MINI-REVIEW

Prevention of Prostate Cancer with Vitamins - Current Perspectives

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Abstract

Cancer prostate is the most common solid malignancy in males of developed countries. With increasing knowledge of the aetiology, pathogenesis and natural history of the disease, influences of dietary factors on prostate cancer development have become more evident. There is ample evidence in the literature of significance of dietary constituents for prostate cancer including vitamins A, D and E. Different vitamins have been found to effect the growth and proliferation of prostate cancer cells as evident in epidemiological, experimental and clinical studies. Various factors play the major role in determining the relationship between these vitamins and prostate cancer in terms of environmental, pharmacological, or genetic aspects. To explore these aspects, the present article reviews the literature on the present status of vitamin use for prevention and management of prostate cancer.

Keywords, Prostate cancer - vitamins A - vitamin D - vitamin E

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Introduction

It is well known that the nutritional intervention plays a major role in cancer treatment and prevention. Most of the cancers can be prevented by proper nutrition, healthy diets, physical activity, and reduction in body weight by 30-40% as suggested by World Cancer Research Fund (1997). Prostate cancer incidence varies greatly with the geographical distribution and diet may be the major factor responsible for this.

Indeed, prostate cancer may be the well suited for chemoprevention strategies trials as it has the long latency of disease onset with relatively slow growth. So there is lot of scope to prevent its growth at different stages by intervening through dietary factors. Also it has been observed that prostate cancer patients had higher intake of the dietary supplements than that in healthy men in the general population as indicated in various studies (Wiygul et al., 2005; Rock, 2007; Velicer and Ulrich, 2008). Several observational studies have examined the relation of intakes of vitamins, minerals, fruit, vegetables and other dietary supplements with prostate cancer risk (Giovannucci et al., 2003; Bosetti et al., 2004; Key et al., 2004). This review focus on the role of vitamins A, D and E in prostate cancer and status of these vitamins in the experimental, epidemiological and randomized trial studies.

Literature Survey

A PubMed search was conducted with the key words 'prostate cancer'; prevention in prostate cancer; 'epidemiology factors'; 'vitamins and prostate cancer'. The specific role of vitamins was searched in prevention of prostate cancer as 'vitamins A'; 'vitamin D'; 'vitamin E. In addition, the 'related articles' search option on PubMed and references of relevant articles were also looked for with knowledge of epidemiological and other experimental study. At the end of literature research, the most relevant articles were selected for the discussion of role of vitamins in cancer prostate in this review.

Vitamin A

Vitamin A and Retinoids, the natural or synthetic derivatives of vitamin A, demonstrated the effects on proliferation and differentiation in different organs and deficiency of this vitamin resulted in multiple developmental defects (Clagett-Dame DeLuca, 2002; Duester, 2008). Important metabolites of vitamin A (retinol) are All trans-retinoic acid (ATRA) and 9-Cis-Retinoic Acid (9-CRA) and both of these have diverse physiological functions in the body (Duester, 2008). These retinoids, in carcinogen induced prostate cancer mouse models, have been shown to reverse hyperplasia (Chopra

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and Wilkoff, 1979; Mongan and Gudas 2007). Due to effects of both ATRA and its synthetic derivatives on prostate gland or prostate cell lines, it regulates the prostate growth and suppresses the development of prostate cancer. Due to either decreased content or altered metabolism in prostate cancer cells, it can play a key role in abnormal cellular differentiation pathways, and the anti-proliferative effects may be lost.

Cancer-preventive potential of vitamin A have been elaborated in many vitro and animal studies demonstrating a key role of retinol in regulating the growth, and apoptosis of normal and malignant cells. No consistent association between vitamin A and prostate cancer risk has been established, although several epidemiological studies and randomized clinical trials have been done so far (Mongan and Gudas, 2007).

The experimental study of Jiang et al demonstrated that prostate cancer cells could be arrested in G1 phase with 9-cis RA. Cell mitosis was reduced, and expression of homeobox gene NKX3.1 was upregulated which acts as a tumor suppressor gene in the prostate and play role in prostate differentiation (Jiang et al., 2006).

Author in their *in vitro* and *in vivo* data, in transgenic adenocarcinoma of the mouse prostate (TRAMP) model system, demonstrated that All-trans retinoic acid not only hampers the prostate tumor cell proliferation, apoptosis was induced as well. It also halts the emergence of the neuroendocrine phenotype. Also ATRA intervention therapy can differential regulates p27 and p21 pathways and inhibit the formation of spontaneous prostate cancer (Huss, 2004).

The association between retinol and various carotenoids was evaluated in a multicentric case-control study conducted in Italy between 1991 and 2002 (Bosetti et al., 2004). This included 1,294 incident prostate cancer cases which were confirmed on histology and 1,451 controls below age 75 years. Although, with increasing intake of retinol (OR=0.79 for highest versus the lowest quintile of intake), carotene (OR=0.70), and beta-carotene (OR=0.72) and alpha-carotene (OR=0.85), the risk of prostate cancer tended to decrease, significant values were seen for carotene and beta-carotene only. Also no important associations were found for non-provitamin A carotenoids, such as lycopene (OR=0.94) and lutein/zeaxanthin (OR=0.91). Thus, carotene, particularly beta-carotene, had found produce little protective effects on the risk of prostate cancer as found in this study.

In a nested case-control study 'The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening' trial, authors estimated risk of prostate cancer in 692 patients and 844 controls. Multivariate conditional logistic regression was used and it was found that overall prostate cancer risk was not associated with serum retinol concentrations. Nevertheless,42% reduction in aggressive prostate cancer risk was seen with the highest as compared to lowest concentrations of serum retinol (p=0.02), with the strongest inverse association for high-grade disease (stage 3 or 4 or Gleason 7+; n=269) (p=0.01). These results suggested the risk of aggressive prostate cancer was decreased with higher circulating concentrations of retinol (Schenk et al., 2009).

