ.The protein ZIP1 is responsible for active transport of zinc into prostate cells. Zinc plays an important role to change the metabolism of the cell in order to produce citrate which is an important component of semen and apoptosis. The process of zinc accumulation, alteration of metabolism and citrate production is energy inefficient and prostate cells sacrifice enormous energy (ATP) in order to complete this task. Prostate cancer cells are generally devoid of zinc. This allows the prostate cancer cells to save energy and utilize this energy to grow and spread. The absence of zinc is thought occur via a silencing of gene that produces the transporter protein ZIP1. Zinc level in malignant prostate tissue are 62-75% lower than normal tissue. In addition prostate cancer patients have lower zinc levels in blood compared to healthy controls[31].

Experimental studies have provided evidence that zinc has a protective effect against development and progression of prostate cancer. However, epidemiological studies have reporter inconsistent findings. We evaluated the association between pre diagnositc serum zinc and prostate cancer risk in a cohort of multiethnic population.

This case-control study is nested within the multiethnic Cohort of African Americans, Native Hawaiians, Japanese Americans, Latinos, and whites in Hawaii and California. The analysis included 392 prostate cancer cases and 783 controls matched on age, race/ethnicity, date/time of blood draw and fasting status. Conditional logistic regression was used to estimate odds rations (OR) and 95% confidence intervals (CI).

The mean serum zinc concentrations did not significantly differ between cases (94.9 μg/dl) and controls (93.9 μg/dl). No association was found between serum zinc levels and prostate cancer either overall or by tumor stage/grade. In ethnic specific analyses, positive associations were found in Japanese Americans (OR for the highest vs. the lowest tertile= 2.59, 95% CI: 1.09-6.17) and lotions (OR=2.74, 95% CI:1.05-7.10), whereas no association was observed in African Americans and whites[32].

They found no evidence to support an inverse relationship between serum zinc and prostate cancer risk, and, to the contrary, found a suggestion in the ethnic specific results of a possible increase in risk; however, blood concentrations of zinc may not adequately reflect the levels in prostate tissue. Further study with a larger sample size, and if possible, with assessment of zinc tissue levels, is warranted to confirm these findings.

Another study investigated whether the measurement of serum zinc may improve the detection of prostate cancer (PCa) in men who had total prostate-specific antigen (PSA) levels higher than 4.1 ng/ml. Methods: A mass screening for Pca of 3940 men over 50 years old was undertaken using total serum PSA. Of the 190 men (4.8%) with elevated PSA, 143 (3.6%) underwent a transrectal ultrasonograpy (TRUS)- guided biopsy of the prostate, and 42 men (1% of total and 29.3%) of men undergone biopsy) were found to have cancer. The areas under the receiver operating characteristic curves (ROC-AUC) were used to compare the diagnostic power of cancer detection by means of serum zinc, and free PSA/total PSA ratio (f/t). Results: The men with levels of serum zinc that ranged form 40 ng/mL-60 ng/mL, had an age adjusted odds rations (OR) of 5.0. A cutoff value of 100 μg/mL for serum zinc concentration provided a sensitivity of 90.5% and a specificity of 32.7% in elevated PSA range, and a sensitivity of 93.3% and specificity of 27.1% in gray zone, respectively. In the gray zone ranges of 4.1 ng/mL-10.0 ng/mL, the ROC-AUC for zinc was 73.0% higher than 62.7% of f/t PSA ratio and 56.7% of total PSA. It was concluded that: Pca displays a lower serum zinc concentration. The measurement of zinc levels improves Pca detection in the gray zone compared with the f/t PSA ratio and total PSA[33].

Zinc is a very important trace element and different studies have shown their association with diarrhea, growth retardation and different prostatic lesion including BPH. Serum zinc level was studied in different parts of the world with conflicting results. One study Bangladesh showed gradual progressive increase level of serum zinc in benign, premalignant and malignant lesion of prostate. In BPH the serum zinc level was (mean±SD) 101±26.15, in HGPN 147±20.95 and prostate cancer 139±11.09. This gradual increase in zinc level was statically significant ($p<0.017$) In other study in India researchers found strong correlation between plasma zinc level and various prostatic disease. Out of 80 cases studied (20 normal, 50 BPH, 10 cancers). Serum zinc analyzed by atomic absorption photometry the mean zinc level in normal was 94.5±10.38, BPH, 145.4±9.67 and 59.6±3.08 which were highly statistically significant. Another study measured zinc, vitamin A, albumin, copper and retinoid binding protein content in 27 patients with BPH and 19 patients with prostate cancer. A significantly lower zinc level was found in cancer groups ($p<0.05$)[37].

