TRACE MINERALS AND HEAVY METALS: IMPLICATIONS IN PROSTATE CANCER

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ABSTRACT – *Dietary minerals and environmental heavy metals are modifiable factors that have been studied over the years for associations with prostate cancer risk. This review considered the recent evidence in this field and concludes that the role of dietary minerals and environmental elements in prostate cancer progression or prevention is not yet clear and further research is needed to elaborate on the current knowledge.*

INTRODUCTION

Prostate cancer (PC) is one of the most common malignancies affecting men, particularly in the developed world. By 2030, the global annual incidence of PC is predicted to rise to 1.7 million. PC incidence rates vary greatly worldwide, being highest in western countries and relatively low in Asia. However, PC incidence is rising rapidly in Asia and factors responsible for this rapid rise include aging population, westernized dietary habits and increasing use of prostate-specific antigen (PSA) testing[1,2].

Prostate tumors are predominantly adenocarcinomas, having a heterogeneous and multifocal nature, and multiple mechanisms have been proposed for their initiation and progression[3]. A salient aspect of PC disease process is its close association with aging; pre-neoplastic morphological changes are common in early life but progression to invasive carcinoma occurs late in a limited population as a consequence of aging. Familial inheritance is generally associated with early onset disease and accounts for about 10% of PC[4]. Androgen receptor signaling has a central role in all stages of prostate carcinogenesis and transition to androgen independence is a hallmark feature of advanced disease[5].

In addition to these somewhat established pathophysiologic causes, diverse environmental factors including trace minerals and heavy metals are presumed to play a key role in prostate carcinogenesis. These factors can affect various aspects of cancer development which involves genetic alterations and selection for cells with increasing ability for proliferation, survival, invasion and metastasis[6]. Diet and supplementation are modifiable factors that have been studied for associations with PC risk and over the past few years, substantial research, focusing particularly on PC chemoprevention, has been carried out in this respect[7]. The present review summarizes recent clinical evidence regarding dietary minerals, their supplements and other environmental heavy metals implicated in PC.

SELENIUM

The trace element selenium (Se) is present in foods like grains, meat, poultry, fish, eggs and dairy products. Se occurs in both organic and inorganic forms including selenomethionine, selenocysteine, selenate and selenite and its bioavailability depends upon the chemical form[8,9]. The organic form enters through the food chain via the consumption of plants grown in soil containing the inorganic form. Following metabolism, Se is incorporated into selenoproteins which protect cellular mem-

branes from oxidative damage and are also involved in reproduction, thyroid activity, DNA synthesis, muscle function and several other metabolic functions[10,11].

Recent evidence has suggested the role of Se in reducing the risk of a variety of malignancies. Proposed mechanisms for anti-cancer actions of Se include antioxidant protection, enhanced carcinogen detoxification, enhanced immune surveillance, modulation of cell cycle, inhibition of tumor cell invasion and inhibition of angiogenesis (10). Several studies have shown evidence of a link between low selenium levels and higher PC incidence and it has been suggested that higher levels of Se may slow PC tumour progression[11-13]. Results from the Nutritional Prevention of Cancer (NPC) trial of 200 µg/day Se showed two-third reduction in PC incidence among men with low baseline PSA values (< 4 ng/mL) but no such reduction was seen in participants with higher values. Interestingly, only participants with low baseline plasma selenium concentrations had significant reductions in PC incidence[14].

Data from the Health Professionals Follow-Up Study showed that high baseline Se levels reduce the risk of advanced PC by more than half[15]. Results from a recent prospective study showed that toenail Se was associated with a reduced risk of advanced PC[16]. The Selenium and Vitamin E Cancer Prevention Trial (SELECT) tested Se and vitamin E separately and in combination but neither had any effect on the risk of PC[17]. Results from the Prostate Cancer Preventive Trial revealed no evidence that dietary or supplemental intake of Se was associated with risk of PC[18]. These conflicting findings about the role of Se in preventing PC could possibly be due to the type of Se administered or genetic susceptibility to its effect. Further work is needed to determine the effective type and dosage of Se before any recommendation can be made for its use in the prevention of PC or otherwise.

ZINC

Zinc (Zn) is an essential trace element possessing antioxidant properties and is a component of many proteins involved in physiological regulation of apoptosis, transcription and cellular differentiation. Zinc is abundant in many food sources, including red meat and poultry, beans, nuts, seafood, and whole grains, and can also be found in fortified breakfast cereals[11]. Zn accumulates greatly in the normal prostatic tissue, up to 10 times as much as in other soft tissues. Intraprostatic Zn is known to inhibit the mitochondrial enzyme aconitase, thereby limiting citrate oxidation and subsequent energy generation via Krebs cycle. It has been sug-

gested that malignant cells become energy efficient by completing the Krebs cycle following loss of this inhibition by low Zn levels[19,20]. Conversely, high tissue Zn enhances the activity of telomerase which could possibly increase PC risk since telomerase is involved in unrestricted tumor cell proliferation[21].

Results from clinical studies regarding the role of Zn in PC are not clear. Data from the Prostate Cancer Prevention Trial (18) showed that high dietary Zn intakes modestly reduced the risk of high-grade disease. Epstein et al[22] observed a potentially reduced PC risk in a recent study which showed an association between high dietary intake of zinc and lower PC-specific mortality after diagnosis, particularly in localized disease. On the contrary, data from the Health Professionals Follow-Up Study[19] demonstrated an increased likelihood of advanced PC with Zn in a daily dosage of more than 100 mg/day but dietary Zn intake was not associated with PC risk. In a case-control study, Gallus et al[23] found an association between high Zn intake and risk for advanced PC. These contradictory findings warrant further clinical exploration to explicate the potential mechanisms of PC development or prevention as a result of varying Zn concentrations.