Other cohort studies which supported the concept that increased concentrations of serum retinol decreases the risk of aggressive prostate cancer are the National Health and Nutrition Examination Survey (NHANES) I Epidemiologic Follow-up Study in which the high retinol concentrations were associated with a decreased risk of prostate cancer (Reichman ME et al., 1990) and in CLUE I study in which, inverse association between prostate cancer and serum retinol found which was non-significant (Hsing et al., 1990). Main limitations of these studies were that these were limited to total prostate cancer, and stage or grade of disease had not considered in this study which may impact the association (Eichholzer et al., 1999; Key et al., 2007).

Thus, it is generally postulated that Retinol, which is the most biologically active form of vitamin A, prevent various cancer including the prostate, by different mechanisms as promoting cell differentiation and apoptosis, increasing levels of other antioxidants, and regulating DNA transcription by inhibiting DNA polymerase activity (Willis and Wians, 2003; Mondul et al., 2011). Contrary to this, there is also growing evidence that under some conditions, retinol may stimulate growth and de-differentiation of prostate cells (Peehl and Feldman, 2003).

Serum concentrations of carotenoids were measured by high-performance liquid chromatography in 997 middle-aged Finnish men (56.1±6.6 yr) in the Kuopio Ischaemic Heart Disease Risk Factor (KIHD) cohort in a perspective study. A total of 68 prostate cancer cases occurred during the mean follow-up time of 15 yr. After adjusting for other parameters, there was 2.3-fold higher risk of prostate cancer in men with highest tertile of β-carotene as compared to patients with lowest tertile (RR=2.29, p=0.023). α-Tocopherol and retinol were not found to be associated with prostate cancer (Karppi et al., 2012).

In the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study cohort (Anon, 1994) which is considered as the largest study evaluating the association between circulating retinol concentration and incident prostate cancer, authors prospectively examined prostate cancer risk and serum retinol levels, at baseline (n=29,104) and after 3 years (n=22,843). Higher retinol concentrations at baseline were associated with more chances of prostate cancer (hazard ratio=1.19; p=0.009). Aggressive disease had the same results. Men had the greatest increased risks that were in the highest quintile at both at beginning and end of the study period. In this large study in determining the status of vitamin A with subsequent risk of prostate cancer, elevated risk was found with higher serum retinol, with sustained high exposure conferring the greatest risk. The molecular mechanisms of the retinol-prostate cancer association may be clarified with future studies. Risk of total and also aggressive prostate cancer was positively associated with retinol concentrations, for men in the highest retinol quintile showed a 20% greater overall risk.

In randomized, double-blinded placebo-controlled Carotene and Retinol Efficacy Trial (CARET), dose of 30 mg β-carotene+25,000 IU retinyl palmitate on daily basis was given for lung cancer prevention (Neuhouser

et al., 2009). Prostate cancer was also assessed as secondary outcomes. Prostate cancer cases were noticed in 890 patients after 11 years of follow-up. It was found that although the CARET or other supplements were associated with total prostate cancer risk, the use of additional supplements in men in the CARET intervention arm had increased the relative risk for aggressive prostate cancer (Gleason≥7 or stage III/IV) of 1.52($p<0.05$) relative to all others. This study included only the smokers so these findings were confined to smokers.

Thus this trial presents the modest evidence that a risk of aggressive prostate cancer was increased by use of high-dose of β-carotene and retinyl palmitate plus one other dietary supplement. Other recent studies, which used various high-dose supplements, also had similar results (Cole et al., 2007).

Hence, clinical and epidemiologic studies of association of circulating retinol concentration and prostate cancer have been found to have mixed results, most studies showed an inverse association (Reichman et al., 1990; Knekt et al., 1990; Lu et al., 2001) or no association (Milne and Botnen, 1986; Omenn et al., 1996; Cook et al., 2000; Huang et al., 2003; Key et al., 2007; Gill et al., 2009). Positive association was also found in some studies (Heinonen et al., 1998; Coates et al., 1998; Gann et al., 1999). Main limitations of these investigations were that some of these were relatively small and underpowered to detect modest associations. Stage or grade of disease was taken into consideration in some of these studies only in finding associations of prostate cancer risk with retinol concentration. Also, most of these studies measured retinol only at 1 point in time.

There are still inconsistent results found from epidemiologic studies in relation of the risk of prostate cancer with the circulating carotenoid concentrations. The exact biologic pathogenesis through which higher circulating retinol might impact the risk of prostate cancer is still to discover. Further research is definitely required to better understand the significance of serum retinol elevated concentrations in cancer prostate patients.

Vitamin D and Calcium

Vitamin D and calcium is essential for bone health in all ages so as to prevent rickets or osteoporosis and play an important role for adequate bone mass during skeletal development. There is also growing evidence from epidemiological studies and clinical intervention trials that altered vitamin D status or calcium nutrition are predisposing conditions for other pathologies as well including chronic diseases, autoimmune pathology, hypertension and various cancers (Peterlik and Cross, 2009).

In 1990, for the first time, an inverse correlation was found between ultraviolet exposure and prostate cancer mortality in the United States. Schwartz and Hulka first proposed the preventive role of vitamin D in the prostate cancer (Schwartz and Hulka, 1990). Human prostate cancer cells are said to have receptors for (2) 1,25-Dihydroxyvitamin D hormone and anti-proliferative effects of this hormone on prostate cells inhibits invasiveness and metastasis, thus establishing the role of vitamin D in prostate cancer (Liu et al., 2003; Ahn et al., 2008). In recent years, various studies of analytic epidemiology, molecular mechanisms and preventive trials have been conducted concerning the relation of dairy products, calcium and vitamin D with prostate cancer risks (Jacobs et al., 2004; Faupel-Badger et al., 2007; Li et al., 2007). Some of these epidemiologic studies established the relation between high serum 25 hydroxyvitamin D3 (25OH D) levels to reduce prostate cancer risk (Hanchette and Schwartz, 1992; Ahonen et al., 2000), while others did not (Ahn et al., 2008).

