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ROLE OF TRACE ELEMENTS AND ANTIOXIDANTS IN THE PATIENTS OF PROSTATE CANCER

Sunil Kumar[1]*, Shikhaa Mahajan[2], Suvarana Prasad[3], Neeru Bhaskar[4], Shilpa Rattan[1], Rooma Devi[1]

[1]M.Sc Student, Department of Biochemistry, M.M.I.M.S.R, Mullana, Ambala, Haryana, India.

[2]Associate Professor, Department of Biochemistry, M.M.I.M.S.R, Mullana, Ambala, Haryana, India.

[3]Professor and Head, Department of Biochemistry, M.M.I.M.S.R, Mullana, Ambala, Haryana, India.

[4]Professor and Head, Department of Biochemistry, Adesh Medical College and Hospital, Ambala, Haryana, India.

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***Corresponding Author**
Sunil Kumar
M.Sc Student, Department of Biochemistry, M.M.I.M.S.R, Mullana, Ambala, Haryana, India.

ABSTRACT

Cancer is defined as a relatively autonomous growth of tissues. The cells which divide abnormally having uncontrolled growth. The agent that is responsible for causing cancer is termed as carcinogen and the process of cancer development is referred to as carcinogenesis and the agents which increases the frequency with which normal cells are converted to transformed cells are said to be carcinogenic. In addition to being most commonly encountered cancer among men, prostate cancer is second leading cause of death among cancers, following lung cancer Some trace elements like zinc, iron and copper play important role in the development or proliferation of tumor cell. It has been illustrated that in case of prostate cancer, cellular level of Zinc decreases, in contrast of which cellular level of copper and iron increases. Alteration in the levels of these trace elements causes increased growth and proliferation of the cells, which on progression acquire malignant properties. And thus they play an indirect role in development of prostate cancer. Thus variation in the levels of these trace elements may have a causative effect on prostate cancer.

KEYWORDS: Prostate Cancer, Trace Element- Zinc(Zn), Iron(Fe), Copper(Cu), Reactive Oxygen Species(ROS), Antioxidant.

INTRODUCTION

Cancer is defined as a relatively autonomous growth of tissues. The cells which divide abnormally having uncontrolled growth and are capable of invading other tissues. These cells may extend to other organs via help of blood and lymph. The responsible agent, causing cancer is termed as carcinogen and the development process of cancer is referred to as carcinogenesis and the agents which enhances the frequency due to which normal cells are converted to transformed cells are known to be carcinogenic.[1] In 2013 about 174,100 deaths were caused due to cancer because of tobacco use, excess weight and poor nutrition in accordance to American Cancer Society.[2]

Prostate cancer is the most frequently diagnosed non-cutaneous malignancy in males, statistics from the American Cancer Society project 186,000 new cases and 28,000 deaths in US for the year 2008.[3]

In addition to being most commonly encountered cancer among men, prostate cancer is the second leading cause of death among cancers, following lung cancer.[4] In recent years, increasing screening studies and use of prostate specific antigen as a marker of disease resulted in diagnosis at early stage.

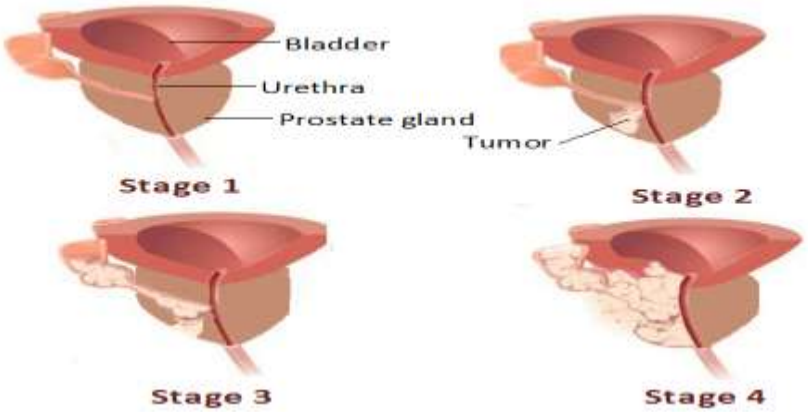

Fig.1 Diagram showing the stages of prostate cancer

Genetic and environmental factors, dietary habits, smoking, alcohol consumption, sexual and physical activity, hormones and body size have an associated impact on increased risk of prostate cancer. These factors play a vital role in the development or proliferation of tumor

cells either via directly by activating carcinogenic pathways or indirectly by inducing susceptibility in generelated diseases. These indirect mechanisms shows that carcinogenic agents are involved in either metabolic regulation or hormonal regulation.[5]

Various epidemiological studies given that increased contact to heavy metals have severe toxic and carcinogenic impact on both humans and animals. Heavy metals such as lead, cobalt and iron are potential carcinogens for humans which is fairly proven by epidemiological evidences.[6]

It has been thought that environmental and occupational exposure to these metals is primary reason for metal related cancers as well as increased cancer risk. It was observed that cadmium has a strong contribution to mortality due to prostate cancer.[7] Studies on concentrations of trace elements play role to improve our insight about various processes occurring.

