PAKISTAN JOURNAL OF UROLOGY

Open Access

ISSN: 3005-7582 (Online) : ISSN: 3005-7574 (Print)

**A Comprehensive Review**

# The Interplay Of Essential And Toxic Trace Elements In Prostate Cancer A Comprehensive Review Of Risk Factors, Prevention, And Clinical Implications

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**ABSTRACT**

Prostate cancer (PCa) is one of the most common cancers in men, and is influenced by genetic, hormonal, environmental, and lifestyle factors. Recent research has expanded the understanding of PCa initiation and progression, and has emphasized the importance of both essential and toxic trace elements in this process. Trace elements are naturally-occurring, and many essential trace elements, like zinc and selenium, may provide a protective effect through antioxidant and host defense mechanisms. However, excessive exposure to trace element toxicants may contribute to PCa carcinogenesis through increased oxyradicals, oxidative stress and direct DNA damage, as well as hormonal dysregulation. Several socio-demographic variables like age, race, and socioeconomic status have an effect on PCa risk and clinical outcomes, while lifestyle factors such as obesity, diet, smoking and alcohol consumption shape the progression of disease. Importantly, nutrient and trace elements may also function as diagnostic biomarkers for PCa, but inconsistencies in findings limit their clinical application. Prevention-focused approaches are possible through healthy living, avoidance of toxins, and balanced nutrition. The aim of this review is to explore roles of essential and toxic trace elements in prostate cancer risk, associated factors, diagnosis, and prevention. Future research should address population-specific differences, mechanistic pathways, and prospective studies to clarify trace element interactions in PCa risk, diagnosis, and therapy.

**Keywords:** Prostate Cancer, Trace Elements, Zinc, Copper, Risk factors, Preventions.

**How To Cite This Article:** **Zaidi K, Jamal MR, Zaman Q, Javaid S, Hussain MB.** The interplay of essential and toxic trace elements in prostate cancer: a comprehensive review of risk factors, prevention, and clinical implications. **Pak J Urol. 2025;3(2):11–30.**

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**ARTICLE TRACKING**

| | |
|---|---|
| **Received:** | **14- JULE -2025** |
| **Revision:** | **16-AUG-2025** |
| **Accepted:** | **21-SEP-2025** |
| **Published:** | **10-JAN- 2025** |

**DOI:** 10.69885/pju.v4i1.109

## INTRODUCTION

Globally, PCa is the second most prevalent type of cancer and the fifth leading cause of cancer-related death among men [1,2]. The pathogenesis of PCa is multifactorial, and a complex interplay among genetic predisposition, hormonal changes, lifestyle choices, and environmental exposure has been recognized [3,4]. Over the last few years, there has been increased focus on trace elements in the development and progression of PCa [5].Although PCa is considered one of the most common malignancies in men, Alterations associated with this include loss-of-function mutations in genes such as PTEN, TP53, and BRCA2. These alterations lead to uncontrolled cell growth and resistance to apoptosis [6,7]. Chronic inflammation caused by bacterial infections, lifestyle choices, or environmental toxins can cause continuous oxidative injury and gene mutations [8,9].Trace elements can either augment or inhibit carcinogenesis depending on their concentrations and bioavailability. They mediate all these pathways, which ultimately contribute to prostate carcinogenesis. However, there remains an urgent need to unravel the genetic and molecular pathogenesis of PCa, which may help in the prevention and treatment of PCa [10]. This review examines the roles of these trace elements are hypothesized to play in the progression of PCa, their mechanism of action, their potential association with PCa risk, and their possible diagnostic and preventive implications.

## Medical Factors effecting Prostate cancer

### Genetic Factors

Genetic susceptibility is an important risk factor for PCa. Germ-line mutations, with a presence in every cell of the body, account for about 10% of PCa cases and are referred to as hereditary PCa [11]. The Nordic Twin Study of Cancer [12,13] found that genetic factors estimate about 57% of PCa risk, establishing it as one of the most heritable cancers. Acquired mutations occur from either error during replication or environmental exposures, and they cause somatic tumor evolution through repetitive mutations in the tumor cell lineage [14].

### Hormonal Factor

Hormonal factors have important roles in the carcinogenesis of PCa. Elevated testosterone and its potent metabolite, dihydrotestosterone (DHT), are significant in PCa cell growth as higher androgen levels or androgen receptor (AR) sensitivity amplify tumor risk [15]. Androgen deprivation therapy (ADT) is a standard treatment; however, long-term utilization typically ends up with the development of castration-resistant prostate cancer (CRPC) [16].