The present study showed that there is gradual progressive increase level of serum zinc found in benign, premalignant and malignant lesion of prostate. In BPH the serum mean±SD zinc level was 101±26.15, in low grade PIN 116±21.34, high grade PIN 147±20.95 and in frank prostatic carcinoma it was 139±11.09 μgm/dl. This gradual increase in zinc level found in patients having prostatic lesions is statistically significant ($p<0.017$)[34].

Previously two other studies showed the different

type of results. In one study in India the researches found strong correlation between plasma zinc levels and various prostatic diseases. Out of 80 cases studied (20 normal, 50 benign, 10 carcinomatous) serum zinc level analyzed by atomic absorption spectrophotometer the mean±SD plasma zinc level in the normal case was 94.5±10.38, for benign prostatic lesion it was 145.4±9.67, 162.4±2.22, 172±5.27 (78% rise compared to normal patient) in those with fibromusclualr prostate, chronic prostatitis and benign prostatic hyperplasia respectively. Patients with malignancy had a plasma zinc level of 59.6±3.08, (37% fall compared to normal patients). There was highly statistically significant prostatic disease[35].

Another study measured zinc, vitamin A, albumin, copper and retinoid binding protein content in 27 patient with benign prostatic hyperplasia and 19 patients with carcinoma prostate. A significantly lower ($p<0.05$) level of serum zinc was found in cancer groups as well as a significant zinc/vitamin A correlation ($p<0.05$).

Prostatic Specific Antigen (PSA)

Prostate specific antigen (PSA) is an important tool to detect prostate cancer, the most common malignancy of the male throughout the world, yet increased PSA alone does not reflect the presence of prostate cancer. Prostate specific antigen (PSA) is a glycoprotein (molecular weight 33-34,000 Dalton containing 7% carbohydrate by weight) which is kallikrein like serine protease secreted by secretary cells located in the luminal side of the prostatic gland. PSA is immunologically specific for prostatic tissue; it is present it normal, benign, hyperplasic and malignant prostate tissue, in metastatic prostatic carcinoma and also in prostatic fluid and seminal plasma. PSA is not found in any other normal tissue obtained form men or other cancers and also not found in apparently healthy woman or women with cancer. Besides it is functionally and immunologically distractive form prostatic acid Phosphates (PA). PSA test is one of the best ways to screen for prostatic cancer. Many studies in the developed countries consider the normal PSA reference value 0-4ng/ml and >20ng/ml is considered highly elevated. However any abnormal PSA value does not necessarily mean cancer. Other pathological prostatic conditions such as prostatitis and benign prostatic hyperplasia (BPH) may also increase the level of PSA. In such abnormal cases, repeat and serial PSA dilution is advised and a digital per rectal examination, per rectal ultrasonogrpahy or MRI is advised. Recommended age specific upper reference range of serum PSA accepted internationally are:

Age range	PSA level
40-49 years	2.5 ng/ml
50-59 years	3.5 ng/ml
60-69 years	4.5 ng/ml
70-79 years	6.5 ng/ml

PSA is organ specific but not cancer specific. Serum PSA level is less perfect for detection of early prostate cancer but there is little doubt that serial measurements of PSA are of great value in assessing response to therapy. Any rise after surgery indicates recurrence, disseminated disease or residual cancer. The preoperative PSA value is a significant independent clinical factor for relapse after radical prostatectomy and also predictive for larger, more aggressive and more locally advanced tumors. In one study out of 190 men with elevated PSA 143(3.6%) under went trans rectal ultra sonography guided biopsy of the prostate and 42 men (1% of total 29.3% of men undergoing biopsy) were found to have cancer[36].