It is well known that heavy metals are essential while some have toxic as well as carcinogenic effects on humans.[8] Insufficiency of certain trace elements has been considered as risk factor for prostate cancer. Studies based upon concentration of these trace metals in human play an important role in better understanding of metabolic and biochemical processes occurring in cells.

Instability (overabundance or deficiency) in the composition of these trace metals can play a critical role in cancer biology, on the other hand, their precise role in initiation, promotion and inhibition of carcinogenic is still undefined.[9]

Prostate cancer is chiefly a disease of aging and most of the cases are men over the age of 55. As a result, progressive inherent or acquired changes in cellular metabolism occurring over the years may play a very important role in the development of this disease. A no. of factors like diet, environmental carcinogens and other inflammatory diseases have also been found to be linked with an increased risk of prostate cancer.[10]

Axioms of relationships of cellular activity, cellular metabolism, and malignancy

The following are important generalizations that we consider to be axiomatic.

1. In every cell, the existing cellular intermediary metabolism provides the bioenergetics, synthetic and catabolic requirements those are essential for the manifestation of the cell's current activities that is function, growth and proliferation.

2. When there occur any change in cell's activity, there must be consistent adjustment in any newly established bioenergetics/synthetic/catabolic requirement.

3. Malignant cells have a parasitic property. They have no specific function other than the activities essential for their generational propagation that is growth and proliferation, which takes place at the expense of their host.

4. Malignant cells are originate from normal cells that have undergone a genetic transformation to neoplastic cell phenotype that is endowed with malignant potential.

5. Manifestation of malignant potential of the neoplastic cell necessitates alteration in its metabolism (.i.e. a metabolic transformation) to provide the bioenegetics/synthetic requirement of malignancy.

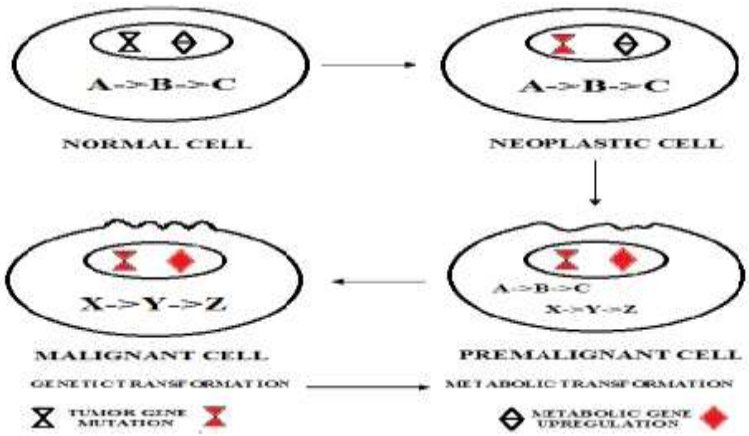

Fig.2: Diagram showing the process of development from normal cell to malignant cell.

6. Absence of the metabolic transformation causes incomplete progression of neoplastic cell toward malignancy. On the contrary, the metabolic transformation, in the absence of the genetic transformation to a neoplastic malignant cell, will not cause malignancy.

7. Common to all malignant cells is the metabolic requirement for de novo lipogenesis/cholesterogenesis, for membraneogenesis, which is necessary for their proliferative existance.[11]

For a better understanding about the association among prostate cancer and metals, it may be significant to make out differences in homeostasis of trace elements linking two common diseases of aging prostate that is benign prostatic hyperplasia (BPH) and prostate cancer (PCa). As both of these conditions have dissimilar histopathology and clinical activities,

different metabolic alterations should report for these pathological processes. Variation in the levels of certain trace elements mainly zinc have been identified in prostate cancer.[9] Thus, in addition to absolute tissue levels of different metals, their ratios and reciprocal co-relation may help in understanding the complex metabolic dynamics of trace elements in prostate cancer. Only isolated studies have observed this complex interrelationship or ratio of the trace elements in tissue having prostate cancer. The understanding of distributed homeostasis of trace elements in cancerous tissue may have significant role in development of elements related to preventive or therapeutic intervention for prostate cancer.[12]

It has been studied that serum levels of trace elements like Fe, Cu, Mg and Pd ($p<0.05$) increases, whereas serum level of Mn and Zn level decreases in case of prostate cancer.

