Review Article

The role of nutritional interventions in prostate cancer: A review

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The high prevalence rate in conjunction with the long latency period made prostate cancer (PCa) an attractive and reasonable candidate for preventive measures. So far, several dietary and nutritional interventions have been implemented and studied with the aim of preventing the development or delaying the progression of PCa. Calorie restriction accompanied by weight loss has been shown to be associated with decreased likelihood of aggressive PCa. Supplements have played a major role in nutritional interventions. While genistein and lycopene seemed promising as preventive agents, minerals such as zinc and selenium were shown to be devoid of protective effects. The role of vitamins has been widely studied, with special emphasis on vitamins with antioxidant properties. Data related to Vitamin A and Vitamin C were rather controversial and positive effects were of insignificant magnitude. Vitamin E was associated with a decreased risk of PCa in high-risk groups like smokers. However, when it comes to Vitamin D, the serum levels might affect the risk of PCa. While deficiency of this vitamin was associated with increased risk, high serum levels imposed the risk of aggressive disease. Despite the seemingly promising effects of dietary measures on PCa, no firm recommendation could be made due to the limitations of the studies and evidence. However, the majority of these advices could be followed by the patients with the intent of living a healthy lifestyle.

Key words: Diet, nutritional interventions, prostate cancer, supplements

How to cite this article: Nowroozi MR, Ghaedi E, Behnamfar A, Amini E, Momeni SA, Mahmoudi M, *et al.* The role of nutritional interventions in prostate cancer: A review. J Res Med Sci 2021;26:29.

INTRODUCTION

Extensive evidence exists related to the role of different nutrients and diets in prostate cancer (PCa) development.[1,2] In fact, several studies have shown that a healthy diet can prevent up to 40% of all cancers.[3] PCa is the second most prevalent cancer in men; it imposes an overwhelming financial burden on medical systems. Therefore, it is justified to make every effort to prevent its development and halt its progression.[4] The long latency period between the initial evidence of PCa and the development of overt disease provides us with the opportunity to affect the course of the disease through dietary and nutritional interventions. In this review, we intend to outline the dietary and nutritional interventions which have been implemented with the aim of modifying the risk of development and progression of PCa.

CALORIE RESTRICTION AND WEIGHT LOSS

So far, obesity has reached epidemic proportions in developed countries due to the increased availability of food resources in addition to hereditary and behavioral and psychological factors. As such, the number of overweight and obese people has doubled worldwide in the past two decades.[5]

Access this article online

Quick Response Code:

Website: www.jmsjournal.net

DOI: 10.4103/jrms.JRMS_975_20

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Submitted: 07-Sep-2020; **Revised:** 22-Sep-2020; **Accepted:** 25-Dec-2020; **Published:** 27-May-2021

Obesity has been found to be associated with PCa progression and aggressiveness. In addition, it was correlated with increased biochemical recurrence, poor nonsurgical treatments outcome, and higher cancer-specific mortality.[6-9] Therefore, it seems rational to assume that calorie restriction accompanied by weight loss can reduce the likelihood of aggressive form of PCa. Calorie restriction reportedly slows the progression of PCa in TRAMP mice and prolongs its survival.[10] In addition, 30% calorie reduction in Hi-Myc transgenic mice delays PCa development.[11] Moreover, it has been shown that weight loss of more than 11 pounds in a period of 10 years reduced the incidence of nonmetastatic high-grade PCa by 45%.[12] However, a 6-month low-carbohydrate regimen in patients with biochemical recurrence was not associated with improvement in PSA doubling time compared to the control group.[13] More studies are needed to assess the effects of weight loss on PCa progression.

SUPPLEMENTATION

Soy and Soy products

Epidemiologic studies have suggested that higher consumption of soy and soy products is associated with the reduced risk of PCa. The Adventist Health Study showed that participants who consumed soy milk more than once a day had a 70% lower risk of PCa (RR = 0.3). High concentrations of isoflavonoids in the prostate fluid may block cellular proliferation and also decrease the toxic byproducts of oxidation through its antioxidant activity.[14]

Genistein is the major isoflavone in soy products. Its effect on PCa cells has been widely studied. An animal study showed that dietary soy products may decrease the growth of transplantable human prostate carcinoma in mice.[15] Although there are some data in favor of preventive role of genistein, a scarcity of evidence exists related to its use as a treating agent in PCa.[16]