Kovalenko et al in their study demonstrated that low vitamin D status increased prostate epithelial cell (PEC) proliferation and reduced cell apoptosis (Kovalenko et al., 2011). In TgAPT121 mice on a low vitamin D diet, advanced prostatic intraepithelial neoplasia (PIN) phenotypes was seen in the majority of prostate epithelium. Thus, the balance between apoptosis and proliferation in the epithelial cell of the normal prostate may be disrupted by low vitamin D status. Reduced signalling through the Vitamin D receptor (VDR) can influence the epithelial cells independent of androgen status. The authors hypothesized that beneficial effect of high vitamin D status may be exerted during adolescence life when genetic or epigenetic events are initiated and the prostate is more susceptible to cancer (Sakr et al., 1993).

Although results from phase II clinical trial and experimental studies give some evidence of role of vitamin D in the etiology of prostate cancer(Peehl DM et al., 1994; Liu et al., 2003), no clearly supported evidence was found from prospective studies in the Nordic and United States countries about such association (Hanchette et al., 1992; Faupel-Badger et al., 2007; Li et al., 2007; Ahn J et al., 2008).

In a European Prospective Investigation into Cancer and Nutrition (1994-2000) case control study, vitamin D concentrations in 752 controls were matched to 652 prostate cancer cases in 7 countries. When serum concentrations of 25-hydroxyvitamin D were measured after a median follow-up time of 4.1 years, circulating concentrations of vitamin D found to have no protective effects on the risk of prostate cancer (Travis et al., 2009).

Chadha et al conducted a phase 2 trial of intravenous calcitriol at a dose of 74 μg weekly and dexamethasone in patients having castration-resistant prostate cancer (CRPC) and concluded that the although the combination was well tolerated but no PSA or clinical response was evident in men with CRPC (Chadha et al., 2010).

Numerous epidemiologic studies had studied the association of diets high in calcium and risk of prostate cancer. Although positive associations were found in some of these studies, the mechanism underlying the association between dietary calcium and prostate cancer risk is unclear (Gao et al., 2005; Tseng et al., 2005).

Both Agency for Health Care Research and Quality (AHCRQ) (Chung et al., 2009) and the World Cancer Research Fund (WCFR)(2007) proposed calcium as a probable cause of prostate cancer. On meta-analysis, dose-response relationship was found among increased risk of prostate cancer and higher intake of calcium.

Prostate cancer mortality increased by 2-3 folds with high levels of calcium even within the high normal reference range (high normocalcemia) as found in two recent prospective studies (Skinner and Schwartz, 2008; Skinner and Schwartz, 2009).

It was observed that the individuals who were high absorbers of calcium, risk of prostate cancer were substantially increased in them. Rowland et al indicated in their study that, although risk of prostate cancer increases in all African American men as a cohort with a high calcium intake, significantly greater risk was found among high absorbers of calcium (men with the AA genotype) (Rowland et al., 2012).

Polymorphisms in genes may influence the efficiency of calcium absorption and these can affect prostate cancer risk. Calcium absorption is regulated by VDR whose expression is regulated by the CDX-2 transcription in the small intestine, which ultimately binds a polymorphic site in the VDR gene promoter. California Collaborative Prostate Cancer Study was conducted in 533 African American prostate cancer cases and 250 controls. The conclusion of the study was that men in the highest quartile of calcium intake had an approximately twofold increased risk of localized and advanced prostate cancer with a significant dose-response relationship in comparison to men in the lowest quartile. (Odds ratio=2.20) (Rowland et al., 2012).

There are few epidemiologic studies concerning effects of serum Parathormone (PTH) along with serum calcium in prostate health. Skinner et al studied the relationship between serum levels of calcium, PTH and Prostate-Specific Antigen (PSA) in 895 men who did not have clinical prostate cancer with age ≥40 years. The authors concluded that serum levels of PTH and calcium both were correlated significantly with free PSA (p=0 .05 and 0 .008) after adjusting for age, race, BMI and serum levels of 25-Hydroxyvitamin D (Skinner and Schwartz ., 2009).

The relationship between calcium along with dairy food intake in fatal prostate cancer was evaluated in the Health Professionals Follow-up Study (Giovannucci et al., 2006). A large population study in which 47,750 healthy males were followed over 16 years. In this period, 3,544 patients developed prostate cancer of which 523 were advanced and 312 had a fatal disease. It was found that although higher calcium intake was not associated with total or non-advanced cases, the prostate cancer patients with advanced or fatal cases had significantly higher calcium intakes of 1,500 to 1,999 mg/day, with RR of 1.87. Those with calcium intakes ≥2,000 mg/day had a higher RR of 2.43 (p=0.003). The researchers concluded that high calcium intakes (≥1.500 mg/d) were correlated not with moderate to well-differentiated cancer but with clinically advanced and fatal poorly differentiated prostate cancer (Martini and Wood et al., (2009).

Dairy food intake has been associated with prostate cancer in previous work, but the exact mechanism by which this occurs is unknown. It is postulated that circulating levels of potentially cancer-protective 1,25-hydroxyvitamin D (1,25(OH)2D) may be suppressed by dairy calcium. Though Tseng et al in a study of 296 men (194 black, 102 non-black) at high risk for prostate cancer found that, dairy milk, and calcium intake were not associated with reduced 1,25(OH)2D levels after adjustment for age, race, energy intake, BMI and other parameters (Tseng et al., 2009).

Additionally, presence of estrogens and insulin like growth factor (IGF-I) in milk has been hypothesized to be associated with risk of prostate cancer (Carruba, 2007; Weaver, 2009). But even five cups of milk/day would supply about only 1.3 mg calcium/day, which is too low to produce any significant impact on plasma estrogen concentration (Weaver, 2009). Serum IGF-I concentration increased with consumption of animal protein, including milk, fish and poultry as observed by Giovannucci et al and found to have a role in chronic diseases and multiple vascular pathologies but definite role in cancer pathogenesis is yet to established (Giovannucci et al., 2003; Delafontaine et al., 2004). Further investigations are deemly required for establishing strong relation between estrogen content and IGF-1 in milk and its association with prostate cancer. Nevertheless, a meta-analysis of 45 observational studies including 26,769 cases of prostate cancer did not support an increased risk of prostate cancer with dairy product consumption (Huncharek et al., 2008).