### Medication

There has been considerable interest surrounding the

potential effects an anti-diabetic drug, metformin, could have on PCa as an antineoplastic agent [17]. While some studies have demonstrated an association between metformin and lowered PCa incidence and progression, while others have shown little to no association [18,19]. There is a significant proportion of metformin used globally which leaves a gap noted in the clinical literature and particularly cohort studies which have shown weak associations between metformin and PCa [20]. There is an enduring comprehensive clinical trial underway that aims to study the use of metformin as a standalone drug and in conjunction with androgen deprivation therapy for patients with metastatic disease [21]. Another pharmacological agent, statins, has also been associated with slowed progression of PCa. In a retrospective study of 11000 patients of a UK-based cohort, users of statins after diagnosis of cancer showed a 34% reduction in cancer-related mortality, particularly pronounced in users of statins before the diagnosis [22].

**Metabolic Syndrome and Obesity**

Prostate cancer progression and mortality is critically augmented by both obesity and metabolic syndrome. According to a meta-analysis each incremental 5 kg/m² increase in BMI elevates the risk of dying from PCa by 20% [23,24]. The underlying causes of such phenomena may be connected to disrupt hormonal signaling [25,26]. Several studies have indicated that a combination of hypertension, hyperglycemia, and central obesity are important in aggressive disease and recurrence [27]. In the Reduce trial, having 3 or more metabolic syndrome components showed strong associations to high-grade PCa [28].

**Inflammation and Infectious Agents**

Chronic inflammation and infection contribute to pathophysiology of PCa. Similar inflammatory conditions such as prostatitis may induce changes in the connective tissue of the prostate, which enhances the risk of cancer [29,30]. Moreover, some of these infectious agents have been surveyed owing to their possible role in inflammation, resulting in tumor propagation in the prostate gland [31]. Understanding such relationships forms the basis of identifying at-risk populations and developing targeted interventions.

**Alcohol, Narcotics, and Smoking**

The role of modifiable parameters, such as alcohol abuse and smoking, among other factors, has been widely researched. However, it should be noted that while a meta-analysis [32] involving 24 cohort studies has shown that there is no direct relationship between smoking and PCa incidence, heavy smokers have been shown to have an incidence of death from PCa that is 24%–30% higher than non-heavy smokers, where ex-smokers also appeared to have a higher risk. Alcohol intake has shown similar trends in risk with increasing

doses of PCa courtesy of a systematic review [33] of 340 studies suggesting a significantly increased risk with increasing doses.

**Socio-demographic Factors**

Several socio-demographic factors can influence the diagnosis and treatment of PCa.

**Age**

Age is a significant risk factor for PCa and the likelihood of developing the disease increases with age. PCa is uncommon in men under 40 years of age; however, its incidence increases notably after that age [34,35]. This trend is consistent in both developed and developing countries. The risk of developing PCa increased from 0.5% in men aged 40-49 while 6.4 % in those aged 50 to 59, and further to 30.3 % in men aged 60 and 69 years old. Additionally, histological diagnosis rates are high in older age groups, with approximately 42.4 % of men aged 70–79 years showing signs of malignancy on examination [36]. For those aged ≥ 80 years, the ratio dropped by 3.8 %. Fortunately, most of these diagnoses are low-grade and low-volume, typically following slow progression without a significant risk of mortality [37]. Most cases being diagnosed in men aged ≥ 65 years. Older unmarried patients may be less likely to choose radical prostatectomy as a treatment option [38].

**Socioeconomic Status**

A lower socioeconomic status (SES), characterized by low income and inadequate insurance coverage, is associated with a higher likelihood of being diagnosed with advanced-stage PCa. Research indicates that uninsured and Medicaid-insured patients are particularly vulnerable, often facing diagnoses at a younger age [39]. This discrepancy arises from several determinants of health-related social conditions, access to medical care, education, and other factors. Research has indicated that men from lower socioeconomic backgrounds are more likely to present with metastatic disease, with one analysis reporting that men at the 25th percentile of income had a 39% increased risk of advanced-stage diagnosis compared with men at the 75th percentile [40].