The rate of rise of PSA in a man having cancer and man without cancer is 0.75ng/l per year. For valid test it requires that there be at least PSA measurement per year over a period of 1.5-2 years. This is because there is substantial short term variability (20%) between PSA measurements. PSA exists in two forms free PSA (minor fraction) and total PSA (major fraction bound to antichymotrypsin and minor fraction bound to alpha 2macrobolobulin. Any remaining PSA is in the free from. The percentage of free PSA (free PSA/total PSA X100) is lower in men with prostate cancer and higher in benign prostatic lesion. It is more so when the total PSA level is in grey zone ie 4-10ng/ml. When free PSA% is above 25%, it indicates low risk or cancer free PSA% lower than 10% are worrisome for cancer. In one study in USA, PSA value over. 1ng/ml showed sensitivity of 93.8% and slightly better performances in men younger than 70 years[37]. Another study in Brazil showed better chances for curing low grade prostate cancer occur in individuals with normal changes for curing low grade prostate cancer occur in individuals with

normal PSA for whom a biopsy is not usually recommended[38].

Mild elevation of PSA in serum is seen in nodular hyperplasia, prostatic, Prostatic infarct, major trauma to the prostate such as needle biopsy, TURP.

But the elevation is transient and resolve with proper treatment. PSA level also rises after recent sexual activity or a cystoscopy. Larger doses of some medications used to treat cancer such as cylophosphamide, diethylstilbestrol, metho trexate can interfere with test results.

Prostate specific antigen (PSA) is an important tool for the diagnosis, Prognosis and follows up of prostatic cancer, the most common malignancy of the male throughout the world. It is safe, reliable, specific, noninvasive test if done properly. However there are many benign, inflammatory and other prostatic conditions which can also give rise to elevated PSA value and thus limits it use. Different methods of estimation may also give rise to variable PSA level. More over the normal reference range may be variable depending on the age, geographic situation, environmental conditions and other factors[39].

High Fatty Diet (HFD)

The current trend towards an increasingly sedentary lifestyle and increasing consumption of high-caloric 'Western style' high-fat diet (HFD) has contributed to the sharply increasing prevalence of metabolic disorders such as obesity and type 2 diabetes in the United States[40]. Presently, obesity is a major heath concern, and according to the Center for Disease Control & Prevention, approximately 40% of the adults in the United States are obese and-20% of children and adolescents are overweight. A closer examination of obesity has revealed that a preferential accumulation of fat in the abdominal region of men is associated with increased risk of urologic complications including urinary incontinence, erectile dysfunction, benign prostatic hyperplasia (BPH) and perhaps cancer[41].

A strong association between fatty acids and prostate diseases has been reported with several intriguing hypothesis. These including mechanisms involving inflammation, oxidative stress, peroxidation of lipids and accumulation of 8-hydroxy-2' -dexyguanosine and increased androgen synthesis driving the growth the growth of the prostate. High-fat diet induces a low-grade chronic inflammatory response, a phenomenon designated as 'metabolically triggered inflammation or meta-inflammation. The direct effects of HFD on the prostate are still nuclear, though it is considered to cause inflammation and oxidative stress through alternation in various signaling pathways that increase the vulnerability of the prostate to numerous diseases[42]. In this review we focused on the role of HFD in the genesis of oxidative stress and intra prostatic inflammation and their influences on signaling pathways that orchestrate various prostate diseases, including cancer[43].

Accumulative evidence suggests that HFD influences prostatic inflammation and plays a significant role in the development of prostatitis, BPH and prostate cancer. HFD induced chronic inflammation plays a key role in the induction of prostate growth & BPH progression while potentiating of oxidative stress may give rise to PIA lesion making the prostate vulnerable to cancer initiation. They suggested that HFD induced association between NF KB & STAT 3 are possibly are signaling mechanism that drives inflammation in the prostate. They speculated that HFD may also orchestrate other pathway that may trigger inflammation of the prostate leading to BPH or cancer. Dietary fat has been reported to affect the secretion and metabolism of androgen[44].

Diagnostic Modalities of Prostate Cancer

It is evident that early diagnosis of prostate cancer is a must for better prognosis, improvement of quality of life, cancer free interval and prevention of metastasis. Apart from clinical, familial and genetic screening the gold standard trio of accurate diagnosis is Digital Per Rectal Examination(DPRE)[45], Ultrasonography of prostate (USG) and Biopsy. These three can accurately diagnose about 95% of the prostatic cancer. Along with these Magnetic Resonance Imaging (MRI) with Ultrasonography (USG) is an effective tool for tumour extension, targeted therapy and prognosis. Among prostatic biopsy Trans Urethral Resection of Prostate(TURP) is commonly performed, however needle core biopsy, open biopsy is also done in selected cases[46,47,48]. Tumour marker PSA estimation, ratio of free and total PSA, Prostatic Acid Phosphatase(PAP) estimation .Among these PSA is a single widely used markers for diagnosis, prognosis of prostate cancer. Other markers like PSMA, p53, BCL2, ERK5, ki67 are important in metastatic disease, recurrence and bears a bad

prognosis.ER and PR is important markers for prognosis and positive cases are good candidate for antihormone therapy[49].