In a Multiethnic Cohort Study, out of 82,483 men with follow up of eight years, 4,004 cases developed prostate cancer (Park et al., 2007). There was no association seen between calcium, vitamin D intake or dairy products with prostate cancer risk, even in those with calcium intakes ≥1,300 mg/day. However, low/nonfat milk consumption was related to an increased risk of localized or low-grade prostate cancer in this study (RR=1.16).

In conclusion, data about the evidence of the effects of calcium and vitamin D in prostate cancer has conflicting results in the literature. Even if calcium and vitamin D produce some effects on prostate cancer as evident in many epidemiologic studies, the underlying mechanism has been a subject of considerable debate (Fraser, 2007; Schwartz, 2009; Tseng et al., 2009). Nevertheless, it is taken into consideration that as calcium is essential for bone health and also found beneficial for cancers of different organs such as colon cancer, public health recommendations to limit calcium intake must be made cautiously.

Vitamin E

The concept that antioxidants play a role in preventive and therapeutic effects in malignancy has been known for many decades (Gaziano et al., 2009; Lippman et al., 2009) and multiple experimental and preclinical studies are available in prostate and other cancer to suggest this effect (Heinonen et al., 1998; Klein et al., 2011).

Vitamin E is fat-soluble compound with antioxidant property that prevents lipid peroxidation and free radical reactions (Meydani, 1995). It consists of α, γ, δ tocopherols (T) and tocotrienols. All the tocopherols function as an antioxidants; however, γ-T and δ-T, are more effective than α-T in trapping reactive nitrogen species due to the unmethylated carbons at the 5- and 7-positions on the chromanol ring. Vitamin E along with the selenium is the important components of the human diet and the major source of tocopherols (Khandrika et

al., 2009).

It is found that α-T accounted for 34-53% reduction in lung cancer risk (Mahabir et al., 2008) and its relation with other cancer was also evaluated. The Alpha-Tocopherol, β-Carotene Cancer Prevention (ATBC)(1994) is the randomized, double-blind, trial of 29,133 male smokers of age from 50 to 69. In this study, alpha-tocopherol intake did not influence the primary endpoint of lung cancer incidence but the 50 mg/day of alpha-tocopherol decreased the incidence of prostate cancer from 17.8/10,000 person-years in the placebo group to 11.7 in the α-tocopherol group after 5-8 years of follow-up. These preclinical evidence, as well as findings from the Linxian trials, suggested the role of selenium and vitamin E in prostate cancer prevention. There is good evidence of protective effects of selenium against prostate cancer (Karimi et al., 2012; Yang et al., 2013).

In a randomized double-blind Nutritional Prevention of Cancer (NPC) trial (Clark et al., 1996), 1312 eastern US participants were enrolled to testify whether non-melanoma skin cancer could be prevented by selenium supplementation. Total cancer incidence and mortality of lung, prostate, and colorectal cancers were also evaluated as secondary endpoints. Participants were randomized to receive either placebo or selenized yeast which contains 200 μg of selenium daily. After 8271 person-years of follow-up, it was found that the skin cancer was not favorably affected by the selenium intervention; however, prostate cancer was found to be reduced by 64% in the selenium group after 4.5 years and by 49% after 10 years. This decrease was most pronounced in former smokers.

Cheng et al investigated the interaction between serum tocopherols and polymorphisms in myeloperoxidase (MPO) for prostate cancer (Cheng et al., 2011). In this nested case-control study of Carotene and Retinol Efficacy Trial, in 684 men with incident prostate cancer (284 aggressive cancer and 375 nonaggressive) and in 1441 controls, serum α- and γ-tocopherol were assayed. It was found that the higher serum α-and γ -tocopherol concentrations were associated with reduced risks of aggressive prostate cancer among current smokers. Although MPO G/A and A/A genotypes were associated with a nearly 2-fold increased risk of aggressive prostate cancer among current smokers with low serum α -tocopherol concentrations. Thus, high serum α-tocopherol concentrations may be particularly important among men with MPO G/A and A/A genotypes in reducing prostate cancer risk.

Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial was conducted in 680 prostate cancer cases and 824 frequency matched controls for evaluating the relation between serum α -T and γ -T and prostate cancer risk. Serum α-T and γ -T were found to be inversely correlated (r=20.24, p=0.0001). Prostate cancer risk was found to be significantly lower with higher serum α-tocopherol but was restricted to current and recently former smokers and also this effect was more prominently found in less aggressive cancers. (OR=0.63, p-0.05). By contrast, it was found that with the higher γ-tocopherol concentrations, the risk of prostate cancer was elevated but not significantly (OR=1.35, p- 0.41) (Weinstein et al., 2012).

In a much smaller trial in high-grade PIN men, subjects were randomized with a mixture of selenium and soy for three years along with alpha-tocopherol or with placebo, but the prostate cancer cumulative incidence was not found to be decreased (Duffield-Lillico et al., 2003). Authors studied the effects of selenomethionine, selenized yeast, alpha-tocopherol and combinations in prevention of prostate cancer in two animal models, but no preventive activity of these agents were detected (Ozten et al., 2010; McCormick et al., 2010). However, it was found that it was gamma-tocopherol but not alpha tocopherol, which might be preventive against prostate cancer as suggested by epidemiological and animal model evidence (Barve A et al., 2009; Takahashi et al., 2009).

Seven out of 14 case-control studies which evaluated the role of vitamin E showed an inverse association between risks of prostate cancer with dietary or blood levels of tocopherols (Ju et al., 2010). However, it is not the α-T levels but serum levels of γ-T was inversely associated with prostate cancer risk as found in two nested case-control studies (CLUE I and CLUE II) (Helzlsouer et al., 2000; Huang et al., 2003).