**Race and Ethnicity**

Incidences of PCa patch themselves by race, ethnicity, and place and it is Black men who suffer most because of the initial diagnosis, severity, and grim resultant death rates. In the USA, incidence among racial/ethnic populations varies three time and Black men are the highest diagnosed with a higher degree of likelihood resulting in a prostate carcinoma diagnosis [6,34]. Mortality for Black men with Carcinoma Prostate is 2.4 times greater than White men who are diagnosed statistically older, at a later stage of the disease, and with dire prediction [35,41]. This suggests that there is no avoiding the gaps inequities of race and ethnicity

country when primary care is offered.

**Lifestyle related Factors**

Prostate cancer is affected by lifestyle factors. Diets that are high in meats, dairy, and sugary beverages are linked with a higher risk of PCa; whereas fish and foods high in tomatoes may be protective [42]. Maintaining a healthy weight and engaging in physical activity is important because obesity is associated with aggressive forms of the disease [43]. Incorporating lifestyle changes into primary prevention may reduce the incidence and thus, progression of PCa.

**Ecological and Environmental Factors**

Prostate cancer is multifactorial in nature, and various ecological and environmental factors have been implicated in promoting this disease. However, these factors have played a significant role in the etiology of the disease [44,45]. Environmental exposures, including pesticides and pollutants, work hazards, lifestyle choices, and chronic inflammation, continuously aid in the causation and progression of pathology [46]. Knowledge of these effects is important for developing preventive strategies and improving patient outcomes.

**Chemical exposure**

Environmental exposure to certain chemicals is related to an increased risk of PCa. Research has reported an association between pesticides, particularly organochlorine pesticides such as DDT and heptachlor, and a greater incidence of PCa in men aged >50 [47]. A chlordecone, an insecticide, is considered a significant endocrine disruptor that may increase the risk of PCa [48]. These chemicals can interfere with hormonal pathways that promote the carcinogenesis of prostate cells.

**Water Pollution**

Water quality is yet another environmental factor increasing the risk of PCa. Contaminants from fertilizers, such as per-fluorinated acids and nitrates, have shown a correlation with an increase in mortality from PCa [49]. These chemicals in drinking water have demonstrated to disrupt hormonal homeostatic and promote malignancy for the origin.

**Occupational Hazards**

Certain occupations may expose employees to hazardous chemicals that could potentially increase PCa risk. Fire firefighters have been shown to be exposed to the byproducts of combustion, and then to a number of chemicals that are thought to increase risk of PCa [50]. Agricultural workers are also routinely exposed to pesticides and herbicides potentially for prolonged exposure, there is a body of literature demonstrating the association between pesticide and herbicide exposure and increased risk of PCa [51-52]. A cohort study [53] of male pesticide applicators demonstrates associations

between PCa and 45 pesticides used and corroborates workplace applications promotes their carcinogenic potential. Additionally, there may be genetic susceptibility which may alter their risk and add complexity to our understanding of the etiology of disease.

## Diagnostic and Prognostic Value of Trace Elements in Prostate Cancer

### Zinc (Zn)

Zinc is an essential trace element that regulates growth, development, immunity, and the activity of over 3,000 proteins and > 2,000 signaling molecules [54-55]. Zinc is a modulator of DNA synthesis, DNA transcription, and apoptosis and is regulated by cellular transporters known as the Zrt- and Irt-like Proteins (ZIPs) and the zinc transporter (ZnT) to maintain cellular homeostasis [56-57]. The prostate has an optimal high level of zinc, which hints to its importance for prostate health [58-60]. As PCa reports about lower amounts of serum and tissue zinc levels in patients when compared to healthy controls suggest that zinc could play a role in a protective manner [5] [61-62]. In their function, zinc mediates apoptosis, regulates the cell cycle, inhibits the activity of the matrix metalloproteinases, acts as an antioxidant in health and disease [57] [63-64] however, in some populations, zinc levels are actually higher in PCa compared to healthy controls. These inconsistencies could be influenced by differences in populations, assessment approaches, or disease stage [65]. Additional studies will further clarify the relationship of zinc in PCa prevention and/or therapy.

### Selenium

Selenium is an essential trace element and has been reported to hold antioxidant and anticancer effects, which makes it interesting in PCa research [66]. Selenoprotein incorporate selenium, perform antioxidative properties, regulate the immune response, and protect against oxidative stress [67]. Selenium is involved in several key pathways related to PCa, such as androgen receptor signaling, apoptosis, and angiogenesis. This highlights selenium's possible role in prevention, controlling progression, or even therapy [68]. Previous studies have shown that men with PCa have lower levels of selenium in serum and tissue compared to healthy controls [5][59][69]. Higher levels of selenium were associated with lower rates of mortality [69]. Selenium works mechanistically by donating free radicals, antioxidation, and enhancing NK cell functions [70]. Although inconsistent associations have been reported between selenium and PCa, we need more research to determine the best selenium intake method for PCa prevention and understand its possible treatment effects.