Management of Prostate Cancer

The effective treatment of prostate cancer depends on the patient, its sign & symptoms, stage of the disease and presence or absence of metastasis. Many early diagnosed lowgrade cancer occurring in elderly men, grows slowly can be safely followed with active surveillance or watchful waiting[50]. These include monitoring the tumor for signs of growth or appearance of symptoms. The monitoring processes involve serial PSA, physical examination of prostate, repeated biopsies. The best option of treatment is made on staging, by Gleason sore and the PSA level. Other factors considered are age, general health, metastasis, patients view on potential treatment & their side effects. A combination surgery is useful including surgery, radiation, hormone or chemotherapy. Aggressive cancer requires radical prostatectomy, radiation therapy including (HIFU), oral chemotherapy. Castration is helpful in hormone dependent caner. Palliative treatment is needed in terminal patient for improving quality of life. Pain is the most common symptom in metastasis cancer and cancer borne metastatis can be treated with biophophonates, opiods, palliative radiation therapy. Spinal cord compression due to metastasis is relieved by steroid, surgery, or radiation; other symptoms that may come across through palliative care are fatigue, delirium, lymphedema of scrotum or penis, vomiting, weightloss.[51,52,53,54]

Conclusion

From the review of available literature it is evident that etiopathology of prostate cancer is dependent on diversified factors ranging from genetic predisposition, familial clustering, race, diet, inflammatory cytokines, androgen & its active metabolites, genetic polymorphism, trace element zinc, High fatty diet but none is a conclusive one rather most of these factors are interdependable. Similarly diagnostic value of PSA is also not conclusive as if can be raised in other benign inflammatory even normal condition also. However more research covering wider number of patients in different genetic and familial setting the role of inflammatory cytokines, trace element zinc & PSA level, genetic markers, high fatty diet testosterone & its derivative, molecular markers like BCL2, ERK5,ki 67, e-cadherin are still the major avenues for further research on prostate cancer, the outcome of which in future will be able to define better diagnostic, preventive & curative strategies for prostate cancer patients of the world.

Acknowledgement

We have gone through different website, Wikipedia, some text books, research paper for preparation of this review article. This is gratefully acknowledged.

Reference

1. Robbins and cotran. Pathologic Basis of Disease. Editor. Kumar V. Abbas AK, FAusto N, Aster JC. Saunders Elsevier, 2010. 996-98.
2. Hankey BF. "Cancer Surveillance series: interpreting trends in prostate cancer- part I: Evidence of the effects of screening in recent prostate cancer incidence, mortality, and survival rates. J Natl Cancer Inst 1999; 91 (12): 1017-24.
3. Breslow N. "Latent carcinoma of prostate at autopsy in seven areas. The international Agency for Research on Cancer, Lyons, France". Int J Cancer 1977; 20 (5): 680-8.
4. Zeegers MP, Jellema A, Ostrer H. "Empiric risk of prostate carcinoma for relatives of patients with prostate carcinoma: a meta-analysis". Cancer 2003; 97 (8): 1894-903.
5. Friendenreich CM, Neilson HK, Lynch BM. "State of the epidemiological evidence on physical activity and cancer prevention". European journal of cancer (Oxfored, England: 2010): 2593-604.
6. Goldestein AS, Huang J, Guo C, Garraway IP, Witte ON. "Indetificaiton of cell of origin for human prostate cancer". Science 2010;329 (5991): 568-71.
7. Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC. "Family history and the risk of prostate cancer". Prostate 1990;17(4): 337-47.
8. Gallagher RP, Fleshner N. "Prostate cancer: 3. Individual risk factors" (PDF). CMAJ 1998; 159(7): 807-13.
9. Hoffman RM. "Racial and ethnic differences in advanced-stage prostate cancer: the prostate cancer outcomes study". J. Natl. Cancer Inst. 2001; 93(5): 388-95.