Various mechanisms have been proposed for tocopherols action but none is confirmatory (Ju et al., 2010). Recent studies had the opinion that while all forms of tocopherols are antioxidants, γ-T and δ-T effectively inhibit carcinogenesis and xenograft tumor growth and α-T does not. Due to the unmethylated 5-position of the chromanol ring, the γ-T and δ-T quench reactive nitrogen species more effectively. ω-oxidation/β-oxidation pathways are involved in the metabolism of γ-T and δ-T via side-chain degradation and these metabolites may trap reactive nitrogen and oxygen species in the cytosol. It has been shown that γ-T and δ-T activate PPARγ more effectively in comparison to α-T (Lee et al., 2009), and this may be a mechanism for cancer prevention. γ-T and δ-T were more active than α-T in inducing apoptosis of different cancer cell lines and inhibiting the growth (Ju et al., 2010). Nevertheless, exact mechanisms still remain to be elucidated.

In Selenium and Vitamin E Cancer Prevention Trial (SELECT), randomization was done into four arms to receive selenium (200 μg/day), vitamin E (400 IU/day), both, or placebo (Lippman at al., 2009) involving 35,533 men. In contrast to previous studies, no statistically significant differences noted between the groups on decreasing prostate cancer risk after 7 years. On the contrary, the vitamin E group patients had shown 17% increased risk of prostate cancer (p=0.06) and the selenium group showed increased risk of type 2 diabetes mellitus (p=0.16), although the results did not reach statistical significance. The finding of this study that even combination of two antioxidant agents were not effective in decreasing prostate cancer incidence, and in addition, may be potentially harmful, further studies are definitely needed for study before their widespread use (Lippman et al., 2009; Klein et al., 2011).

Mahabir et al had the view that all types of vitamin E are cancer preventive at the nutritional level as inverse relation was found with dietary intake of α-T and other

tocopherols in prostate cancer risk. This effect was particularly found among smokers, who are under stronger oxidative stress as found in many observations (Mahabir et al., 2008). Although several recent cancer prevention trials (Gaziano et al., 2009; Lippman et al., 2009; Klein EA et al., 2011), concluded that α-T is not cancer preventive at the supra-nutritional level. In the SELECT, the mean baseline serum level of α-T was 12.5μg/ml indicating that there was no nutritional deficiency of vitamin E of the participants. Recent results further showed that δ-T and γ-T are cancer preventive in animal models (Lu et al., 2010; Li et al., 2011; Barve et al., 2011; Zheng et al., 2012), and also in humans. The results of SELECT model can be interpreted by this concept as the subjects who took daily supplementation of α-T (400 IU), enhanced prostate cancer risk was found in them. This could be explained as supplementation of α-T actually caused a 50% decrease in the median plasma γ-T level, and this may decrease the cancer preventive effect of γ-T (McNeil C,(2011).

Nevertheless, as a beneficial effect of vitamin E supplements was found only in smokers as shown in a randomized trial but not in other two trials not specifically recruiting smokers, the major issues over the association of prostate cancer and vitamin E persists at present (69,70). Whether the beneficial association exists only among smokers or vitamin E is harmful or other genetic polymorphisms play a role is still inconclusive. Nevertheless, certain interpretation can be done based upon the above studies, as for cancer prevention, γ-T and δ-T seems to be more important than α-T, though optimal levels for these tocopherols remains to be determined for cancer prevention. The bio-effects of these anti-oxidants on cancer prevention, their doses and possible adverse effects of tocopherols warrant further investigation.

Conclusions

It is generally assumed that the consumption of vitamins, minerals and other dietary supplements in patients with various cancers may have a preventive role. As discussed, various studies had showed positive, negative or null effect on reducing PC risk with the use of vitamins A, D and E. Even randomized trials and intervention studies vary in their results in determining the role of vitamins in prostate cancer. Some studies even showed the proliferative effects of vitamins in increasing the prostate cancer risks. Many factors should be considered in the interpretations of these studies, including statistical methods used to analyse the results and detection methodologies, dose of vitamins, absorption rates, metabolic pathways, genetic and racial factors. Other micronutrient and dietary factors may also potential effect the absorption of these vitamins. So isolated effect of any individual vitamin is difficult to interpret. Still mechanisms of vitamins alongwith gene interactions related to the prostate cancer are the pathways to be explored to exactly understand the impact of these vitamins. It is important to amplify the gene nutrient disease association research and the clinical investigations needed to know the effect of these vitamins in the prostate diseases. Randomised, placebo-controlled trials are required to know the efficacy of these vitamins in suitable cohorts of patients with repeated dietary measurements. Along with that need of potential biomarkers assessing the efficacy of intervention including genetic polymorphism are equally important.

References

Ahn J, Peters U, Albanes D, et al (2008). Serum vitamin D concentration and prostate cancer risk, a nested case-control study. *J Natl Cancer Inst,* **100**, 796-804.

Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P (2000). Serum vitamin D concentration and prostate cancer risk, a nested case-control study. *Cancer Causes Control*, **11**, 847-52.

Anon (1994). The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study, design, methods, participant characteristics, and compliance. *Ann Epidemiol*, **4**, 1-10.

Barve A, Khor TO, Nair S, et al (2009). Gamma-tocopherol-enriched mixedtocopherol diet inhibits prostate carcinogenesis in TRAMP mice. *Int J Cancer*, **124**, 1693-9

Bosetti C, Micelotta S, Dal Maso L, et al (2004). Food groups and risk of prostate cancer in Italy. *Int J Cancer*, **110**, 424-8.

Carruba G (2007). Estrogen and prostate cancer, an eclipsed truth in an androgen-dominated scenario. *J Cell Biochem* **102,** 899-911.

Chadha MK, Tian L, Mashtare T, et al (2010). Phase 2 trial of weekly intravenous 1,25 dihydroxy cholecalciferol (calcitriol) in combination with dexamethasone for castration-resistant prostate cancer. *Cancer*, **116**, 2132-9.