ZINC AND PROSTATE CANCER

Zinc plays an anti-carcinogenic role via structural stabilization of deoxyribonucleic acid (DNA), ribonucleic acid (RNA) and ribosome. Zinc is valuable for the functions of many transcription factors and proteins involved in the recognition of specific DNA sequences and regulation of gene transcription.

Even though the association among dietary zinc or zinc supplements intake and risk of prostate cancer are still blurred and unconvincing, a emergent body of evidence supports that high zinc levels in the prostate are essential for prostate health and protect prostate cells from malignancies. The possible mechanisms include the effects of zinc on the inhibition of terminal oxidation, induction of mitochondrial apoptogenic, suppression of NFκB activity and maintenance of DNA integrity. Zinc plays important role in maintenance of DNA integrity in normal prostate epithelial cells (PrEC) by modulating the expression and activity of DNA repair and damage response proteins, especially p53. Likewise, because of the importance of zinc homeostasis to prostate health, a number of zinc transporters have been identified as tumor suppressors in the prostate. Since experimental animal studies are inadequate compared to the in vitro studies, future studies on the effects of zinc status on prostate function in normal animals or prostate cancer models would be helpful. Moreover, searching for good zinc biomarker would significantly help performing in vivo studies.[13]

Several large observational cohort studies have found that plasma zinc concentrations or dietary zinc intakes are inversely associated with cancer or all cause mortality risks.[13] Specifically for prostate cancer, a case-control study done by Kristal AR et al. observed that

the usage of individual zinc supplements were associated with reduced prostate cancer.[14] Recently the Vitamins And Lifestyle (VITAL) cohort study observed that although long term usage of zinc supplements was not coupled with reduced risk of prostate cancer, it was associated with reduced risk of advance prostate cancer. Furthermore, a study done in South Carolina found that area with minor soil zinc content had higher prostate cancer rate.[13]

Several mechanisms by which zinc may protect prostate cells from malignancies have been proposed.

ZINC AS AN INHIBITOR TO M-ACONITASE ACTIVITY

Prostate epithelial cells naturally have high aerobic glycolysis, low respiration rates and high citrate secretion and high zinc concentrations in the prostate may be required for these properties. Costello et al have concluded that in the prostate epithelial cells zinc characteristically reduces the mitochondrial aconitase activity and causes the inhibition of terminal oxidation in the electron transport chain. The inhibitory action on m-aconitase by zinc may contribute to the properties of high citrate secretion and low respiration in prostate.[13] Zinc depletion in the prostate may remove the inhibitory effects on terminal oxidation and citrate oxidation, and cellular respiration increases. Thus, if cellular zinc levels decreases in the prostate epithelial cells, consequent active release of aconitase can cause increased cell respiration which favors cell growth and differentiation, these cells are enable to acquire malignant properties.[15]

APOPTOGENIC EFFECTS AND AS A PROTECTOR FOR DNA INTEGRITY

Depletion in zinc levels induces apoptosis in living cells. There are some possible mechanisms which includes, activation of caspases, induction of the intrinsic pathway of apoptosis and defects in growth factor signaling pathways.[16] On the other hand, contrary effects of zinc on the prostate is the cells growth; zinc in the prostate provokes mitochondrial apoptogenesis thereby reducing cellular growth. Costello et al. observed the exposure effect of physiological zinc levels on apoptogenesis of mitochondria in three human cancer cell lines, PC-3, HPR-1 and BPH.[17] They found that zinc only induced apoptosis in PC-3 and BPH both of which maintained the capability of highly accumulating intracellular zinc levels, though not in HPR-1 that lost its ability of zinc accumulation. Effects of zinc on apoptosis in the prostate cancer cells may be exerted via modulation of the expression of Bax, its binding capability with mitochondrial membrane[13] and subsequent discharge of cytochrome c from mitochondria.[17] Studies made by Kolenko VM et al recommended that zinc can cause the

suppression of prostatic tumor progress by lessening the activity of NFκB and the successive expression of angiogenic andpro-metastatic cytokines VEGF, IL-6 and IL-8.[18]

ZINC PROTECTS DNA INTEGRITY IN THE PROSTATE

Zinc may have inhibitory effect on terminal oxidation of prostate mitochondria, zinc depletion in the may not only remove the its antioxidant effect, but may also eliminate the inhibitory effect of zinc on terminal oxidation thereby increasing the free radicals generation. That is why, elevated zinc levels may defend the prostate form oxidative stress by suppressing the generation of free radicals and promoting the removal of free radicals.[13]

Furthermore, because of the significance of zinc homeostasis to prostate health, identification of numerous zinc transporters have been done as tumor suppressors in the prostate.