10. Lichtenstein P. "Environmental and heritable factors in the causation of cancer-analyses of cohorts of twins form Sweden, Denmarks, and Finland". N.Engl.J. Med. 2000; 343(2): 78-85.

11. Struewing JP."The risk of cancer associated with specific mutatins of BRCA1 and BRCA2 among Ashkenazi Jews. N. Engl. J. Med1997; 336 (20): 1401-8.

12. Eeles RA. "Multiple newly indentified loci associated with prostate cancer susceptibility". Nature Genetics 2008; 40(3): 316-21.

13. Thomas G. "Multiple loci identified in agenome-side association study of prostate cancer". Nature Genetics 2008; 40 (3): 310-5.

14. Whitaker HC. Vickers, Andrew, ed. "The rs10993994 risk allele for prostate cancer results in clinically relevant chages in microseminoprotein-beta expression in tissue and urine". PLoS ONE 2010; 5 (10): e13363.

15. Leav I, Pleascia J, Goel HL, Li J, Jiang Z, Cohen RJ, Languino LR, Altieri DC." Cytoprotective Mitochondrial Chaperone TRAP-1 As a Novel Molecular Target in Localized and Metastatic Prostate Cancer." Am. J. Pathol. 2010; 176(1):393-401.

16. Wigle DT, Turner MC; Gomes J, Parent ME. "Role of hormonal and other afctors in human prostate cancer". Journal of Toxicology and Environemntal health. Part B, Critical Reviews 2008; 11(3-4): 24259.

17. Qin X. "Folic acid supllementation and cancer risk: A meta-analysis of randomized controlled trials". International Journal of Cancer. Journal International Du Cancer 2013; 133 (5): 1033-41.

18. Jacobs EJ, Rodriguez C, Mondul AM, Connell CJ, Henley SJ, Calle EE, inflammatory drugs and prostate cancer incidence." J. Natl. Cancer Inst. 97(13: 975-80.

19. Shannon J. "Stains and prostate cancer risk: a case -control study". Am. J, Epidemiol. 2005; 162 (4): 318-25.

20. Dennis LK, Dawson DV. "Meta-analysis of measures of sexual activity and prostate cancer." Epidemilogy (Cambridge, Mass.)2010; 13 (1): 72-9.

21. Rosenblatt KA. Wicklund KG. Stanford JL. "Sexual factos and the risk of prostate cancer". American Journal of Epidemilogy 2010; 153 (12): 1152-8.

22. Sarma AV. "Sexual behavior, sexually transmitted diseases and prostatits: the risk of prostate cancer in black men.". The Journal of Urology2006; 176 (3):

23. Liu Y, et al Expression of IL-17A, E, and F and Their Receptor in Human Prostatic Cancer: Comparison With Benign Prostatic Hyperplaisa. Prostate. 2015 Dec; 75 (16): 1844-56.

24. Dennis LK, Lynch CF, Torner JC. "Epidemiologic associatin between prostatis and prostate cancer." Urology 2010; 60 (1): 78-83.

25. Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. "Overweight obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults" N. Engl. J. Med. 2003; 348 (17): 1625-38.

26. Gann PH, Hennekens CH, Ma J, Longcope C, Stamper MJ."Prospective study of sex hormone levels and risk of prostate cancer". J. Natl. Cancer Inst. 1996; 88 (16): 1118-26).

27. Journal-molecular cancer, review, 2006 5:17,

28. Park SY, Wilkens L.R. Morris J.S, Henderson B.E, Kolonel L. N. Serum zinc and prostate cancer risk in a nested case-control study: the Multiethnic Cohort. Prostate. 2013 February 15;73(3): 261-266,

29. Li X-M, et al Measurement of serum zinc improves prostate cancer detection efficiency in patients with PSA levels between 4 ng/mL and 10 ng/mL. Asian J androl 2005: 7 (3): 323-328

30. Banudavi S, Senthikumar K, Sharmila G, Arunkumar R, Vijayababu MR; Arunakaran J, Effect of Zinc onj regulation of insulin like growth factor signaling in human androgen independent prostate cancer cells. Clin Chim Acta. 2010 Feb; 411(3-4): 172-8.