Cheng TY, Barnett MJ, Kristal AR, et al (2011). Genetic variation in myeloperoxidase modifies the association of serum a-tocopherol with aggressive prostate cancer among current smokers. *J Nutr*, **141**, 1731-7.

Chopra DP, Wilkoff LJ (1979`). Activity of retinoids against benzo(a)pyrene-induced hyperplasia in mouse prostate organ cultures. *Eur J Cancer*, **15**, 1417-23.

Chung M, Balk E, Brendel M, et al (2009). Vitamin D and calcium, systematic review of health outcomes, *Evid Rep Technol Assess*, **183**, 1-420.

Clagett-Dame M, DeLuca H (2002). The role of vitamin A in mammalian reproduction and embryonic development. *Ann Rev Nutr*, **22**, 347-81.

Clark LC, Combs GF, Turnbull BW, et al (1996). Effects of selenium supplementation for cancer prevention in patients with carcinoma of the skin. A randomized controlled trial. Nutritional Prevention of Cancer Study Group. *JAMA*, **276**, 1957-63.

Coates RJ, Weiss NS, Daling JR, Morris JS, Labbe RF (1998). Serum levels of selenium and retinol and the subsequent risk of cancer. *Am J Epidemiol*, **128**, 515-23.

Cole BF, Baron JA, Sandler RS, et al (2007). Folic acid for the prevention of colorectal adenomas, a randomized clinical trial. *JAMA*, **297**, 2351-9.

Cook NR, Le IM, Manson JE, Buring JE, Hennekens CH (2000). Effects of beta-carotene supplementation on cancer incidence by baseline characteristics in the Physicians' Health Study (United States). *Cancer Causes Control*, **11**, 617-26.

Delafontaine P, Song YH, Li Y (2004). Expression, regulation and fuction of IGF-1, IGF1R, and IGF 1 binding proteins in blood vessels. *Artherioscler Thromb Vasc Biol*, **24**, 435-44.

Duester G (2008). Retinoic acid synthesis and signaling during early organogenesis. *Cell*, **134**, 921-31.

Duffield-Lillico AJ, Dalkin BL, Reid ME, et al (2003). Nutritional Prevention of Cancer Study Group. Selenium supplementation, baseline plasma selenium status and

incidence of prostate cancer, An analysis of the complete treatment period of the Nutritional Prevention of Cancer Trial. *BJU Int*, **91**, 608-12.

Eichholzer M, Stahelin HB, Ludin E, Bernasconi F (1999). Smoking, plasma vitamins D, E, retinol, and carotene, and fatal prostate cancer, seventeen-year follow-up of the prospective Basel study. *Prostate*, **38**, 189-98.

Faupel-Badger JM, Diaw L, Albanes D, et al (2007). Lack of association between serum levels of 25-hydroxyvitamin D and the subsequent risk of prostate cancer in Finnish men. *Cancer Epidemiol Biomarkers Prev*, **16**, 2784-6.

Fraser DR (2007). Exploration of possible mechanisms linking vitamin D status and dietary calcium to prostate cancer. *Br J Nutr,* **97**, 596-7.

Gann PH, Ma J, Giovannucci E, et al (1999). Lower prostate cancer risk in men with elevated plasma lycopene levels, results of a prospective analysis. *Cancer Res*, **59**, 1225-30.

Gao X, LaValley MP, Tucker KL (2005). Prospective studies of dairy product and calcium intakes and prostate cancer risk, a meta-analysis. *J Natl Cancer Inst*, **97**, 1768-77.

Gaziano JM, Glynn RJ, Christen WG, et al (2009). Vitamins E and C in the prevention of prostate and total cancer in men, the Physicians' Health Study II randomized controlled trial. *JAMA*, **301**, 52-62.

Gill JK, Franke AA, Steven Morris J, et al (2009). Association of selenium, tocopherols, carotenoids, retinol, and 15-isoprostane F(2t) in serum or urine with prostate cancer risk, the Multiethnic Cohort. *Cancer Causes Control*, **20**, 1161-71.

Giovannucci E, Liu Y, Stampfer MJ, Willett WC (2006). A prospective study of calcium intake and incident and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev*, **15**, 203-10.

Giovannucci E, Pollak M, Liu Y, et al (2003). Nutritional predictors of insulin-like growth factor I and their relationship to cancer in men. *Cancer Epidemiol Biomarkers Prev*, **12**, 84-9.

Giovannucci E, Rimm EB, Liu Y, Stampfer MJ, Willett WC (2003). A prospective study of cruciferous vegetables and prostate cancer. *Cancer Epidemiol Biomarkers Prev*, **12**, 1403-9.

Hanchette CL, Schwartz GG (1992). Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. *Cancer*, **70**, 2861-9.

Heinonen OP, Albanes D, Virtamo J, et al (1998). Prostate cancer and supplementation with alpha-tocopherol and beta-carotene, incidence and mortality in a controlled trial. *J Natl Cancer Inst*, **90**, 440-6.

Helzlsouer KJ, Huang HY, Alberg AJ, et al (2000). Association betweenalpha-tocopherol, gamma-tocopherol, selenium, and subsequent prostate cancer. *J Natl Cancer Inst*, **92**, 2018-23.

Hsing AW, Comstock GW, Abbey H, Polk BF (1990). Serologic precursors of cancer. Retinol, carotenoids, and tocopherol and risk of prostate cancer. *J Natl Cancer Inst*, **82**, 941-6.

Huang HY, Alberg AJ, Norkus EP, et al (2003). Prospective study of antioxidant micronutrients in the blood and the risk of developing prostate cancer. *Am J Epidemiol*, **157**, 335-44.

Huncharek M, Muscat J, Kupelnick B (2008). Dairy products, dietary calcium and vitamin D intake as risk factors for prostate cancer, A meta-analysis of 26,769 cases from 45 observational studies. *Nutr Cancer*, **60**, 421-41.