In case of a normal prostate, higher zinc concentration in the tissues causes a block in Krebs cycle and accumulation of citrate in the prostatic fluid. Hence, normal prostate glandular epithelial cells have low respiration which causes low terminal oxidation, energy inefficiency and most likely generate a reduced amount of ROS.[19]

Zinc often shows protective effect against free-radical injury. According to prior studies, serum Zn concentrations were decreased in patients having cervical, bladder, ovarian and renal cancer.[20] It is acknowledged that concentration of zinc is significantly higher in prostate gland when it is compared to other human body tissues.[21] Furthermore, evidences which indicate that Zn concentration is found to be elevated in benign prostatic hyperplasia when it is compared with normal prostatic tissue and there is found a decrease in prostate cancer.[22] On the other hand, mechanism underlying accumulation of Zn in prostate tissue and its significance is still indefinite. Nonetheless, it is recommended that insufficiency of Zn can act as a risk factor for prostate cancer.[23] Now the recent studies demonstrated that there was a significant decrease in concentration of Zn in the prostatic cancer patients in comparison to the controls.

IRON AND PROSTATE CANCER

Though Fe is a necessary key element and is involved in several biological processes ranging from electron transport to ATP production, DNA and heme generation. Yet, tissue having low Fe concentration is not expected at tissues surrounding a tumor, as literature proposed that extreme Fe concentration is coupled to unfavorable effects due to oxidative stress

induction. Quite a few epidemiological and clinical trials demonstrated that low levels of Fe could cause a decreased cancer occurrence including prostate cancer.[24]

Excessive load of iron can increases risk of prostate cancer via stimulating the oxidative stress and endogenous pro- and antioxidant potential, as myeloperoxidase (MPO), and manganese superoxide dismutase (MnSOD) can alter these links.[25]

A constant production of reactive oxygen species (ROS) in the cells is stimulated by carcinogens, environmental toxicants, infection, nutrients, inflammation and mitochondrial respiration and is an expected aging consequence in aerobic organisms. Elevation of free radicals related to age has been related to increased cancer risk. Prostate cancers is a progressive disease, oxidative stress to tumor cells can cause constant genetic variations which may direct to carcinogenesis. Recent studies support the role of ROS in prostate cancer with human variation in response to ROS damage and repair exacerbate ROS-related DNA damage in the prostate. Extreme intake of Fe from either food or nutritional supplement can serve as a resource of ROS, even though, the epidemiologic studies results have been contradictory. Fe, a metal of major prevalence in the living system, reacts easily with hydrogen peroxide and catalyzes the highly reactive hydroxyl radicals generation, thus causes increase in oxidative stress, and as a result increases concentrations of free iron.[26] The modified oxidative stress by dietary intake of iron may be because of antioxidant and endogenous oxidant capabilities which may act to provide a synchronized system of protection against ROS accumulation and oxidative damage. Manganese superoxide dismutase (MnSOD) have a significant role in developing of oxidative stress due to increased iron intake. The iron–sulfur cluster of various enzymes can be attacked by superoxide radicals releasing free iron (ferric iron), that may consequently react with hydrogen peroxide to generate increased levels of ROS.[27] MnSOD catalyzes the translation of superoxide radicals to hydrogen peroxide, and an MnSODvaline to alanine substitution at amino acid _9 which permit MnSOD uptake much efficiently in mitochondria and may result in higher activity compared with the Ala allele.[28] Now its contribution toward hydrogen peroxide production, the MnSODAla variant has been linked with prostate, bladder and breast[29] cancers risk, but the associations is not observed by all the studies.[30] A lysosomal enzyme Myeloperoxidase (MPO) located in monocytes and neutrophills assists the conversion of hydrogen peroxide to hypochlorous acid, which is recognized as a cytotoxic antimicrobial agent. An MPO _463 G to A substitution situated in the consent binding site of a SP1