31. htt;//wwwpca3/en/healthcare

32. Banudavi S, et al Chemopreventive effects of zinc on prostate carcinogentesies induced by N-methy-N-Nitrosourea and Testeterone in adult male Sprague-Dawley rats. J Cancer Res Clin Concol. 2010 June 16.

33. Whelan P, Walker BE, Kelleher J. Zinc, Vitamin A and prostate cancer. Urol Res. 1989 Oct; 55(5): 525-8.

34. Rahaman MT, Sajani TT, Sultana R, Choudhury SR, Siddiqui MMR. Prostate specific Antigen(PSA): Normal reference value in Bangladeshi Male, a Retrospective PSA analysis of 765 male, AKMMCJ 2014; 5(1); 19-23

35. Li XMN, Zhang L, Li J, et al. measurement of serum zinc improves prostate cancer detection efficiency in patients with PSA levels between 4ng/mL and 10 ng/mL. Asian J Androl. 2005; 7:323-8.

36. Thomson IM, Ankerst DP, Chi C. Operating characteristics of PSA in men with an initaila level of 3.0 ng/ml or loer. JAMA. 2005 Jul 6; 294(1): 66-70.

37. Dall' oglio MF. Survival of patients with prostate cancer and normal PSA level treated by radical prostatedctomy. Int Braz J Urol. 2005 May-Jun; 31(3): 222-27.

38. Shah B, Sha D, Xie D, Mohler ER 3rd , Berger JS. The relationship between diabetes, metabolic syndrome, and platelet activity as measured by mean platelet volume: the National Health and Nutrition Examination Survery, 1999-2004. Diabetes Care. 2012; 35:1074-1078.

39. Wang S, Mao Q, Lin Y, Wu J, Wang X, Zheng X. Body mass index and risk of BPH: a meta-analysis. Prostae cancer prostatic Dis. 2012;15:265-272.

40. Nandeesha H. Benign prostaic hyperplasia: dietary and metabolic risk factos. Int Urol Nephol. 2008; 40: 649-656.

41. Powell K Obesity: the two faces of fat. Nature. 2007; 447:525-527.

42. Christensen JH, Fabrin K, Borup K, Barder N, Poulsen J. Prostae tissue and keukocyte levels of n-3 polyunsatureated fatty acids in men with benign prostate hyplerplasia for cancer. BJU int. 2006;97:270-273.

43. Savas M, Verit A, Ciftei H, yeni E, Aktan E, Topal U. Oxidative Stress in BPH. JNMAJ Nepal Med Assoc. 2009; 48:41-45.

44. Gromadzka-ostrowska J. Effects of dietary fat on androgen secretion and metabolism. Reprod Biol. 2006; 6 Suppl 2:13-20.

45. http://ww.cancer.org/ Healty/ FindCancerEarly/ CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection ocancerAmericanCancer.Society American Cancer Society Guidelines for the early detection of cancer Cited: September 2011.

46. Bonekamp D, Jacobs MA, El-Khouli R, Stoianovici D, Macura KJ (May-June 2011)."Advancement in MR imaging of the prostate. From Diagnosis to Interventions. Radiographics 31 (3 Suppl): 677-703.

47. Barentsz JO, Richenberg J. ESUR prostate MR guidelines 2012". European Radiology2012; 22 (4):746-57.

48. Natarajan S. "Clincial application of a 3D ultrasound guided prostate biopsy system" Urol Ocol 2011; 29 (3 suppl): 334-42.

49. Srikumar Chakravarthi, David Low Wee Yang, Thanikachalam P, Nagaraja HS, Nadeem Irfan Bukhari, "Assessment of proliferative index and its associaitn with Ki-67 antigen molecule expression in nodular hyperplasia of prostate". Indian Journal of Science & Technology 2009; 2 (8): 1-4.

50. "Prostate Cancer Treatment (PDQ®)". National Cancer Institute. 2014-04-08. Retrieved 1 July 2014.

51. Lu-Yao GL. "Outcomes of Localized Prostate Cancer Following Conservative Management." The Journal of the American Medical Association 2009; 302(11): 1202-09.

52. Mongiat-Artus P. "[Recommendations for the treatment of prostate cancer in the elderly man: A study by the oncology committee of the French association of urology.]" Prog. Urol. (in French)2009; 19(11): 810-7.