Huss WJ, Lai L, Barrios RJ, Hirschi KK, Greenberg NM (2004). Retinoic acid slows progression and promotes apoptosis of spontaneous prostate cancer. *Prostate*, **61**, 142-52.

Jacobs ET, Giuliano AR, Martı´nez ME, et al (2004). Plasma levels of 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and the risk of prostate cancer. *J Steroid Biochem Mol Biol*, **89-90**, 533-7.

Jiang AL, Zhang PJ, Chen WW, et al (2006). Effects of 9-cis retinoic acid on human homeobox gene NKX3.1 expression in prostate cancer cell line LNCaP. *Asian J Androl*, **8**, 435-41.

Ju J, Picinich SC, Yang Z, et al (2010). Cancer preventive activities of tocopherols and tocotrienols. *Carcinogenesis*, **31**, 533-42.

Karimi G, Shahar S, Homayouni N, et al (2012). Association between trace element and heavy metal levels in hair and nail with prostate cancer. *Asian Pac J Cancer Prev*, **13**, 4249-53.

Karppi J, Kurl S, Laukkanen JA, Kauhanen J (2012). Serum β-carotene in relation to risk of prostate cancer, the Kuopio Ischaemic Heart Disease Risk Factor study. *Nutr Cancer*, **64**, 361-7.

Key TJ, Allen N, Appleby P, et al (2004). Fruits and vegetables and prostate cancer, no association among 1104 cases in a prospective study of 130 544 men in the European Prospective Investigation into Cancer and Nutrition (EPIC). *Int J Cancer*, **109**, 119-24.

Key TJ, Appleby PN, Allen NE, et al (2007). Plasma carotenoids, retinol, and tocopherols and the risk of prostate cancer in the European Prospective Investigation into Cancer and Nutrition study. *Am J Clin Nutr*, **86**, 672-81.

Khandrika L, Kumar B, Koul S, Maroni P, Koul HK (2009). Oxidative stress in prostate cancer. *Cancer Lett*, **282**, 125-36.

Klein EA, Thompson IM Jr, Tangen CM, et al (2011). Vitamin E and the risk of prostate cancer, the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*, **306**, 1549-56.

Knekt P, Aromaa A, Maatela J, et al (1990). Serum vitamin A and subsequent risk of cancer, cancer incidence follow-up of the Finnish Mobile Clinic Health Examination Survey. *Am J Epidemiol*, **132**, 857-70.

Kovalenko PL, Zhang Z, Yu JG, et al (2011). Dietary vitamin d and vitamin d receptor level modulate epithelial cell proliferation and apoptosis in the prostate. Cancer Prev Res (Phila) 4, 1617-25.

Lee HJ, Ju J, Paul S, et al (2009). Mixed tocopherols prevent mammary tumorigenesis by inhibiting estrogen action and activatingPPAR-g. *Clin Can Res*, **15**, 4242-9.

Li GX, Lee MJ, Liu AB, et al (2011). Delta-tocopherol is more active than alpha- or gamma -tocopherol in inhibiting lung tumorigenesis *in vivo*. *Cancer Prev Res (Phila)*, **4**, 404-13.

Li H, Stampfer MJ, Hollis JB, et al (2007). A prospective study of plasma vitamin D metabolites, vitamin D receptor polymorphisms, and prostate cancer. *PLoS Med*, **4**, 562-71.

Lippman SM, Klein EA, Goodman PJ, et al (2009). Effect of seleniumand vitamin E on risk of prostate cancer and other cancers, the Selenium and Vitamin E Cancer Prevention Trial (SELECT). *JAMA*, **301**, 39-51.

Liu G, Wilding G, Staab MJ, et al (2003). Phase II study of 1ahydroxyvitamin D2 in the treatment of advanced androgen independent prostate cancer. *Clin Cancer Res*, **9**, 4077-83.

Lu G, Xiao H, Li G, et al (2010). γ-tocopherols-rich mixture of tocopherols inhibits chemically-induced lung tumorigenesis in A/J mice and xenograft tumor growth. *Carcinogenesis*, **31**, 687-94.

Lu QY, Hung JC, Heber D, et al (2001). Inverse associations between plasma lycopene and other carotenoids and prostate cancer. *Cancer Epidemiol Biomarkers Prev*, **10**, 749-56.

Mahabir S, Schendel K, Dong YQ, et al (2008). Dietary alpha-, beta-, gamma- and delta-tocopherols in lung cancer risk. *Int J Cancer*, **123**, 1173-80.

Martini LA, Wood RJ (2009). Milk intake and the risk of type 2 diabetes mellitus, hypertension and prostate cancer. *Arq Bras Endocrinol Metabol*, **53**, 688-94.

McCormick DL, Rao KV, Johnson WD, et al (2010). Null activity of selenium and vitamin e as cancer chemopreventive agents