### Copper (Cu)

Copper is tracer element required for normal cellular activities while higher levels of copper may be associated with PCa. Higher copper has been reported in the serum and prostate tissue of both PCa patients when compared to controls [5,61] and higher copper concentrations were correlated with increased PCa mortality [69]. Copper increases angiogenesis and tumor growth by activating VEGF THAT promotes vascularization, supports extracellular matrix (ECM) formation, and activating copper-dependent enzymes like superoxide dismutase and ceruloplasmin that also increase oxidative stress resistance [71-74]. Therefore, defining and targeting copper homeostasis, utilizing chelation therapies such as tetrathiomolybdate are being studied as therapeutic approaches in PCa [75-76].

**Cadmium (Cd)**

Cd is a carcinogen, with several mechanisms believed to cause PCa [77-78]. Men with PCa have higher levels of Cd in blood, urine, and prostate tissues than controls [79-81]. Cd is stored in tumor tissue and as explained will hinder androgen receptor (AR) signaling by binding to it. Because of this, AR loses its function and causes abnormal growth of prostate cells [77][80]. As an example, Cd generates reactive oxygen species when introduced to cells, which leads to oxidative stress. Due to this, DNA, proteins, and lipids get damaged and faulty [83]. Urinary Cd above recommended guidelines increases PCa risk [80].

**Arsenic (As)**

Arsenic, a toxic heavy metal, is a recognized carcinogen linked to PCa as well as skin, lung, and bladder cancers [11]. Elevated arsenic levels have been reported in PCa patients, both in serum and tumor tissues compared to adjacent healthy tissue [79][81]. Arsenic promotes carcinogenesis by suppressing DNA repair, inducing oxidative stress, generating reactive oxygen species that damage DNA, proteins, and lipids, and disrupting androgen receptor signaling critical for prostate cell growth and differentiation [11][5][61]. Public health interventions and environmental regulations aimed at reducing arsenic exposure could play a significant role in PCa prevention.

**Lead (Pb)**

Lead is associated with a number of adverse health effects and disease conditions, including developmental delays, neurologic injury, and cancer [84]. While studies have examined the association between exposure to Pb and PCa, although there is still uncertainty about precisely how Pb might cause PCa, it is suggested that it disrupts the DNA repair processes, induces oxidative stress, and disrupts hormone signaling [84]. Pb has shown to inhibit the DNA repair enzymes causing DNA damage to accumulate leading to a greater likelihood of mutations. Pb can implement oxidative stress through

ROS generated by Pb which can damage DNA, proteins, and lipids [85]. Interventions in public health and environmental regulations that reduce Pb exposures, could represent an important opportunity for PCa prevention.

**Iron (Fe)**

Iron is a required part of cellular metabolism, but excess Fe can mechanistically interface with carcinogenesis by promoting reactive oxygen species (ROS) through Fenton reactions [86]. It has been shown that in PCa tissues, there are higher levels of iron deposition, oxidative stress, and DNA damage than normal tissues [87]. Ferritin is iron storage protein is increased in PCa cells and promotes iron sequestration and tumor growth [88]. Aside from cancer risk, iron could be used therapeutically in the treatment of resistant PCa. Researchers are trying to develop means of inducing ferroptosis, a Fe-mediated form of regulated cell death, in order to specifically target resistant PCa cells [89]. In this case, the tumor cells die from excess iron that overloads the cells through ROS production. What is more, the iron storage gene FTH1 may be targeted for therapeutic development, meaning that manipulating iron metabolism may yield novel PCa therapeutic options [90].

**Differential Diagnosis**

Trace element patterns in the serum, urine, and prostate tissue have emerged as potential biomarkers for diagnosing and assessing the risk of PCa [91-92]. Lower serum zinc and selenium levels have been suggested to increase the risk of PCa [93-94]. PCa exhibited markedly lower serum zinc levels than healthy controls, thus making its deficiency a suspected risk factor [95]. Selenium is a very sensitive internalizing protein implicated in antioxidant health activity; hence, it carries the possibility of disrupting these trace element changes, showing biochemical changes that cause PCa progression [5].Although trace elements hold promises as diagnostic tools, conventional methods remain the gold standard. These include Prostate-Specific Antigen (PSA) testing, CT scans, and MRIs. Despite its limitations in terms of specificity and sensitivity, PSA is widely used in clinical practice for PCa screening. CT and MRI provide vital information regarding the size of a tumor and its metastasis; hence, they are valuable in treatment planning [11]. However, their incorporation into routine screening might boost diagnostic accuracy, while providing more insights into individual risk profiles [96]. Further studies are needed to confirm trace elements as reliable PCa biomarkers. Combining conventional tests with novel biomarker strategies may improve PCa management.