53. Picard JC, Golshayan AR, Marshall DT, Opfermann KJ, Keane TE. "The multi-disciplinary management of high -risk prostate cancer" Urol. Oncol. 2009; 30 (1) :3-15.

54. Mohan R, Schellhammer PF. "Treatment options for localized prostate cancer." Am Fam Physician 2011; 84 (4): 413-20.

35. Li XMN, Zhang L, Li J, et al. measurement of serum zinc improves prostate cancer detection efficiency in patients with PSA levels between 4ng/mL and 10 ng/mL. Asian J Androl. 2005; 7:323-8.

36. Thomson IM, Ankerst DP, Chi C. Operating characteristics of PSA in men with an initaila level of 3.0 ng/ml or loer. JAMA. 2005 Jul 6; 294(1): 66-70.

37. Dall' oglio MF. Survival of patients with prostate cancer and normal PSA level treated by radical prostatedctomy. Int Braz J Urol. 2005 May-Jun; 31(3): 222-27.

38. Shah B, Sha D, Xie D, Mohler ER 3rd , Berger JS. The relationship between diabetes, metabolic syndrome, and platelet activity as measured by mean platelet volume: the National Health and Nutrition Examination Survery, 1999-2004. Diabetes Care. 2012; 35:1074-1078.

39. Wang S, Mao Q, Lin Y, Wu J, Wang X, Zheng X. Body mass index and risk of BPH: a meta-analysis. Prostae cancer prostatic Dis. 2012;15:265-272.

40. Nandeesha H. Benign prostaic hyperplasia: dietary and metabolic risk factos. Int Urol Nephol. 2008; 40: 649-656.

41. Powell K Obesity: the two faces of fat. Nature. 2007; 447:525-527.

42. Christensen JH, Fabrin K, Borup K, Barder N, Poulsen J. Prostae tissue and keukocyte levels of n-3 polyunsatureated fatty acids in men with benign prostate hyplerplasia for cancer. BJU int. 2006;97:270-273.

43. Savas M, Verit A, Ciftei H, yeni E, Aktan E, Topal U. Oxidative Stress in BPH. JNMAJ Nepal Med Assoc. 2009; 48:41-45.

44. Gromadzka-ostrowska J. Effects of dietary fat on androgen secretion and metabolism. Reprod Biol. 2006; 6 Suppl 2:13-20.

45. http://ww.cancer.org/ Healty/ FindCancerEarly/ CancerScreeningGuidelines/american-cancer-society-guidelines-for-the-early-detection ocancerAmericanCancer.Society American Cancer Society Guidelines for the early detection of cancer Cited: September 2011.

46. Bonekamp D, Jacobs MA, El-Khouli R, Stoianovici D, Macura KJ (May-June 2011)."Advancement in MR imaging of the prostate. From Diagnosis to Interventions. Radiographics 31 (3 Suppl): 677-703.

47. Barentsz JO, Richenberg J. ESUR prostate MR guidelines 2012". European Radiology2012; 22 (4):746-57.

48. Natarajan S. "Clincial application of a 3D ultrasound guided prostate biopsy system" Urol Ocol 2011; 29 (3 suppl): 334-42.

49. Srikumar Chakravarthi, David Low Wee Yang, Thanikachalam P, Nagaraja HS, Nadeem Irfan Bukhari, "Assessment of proliferative index and its associaitn with Ki-67 antigen molecule expression in nodular hyperplasia of prostate". Indian Journal of Science & Technology 2009; 2 (8): 1-4.

50. "Prostate Cancer Treatment (PDQ®)". National Cancer Institute. 2014-04-08. Retrieved 1 July 2014.

51. Lu-Yao GL. "Outcomes of Localized Prostate Cancer Following Conservative Management." The Journal of the American Medical Association 2009; 302(11): 1202-09.

52. Mongiat-Artus P. "[Recommendations for the treatment of prostate cancer in the elderly man: A study by the oncology committee of the French association of urology.]" Prog. Urol. (in French)2009; 19(11): 810-7.

53. Picard JC, Golshayan AR, Marshall DT, Opfermann KJ, Keane TE. "The multi-disciplinary management of high -risk prostate cancer" Urol. Oncol. 2009; 30 (1) :3-15.

54. Mohan R, Schellhammer PF. "Treatment options for localized prostate cancer." Am Fam Physician 2011; 84 (4): 413-20.