CALCIUM

Calcium (Ca) is an essential element for humans, available only through dietary sources. It is largely concentrated in the skeleton as calcium-phosphate complexes, serving to maintain bone strength and Ca homeostasis. Non-skeletal Ca which accounts for approximately one percent of the total is responsible for a wide range of biological activities, including cell signalling, muscle contraction and nerve impulse transmission[24].

The role of Ca in PC may possibly be due to the regulation of tumor cell growth and apoptosis by intracellular calcium[25]. Moreover, it has been theorized that dietary Ca may indirectly increase PC risk and promote tumor growth by reducing circulating levels of the biologically active form of vitamin D (1,25-dihydroxy cholecalciferol) which inhibits the proliferation of prostate cells[26]. Several studies have demonstrated that a high calcium intake from foods and/or supplements is associated with increased PC risk. Data from the Health Professionals Follow-up Study showed a significant association between high-grade PC (Gleason score >7) and high Ca intake but a non-significant, inverse association was observed for well-differentiated, localized disease. Higher Ca intakes (1500 mg/day) were associated with a higher risk of ad-

vanced disease but not with low grade, organ-confined cancers[27].

Findings from the European Prospective Investigation into Cancer and Nutrition (EPIC) study[28] showed an increased risk of PC with high total dietary Ca intake and dairy Ca intake. No association was observed between non-dairy Ca intake and the risk for PCa. In the Prostate Cancer Preventive Trial[18], Ca intake was associated with an increased risk of low grade PC but inversely associated with high grade disease. Williams et al[29] in a recent study showed that dietary Ca is associated with lower risk for PC overall, particularly among black men, and lower risk for high-grade cancer among all men. The considerable inconsistency in findings regarding the impact of Ca intake on PC development and progression warrants additional investigation.

IRON

Iron (Fe) is the most prevalent metal in the body. Bio-availability of Fe is affected by various factors, such as dietary sources and Fe form (heme or non-heme). Heme Fe content varies between foods from 17 to 80% of total Fe content[30-32]. Heme Fe is more easily absorbed than non-heme Fe but depending on cooking method, its concentrations in meat can vary due to conversion into non-heme Fe. Heme Fe is transported via blood circulation to all body organs including the prostate[33].

Being a transition metal, Fe has loosely bound electrons in the outer shell which facilitate the production of reactive oxygen species (ROS) such as highly reactive hydroxyl radicals. Thus Fe overload can increase oxidative stress and cause DNA breaks and oxidative damage. Heme Fe can cause extensive cellular harm by catalyzing the generation of free radicals and it is also implicated in increased endogenous formation of N-nitroso compounds (NOC) which are known carcinogens in multiple species[32].

Results from the Carotene and Retinol Efficacy Trial (CARET) study[33] showed a significantly increased risk of clinically aggressive PC with higher total dietary Fe but did not reveal any association with overall PC. Associations were stronger among men with low dietary intake of fruits and vegetables which are foods rich in anti-oxidants. Sinha et al[34] studied the risk of PC with dietary iron intake (total and heme) and found no association between total iron intake and the overall PC risk or advanced disease. However, heme iron intake showed an increased risk for advanced cancer. High Fe content of hair and nails has been linked with increased risk of PC[35].

COPPER

Copper (Cu) modulates the activities of multiple enzymes, regulates the redox state, promotes angiogenesis and mediates cellular proliferation. As a result of these activities, Cu appears to play an important role in the carcinogenic process which is evident through the increase seen in Cu levels in cancerous tissues[36]. Previously, a study[37] of serum Cu levels in PC showed no increase as compared to normal controls. However, a recent study[35] documented higher Cu levels in hair and nails of PC patients.

MAGNESIUM

Magnesium (Mg) is the second most abundant intracellular cation in the body, involved with numerous biological activities particularly related to its interaction with Ca. Levels of both these cations are regulated through competition for intestinal absorption and renal reabsorption and also via a negative feedback system[38]. It has been indicated that the physiologic effects of Ca are enhanced in Mg deficiency as they compete for intracellular membrane binding sites[39]. Serum Mg levels, and Ca/Mg ratio have been shown to be associated with high-grade PC. Mg deficiency is linked with chronic inflammation, possibly due to the concurrent Ca levels, which may play a key role in the progression to PC[38].

CADMIUM

Cadmium (Cd) is recognized as a carcinogen based particularly on studies of occupationally exposed individuals having substantial exposure via the respiratory system[40]. Chronic exposure to Cd poses a threat to the general population as it has a widespread presence in the environment[41]. Dietary vegetables and cereals are the main source of environmental Cd while drinking water contributes only a very small percentage[42].

Once absorbed, Cd binds to metallothionein and is stored mainly in the kidneys, liver and other organs. Prostate tissue has also been identified as a target for Cd deposition[43]. It has a long biological half-life (10-30 years) in humans which may cause neoplastic transformations in various organs including prostate[44]. Association between Cd and PC among occupationally exposed men was shown previously but more recent and larger studies did not confirm those findings. In a recent population-based prospective study[45], dietary Cd exposure was associated with a slightly increased overall risk of PC and for localized disease, the risk was more marked in smokers and lean men.

CONCLUSIONS

The current evidence seems a long way off in terms of classifying the exact roles of modifiable factors such as dietary minerals and environmental elements for offering clinically effective strategies aimed at modulating the risk of PC. Results from future experimental and clinical research employing adequately powered prospective study designs may help to clarify the etiologic role and/or chemopreventive potential of mineral elements in PC.

CONFLICT OF INTERESTS:

The Authors declare that they have no conflict of interests.

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