**Prevention and Treatment**

**Prevention**

Dietary and lifestyle modifications aimed at optimizing trace element status could be potential preventive strategies against PCa [42] [97-98]. Healthy lifestyle habits lead to prevent prostate cancer. Eating a balanced diet, exercising regularly, keeping a healthy weight, avoiding smoking and alcohol, and managing stress can reduce inflammation, oxidative damage, and hormone problems that may lead to cancer [99-100]. An adequate dose of minor elements, especially zinc and selenium, is very important, as deficiency in these minerals has been correlated with an increased risk of PCa. Zinc plays a significant role in the normal function of the prostate owing to its antioxidant properties, while mitigating the outcomes of oxidative stress associated with carcinogenesis [101]. Selenium, on the other hand, also has chemo preventive properties via mechanisms that boost immune responses and dampen inflammation, which are crucial for preventing cancer [5][66][68] [70[102].

Reducing exposure to toxic metals like cadmium, arsenic, and lead is important to lower PCa risk, as these metals cause oxidative stress and DNA damage [81][103]. Higher levels of these metals are linked to greater PCa incidence, highlighting environmental factors in prevention [104]. Zinc and selenium may have protective roles, but inconsistent study results call for further research to determine effective dosages and supplementation forms for PCa prevention. Public health actions to limit toxin exposure may significantly impact incidence rates [105]. In addition, understanding the interaction between diet and environmental exposure is important in formulating an approach for the effective prevention of PCa.

**Treatment**

Therapeutic modalities for PCa depend on the stage and risk factors for each patient. Options include choosing to active surveillance for patients with low risk, as well as radical prostatectomy, radiation therapy, and androgen deprivation therapy (ADT) for advanced disease [106-107]. Targeting trace element metabolism may help to stimulate a new approach to PCa treatment. Agents that chelate copper and compounds that are enriched with selenium show quite good promise in preclinical studies and are being investigated in clinical trials [94][108]. Further research is needed to target relevant trace-element-related pathways for therapeutic intervention.

**Challenges and Future Directions**

**Inconsistencies in the Literature**

The literature on trace elements and PCa is often inconsistent, with some studies reporting positive associations, others reporting negative associations, and others reporting no associations. These inconsistencies may be due to differences in study populations, methods of trace element assessment, and stage of PCa at the time

of diagnosis.

**Lack of Mechanistic Understanding**

While progress has been made in understanding the mechanisms by which trace elements may influence PCa development, much remains unknown. Further research is needed to elucidate the specific molecular pathways involved and to identify key target genes and proteins.

**Need for Prospective Studies**

Most of the studies reviewed were cross-sectional or case-control studies, which could not establish a core understanding. Prospective studies are needed to determine whether trace element status can predict PCa risk over time.

**Focus on Specific Populations**

Future studies should examine specific at-risk populations for PCa, such as African-American men, White (European), and fair color (South Asian) population's diet and occupational differences as well as men with a family history of PCa. These populations likely have distinct trace element signatures and may respond differently to supplementation.

**Conclusion**

Trace elements are likely complex and multifactorial in the pathogenesis of PCa even if our evidence base is still evolving. Based on the current understanding, it appears that imbalances in the status of trace elements could play a role in PCa development and/or progression. It seems prudent to ensure adequate dietary intake of the essential trace elements (particularly zinc and selenium), and limit exposure to toxic heavy metals (i.e., cadmium, arsenic, and lead) as an important aspect of potential PCa prevention. However, prospective studies are needed to provide a clearer understanding of the role of trace elements in PCa, and develop those interventions for diagnosis, prevention, and treatment.

**Authors Contribution**

**Zaidi K**: Conceptualization, Methodology, Software

**Jamal MR**:Data curation, Writing- Original draft preparation.

**Zaman Q & Javaid S**: Visualization, Investigation.

**Hussain MB**:Writing- Reviewing and Editing.

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