in the rat prostate. *Cancer Prev Res*, **3**, 381-92.
McNeil C (2011). Vitamin E and prostate cancer, research focus turns to biologic mechanisms. *J Natl Cancer Inst*, **103**, 1731-4.
Meydani M (1995). Vitamin E. *Lancet*, **345**, 170-5.
Milne DB, Botnen J (1986). Retinol, alpha-tocopherol, lycopene, and alpha- and beta-carotene simultaneously determined in plasma by isocratic liquid chromatography. *Clin Chem*, **32**, 874-6.
Mondul AM, Watters JL, Mannisto S, et al (2011). Serum Retinol and Risk of Prostate Cancer. *Am J Epidemiol*, **173**, 813-21.
Mongan NP, Gudas LJ (2007). Diverse actions of retinoid receptors in cancer prevention and treatment. *Differentiation*, **75**, 853-70.
Neuhouser ML, Barnett MJ, Kristal AR, et al (2009). Dietary supplement use and prostate cancer risk in the carotene and retinol efficacy trial. *Cancer Epidemiol Biomarkers Prev*, **18**, 2202-6.
Omenn GS, Goodman GE, Thornquist MD, et al (1996). Risk factors for lung cancer and for intervention effects in CARET, the Beta-Carotene and Retinol Efficacy Trial. *J Natl Cancer Inst*, **88**, 1550-9.
Ozten N, Horton L, Lasano S, Bosland MC (2010). Selenomethionine and alpha-tocopherol do not inhibit prostate carcinogenesis in the testosterone plus estradiol-treated NBL rat model. *Cancer Prev Res*, **3**, 371-80.
Park S-Y, Murphy SP, Wilkens LR, et al (2007). Calcium, vitamin D and dairy product intake and prostate cancer risk. The multiethnic cohort study. *Am J Epidemiol*, **166**, 1259-69.
Peehl DM, Feldman D (2003). The role of vitamin D and retinoids in controlling prostate cancer progression. *Endocr Relat Cancer*, **10**, 131-40.
Peehl DM, Skowronski RJ, Leung GK, et al (1994). Antiproliferative effects of 1,25 dihydroxyvitamin D3 on primary cultures of human prostatic cells. *Cancer Res*, **54**, 805-10.
Peterlik M, Cross HS (2009). Vitamin D and calcium insufficiency-related chronic diseases, molecular and cellular pathophysiology. Eur. *J Clin Nutr*, **63**, 1377-86.
Reichman ME, Hayes RB, Ziegler RG, et al (1990). Serum vitamin A and subsequent development of prostate cancer in the first national health and nutrition examination survey epidemiologic follow-up study. *Cancer Res*, **50**, 2311-15.
Rock CL (2007). Multivitamin-multimineral supplements, Who uses them?. Am. *J Clin Nutr*, **85**, 277S-9S.
Rowland GW, Schwartz GG, John ES, Ingles SA (2012). Calcium intake and prostate cancer among African Americans, effect modification by vitamin d receptor calcium absorption genotype. *J Bone Miner Res*, **27**, 187-94.
Sakr WA, Sarkar FH, Sreepathi P, Drozdowicz S, Crissman JD (1993). Measurement of cellular proliferation in human prostate by AgNOR, PCNA, and SPF. *Prostate*, **22**, 147-54.
Schenk JM, Riboli E, Chatterjee N, et al (2009). Serum retinol and prostate cancer risk, A nested case-control study in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol. *Biomarkers Prev*, **18**, 1227-31.
Schwartz GG, Hulka BS (1990). Is vitamin D deficiency a risk factor for prostate cancer? (Hypothesis). *Anticancer Res*, **10**, 1307-11.
Schwartz GG (2009).Is serum calcium a biomarker of fatal prostate cancer? *Future Oncol*, **5**, 577-80.
Skinner HG, Schwartz GG (2008). Serum calcium and incident and fatal prostate cancer in the National Health and Nutrition Examination Survey. *Cancer Epidemiol Biomarkers Prev*, **17**, 2302-5.
Skinner HG, Schwartz GG (2009). A prospective study of total and ionized serum calcium and fatal prostate cancer. *Cancer Epidemiol Biomarkers Prev*, **18**, 575-8.
Skinner HG, Schwartz GG (2009). The relation of serum parathyroid hormone and serum calcium to serum levels of prostate-specific antigen, a population-based study. *Cancer Epidemiol Biomarkers Prev*, **18**, 2869-73.
Takahashi S, Takeshita K, Seeni A, et al (2009). Suppression of prostate cancer in a transgenic rat model via gamma-tocopherol activation of caspase signaling. *Prostate*, **69**, 644-51.
Travis RC, Crowe FL, Allen NE, et al (2009). Serum Vitamin D and Risk of Prostate Cancer in a Case-Control Analysis Nested Within the European Prospective Investigation into Cancer and Nutrition (EPIC). *Am J Epidemiol*, **169**, 1223-32.
Tseng M, Breslow RA, Graubard BI, Ziegler RG (2005). Dairy, calcium, and vitamin D intakes and prostate cancer risk in the National Health and Nutrition Examination Epidemiologic Follow-up Study cohort. *Am J Clin Nutr*, **81**, 1147-54.
Tseng M, Giri V, Bruner DW, Giovannucci E (2009). Dairy intake and 1,25-dihydroxyvitamin d levels in men at high risk for prostate cancer. *Cancer Causes Control*, **20**, 1947-54.
Velicer CM, Ulrich CM (2008). Vitamin and mineral supplement use among US adults after cancer diagnosis, A systematic review. *J Clin Oncol*, **26**, 665-673.
Weaver CM (2009). Should dairy be recommended as part of a healthy vegetarian diet? Point. *Am J Clin Nutr*, **89**, 1634-7.
Weinstein SJ, Peters U, Ahn J, et al (2012). Serum a-tocopherol and c-tocopherol concentrations and prostate cancer risk in the plco screening trial, a nested case-control study. *PLoS One*, **7**, 40204.
Willis MS, Wians FH (2003). The role of nutrition in preventing prostate cancer, a review of the proposed mechanism of action of various dietary substances. *Clin Chim Acta*, **330**, 57-83.
Wiygul JB, Evans BR, Peterson BL, et al (2005). Supplement use among men with prostate cancer. *Urology*, **6**, 161-6.
WCRF/AICR (1997). Food, Nutrition And The Prevention Of Cancer, A Global Perspective. World Cancer Research Fund / American Institute for Cancer Research.
World Cancer Research Fund/American Institute for Cancer Research.(2007) Food, Nutrition, Physical Activity, and the Prevention of Cancer, A Global Perspective. Washington, DC, American Institute for Cancer Research.
Yang L, Pascal M, Wu X-H (2013). Review of selenium and prostate cancer prevention. *Asian Pac J Cancer Prev*, **14**, 2181-4.
Zheng X, Cui XX, Khor TO, et al (2012). Inhibitory effect of a γ- tocopherol-rich mixture of tocopherols on the formation and growth of LNCaP prostate tumors in immunodefficient mice. *Cancers*, **3**, 3762-72.