transcription factor in the 5# upstream region,[30] confers transcriptional activation to a lower extent than the _463 G common allele in vitro, because of binding site distribution.[31] Hypochlorous acid reacts with other biological molecules so as to cause secondary oxidation products generation, which in synergy with Fe increases oxidative damage.[32] Specified the iron as a pro-oxidant to excite DNA damage and lead to subsequent carcinogenesis. It is a study on estimated associations among dietary iron intake and risk of prostate cancer as well as clinically destructive prostate cancer. Even though, it has been reported previously that there are no major effects with regards to MnSOD polymorphism and prostate cancer risk in the Carotene and Retinol Efficacy Trial (CARET) cohort,[33] it is evaluated, whether genetic polymorphisms is known to affect the MnSOD activity and MPO modified potential relations among iron intake as a source of ROS and risk of prostate cancer.

In accordance to some observations the association between iron intake and prostate cancer risk were modified by dietary antioxidants intake, while previous studies have shown petite evidence for an association among dietary antioxidants and risk of prostate cancer.[34]

Now it is suggested that these associations are significantly modified by endogenous capacity to hold an oxidative load, and the other nutrients such as antioxidants, that when inhaled in lower amounts, favors to further increase the risk related to iron-association.[25]

On the other,[35] reported results indicate that increased iron stores were not related with prostate cancer. It may be likely that increased load of Fe can predispose to prostate cancer, other than decreased iron stores may be because of cancer development. Regulation of total iron is highly complex in the body. There are several metabolic control points which can eliminate least amounts of iron in physiological manner so as to avoid iron overload. The study results indicated a significant difference in serum Fe levels between patient and control groups. Interleukin-6 (IL-6)-hepcidin axis induced regulation of iron metabolism is one of the mechanisms which clarify this finding of low iron levels in patients having poor prognosis. The prostate cancer subjects with poor prognosis have higher levels of circulating IL-6.[36] It is known that the cytokine results in production of hepcidin in liver.[37] One of the principal roles of hepcidin is to decrease Fe export from intestinal epithelial and iron storing macrophages to circulation.[38] Further observation is that low level of iron in prostatic micro environment can previously be present before onset of prostate cancer leading to more violent outcomes. The latter hypothesis can imply significant consequences in treatment and chemo preventive activity related terms.

COPPER AND PROSTATE CANCER

Copper, an essential trace element for every living organism. The amount of copper in an organism is specifically regulated. A no. of cancer types have shown elevated levels of copper including prostate. Consistently, angiogenesis (the formation and differentiation of blood vessels) play a vital role tumor growth, invasion, and metastasis. Indeed, its molecular processes of requires copper, as an essential cofactor.

The prostate cancer patients are observed with elevated serum copper levels due to cupric ions which may inhibit the generation of singlet oxygen, this is of a particular physiological significance, because of its capability to cross cell membrane and high activity towards a variety of biomolecules. Increased Cu levels in serum of prostate cancer patients may be due to the discharge of cytosolic and nuclear copper into the extracellular compartment.[39] Even though, instead of being essential element to every individual, high Cu levels may lead to cancer by causing DNA damage via toxic free radicals.[40]

An additional attractive tumor specific characteristic is high levels of copper found in many types of human cancers including prostate, breast, colon, lung, and brain.[41] The molecular procedure of angiogenesis includes the requirement of copper, but not other trace metals, as an essential cofactor, tumor cytokine production induced endothelial growth (*i.e.*, vasoendothelial growth factor), extracellular matrix proteins degradation by metalloproteinases, and migration of endothelial cells mediated by intergrins.[42]

It has been observed that cancerous cells are show more sensitivity toward proteasome inhibition as compared to normal cells.[43] It is now assumed that an inactive ligand can bind with elevated copper in tumor tissues thus leading to a complex formation which is able to inhibit proteasome activity. Afterwards the binding of ligand with endogenous tumor cellular copper, the formed complex would cause proteasome inhibition, resulting in inhibition of the processes of angiogenesis in tumor tissues thus inducing apoptosis in the tumor cells.[42]

It is to describes the synthesis and structural characterization of novel copper quinoline-2-carboxaldehyde complexes. These synthesized Schiff base compounds are different with respect to their various functional groups attached to the quinoline ligand. The cytotoxic activity is also affected by the nature of the side chains at position C2, and our in vitro findings show that these compounds have high anti proliferative activity against prostate cancer cell lines PC-3 and LNCaP. Furthermore, these compounds are capable of inducing

apoptosis in prostate cancer cells without oxidative stress, as indicated by the H2O2 assay. The highest cytotoxic activity was observed for the copper complex **2** that inhibited chymotrypsin-like proteasome activity in intact prostate LNCaP cancer cells. Some studies strongly suggest that the strategies adopted in modifying the parent ligand with introduction of cytotoxic thiocarbonyl side chains enhance the antitumor property with subsequent lowering of IC50 values. Furthermore, the Schiff base copper complex **2** can inhibit the proteasome and induce apoptosis as shown by PARP cleavage in prostate tumor LNCaP cells. In conclusion, some studies indicate that introduction of a thiocarbonyl group at the C2 position in the quinoline moiety upon copper complexation leads to generation of a potent anticancer agent that can be used for targeting the ubiquitin-proteasome pathway for the treatment of prostate cancer.[44]

ANTIOXIDANTS AND PROSTATE CANCER

Hydroxyl radicals, peroxides and superoxides are ROS that are generated during everyday metabolic processes in a normal cell. ROS, generated either endogenously (mitochondria, metabolic process, inflammation etc.) or from external sources, play a vital role in regulating several biologic phenomena. While ROS generation has traditionally been associated with tissue injury or DNA damage, mitochondrial DNA mutations and cellular proliferation. An essential role for increased ROS generation in several cellular processes associated with neoplastic transformation and aberrant growth and proliferation. Recent studies have indicated that oxidative stress is higher in the epithelium of prostate cancer patients than men without the disease, the association of ROS mediated oxidative stress and prostate cancer risk remains to be elucidated. Theories abound regarding their role in initiation of prostate cancer, and include but are not limited to, failure of antioxidant defense mechanism (due to persistent oxidative stress that leads to inherited and acquired defects in the defense system), mtDNA mutations, chronic inflammation, defective DNA repair mechanism and apoptosis etc., finally leading to the development of prostate cancer. Thus, many of the factors that are associated with prostate cancer like aging, imbalance of androgens, antioxidant system, dietary fat, and pre malignant conditions like high grade prostate intraepithelial neoplasia etc. may be linked to oxidative stress.[45]

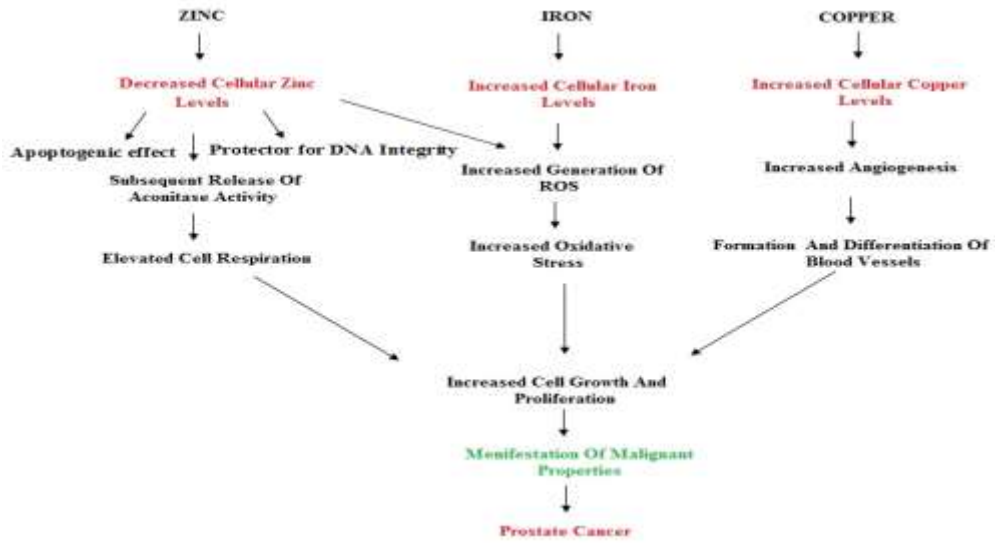

Fig. 3 Indicating the role of trace elements in prostate cancer

CONCLUSION

The alteration in the levels of trace elements e.g. zinc, iron and copper causes prostate cancer. The levels of zinc decreases while the levels of iron and copper increases. Excessive production of ROS or inadequacy in a normal cell's antioxidant defense system (or both) can cause the cell to experience oxidative stress and the increased ROS may play a broader role in cellular processes associated with initiation and development of many cancers including Prostate Cancer. It is now Hypothesized that trace elements do have a immense effect on prostate cancer. Which is clearly described in Fig. 3. In addition ROS also causes prostate cancer.

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