A randomized controlled trial (RCT) evaluated the effect of a combination of Vitamin E, selenium, and soy on progression from high-grade prostatic intraepithelial neoplasia (HGPIN) to PCa. The hazard ratio for this combination to prevent PCa was 1.03 (95% CI, 0.67–1.60; P = 0.88). Therefore, the authors believed that these agents have no role in the primary prevention of invasive PCa in men with HGPIN at biopsy.[17] However, in a systematic review and meta-analysis conducted by Applegate *et al*., there was a statistically significant association between soy consumption and decreased risk of PCa.[18]

Lycopene

Lycopene is a powerful antioxidant mostly present in tomatoes. Several epidemiological, experimental, and clinical studies over the past decade reported that consumption of tomatoes and tomato products is associated with a reduced risk of PCa. Lycopene is responsible for the red pigment of tomatoes and watermelon. It exists in prostate tissue in large amounts.[19] A large cohort study reported that consumption of two to four servings of raw tomatoes weekly is associated with a 26% reduction of PCa risk. The risk is reduced even more (35%) by increasing the number of servings to more than 10. Other studies also reported an inverse association between serum lycopene level and PCa risk in subjects older than 65 years old.[20]

In a trial, PCa patients consumed tomato sauce-based pasta for 21 days prior to radical prostatectomy. Lycopene consumption significantly decreased prostate-specific antigen (PSA) levels and leukocyte oxidative DNA damage.[21] A decrease in PCa risk also has been shown in a large meta-analysis (relative risk [RR] = 0.78, 95% confidence interval [CI]: 0.66–0.92).[22] It has been postulated that lycopene may exert its protective effects through saving 2-deoxy-guanosine from reactive oxygen species, decreasing insulin-like growth factor-1-induced cell proliferation,[23-25] and decreasing carcinogen phosphorylation of tumor suppressor genes like p53.[26] Moreover, lycopene has been noticed to be able to downregulate androgen metabolism and signaling in PCa.[27]

Minerals

Selenium theoretically plays a role in the pituitary–adrenal–gonadal axis and a clinical trial revealed that it may exert a protective effect against PCa development.[28] Furthermore, another RCT showed that intake of 200 μg of selenized yeast was associated with a 49% reduction in the risk of PCa, especially in low baseline serum selenium levels and age of younger than 65 years with a PSA of <4 ng/mL.[29] However, the protective effects of selenium have been contravened by upcoming trials. According to the Selenium and Vitamin E Cancer Prevention Trial (SELECT) trial, neither selenium or Vitamin E alone nor their combination did not decrease PCa risk. In fact, selenium supplementation was associated with an increase in PCa risk. Based on this well-conducted study, the authors recommended against using these supplements as preventive agents.[30,31] Later, a Mendelian randomization analysis confirmed SELECT findings and showed that not only selenium had no effect on PCa prevention but also was associated with advanced PCa.[32]

Zinc with its antioxidant characteristics has been reported to be present in high amounts in the prostate tissue; *in vitro* studies showed that it inhibits PCa cell growth.[33,34] In a study, dietary zinc was not found to be associated with a decrease in PCa risk overall. However, the risk of advanced PCa reduced with a greater intake

of supplemental zinc.[35] A comprehensive review claims that zinc supplementation is a credible approach for the prevention of PCa development.[36]

Pomegranate

Pomegranate extract was shown to be able to inhibit the growth of PCa cells and induce apoptosis of aggressive human PCa cells.[37] An experimental study on human metastatic PCa cell lines revealed that pomegranate juice and peel extracts exert anti-cancer effects against PCa cells through the mechanistic target of rapamycin signaling cascade.[38] In a Phase II RCT of men with rising PSA following radical prostatectomy or radiotherapy, daily consumption of pomegranate juice for several months led to prolongation of PSA doubling time implying that this supplement may slow down the progression of PCa.[39,40] Thus, this agent might be used in PCa patients with the aim of improving their treatment outcomes and hopefully survival.

Green tea and black tea

Polyphenolic antioxidant of tea has been reported to be able to prevent cancer formation in prostate cells.[41] In a trial, 20 men who were scheduled for radical prostatectomy were randomly assigned to three groups of green tea, black tea, and caffeine-matched soda (as control group). The patients consumed these drinks in a daily fashion for 5 days prior to the operation. Green tea and black tea led to higher polyphenols concentration in prostate tissue compared to soda. Interestingly, the proliferation of PCa cells could be blocked by adding the serum of the patients who took green or black tea to the medium. In addition, the study verified the bioavailability of theaflavins in prostate tissue; where they may exert their preventive effects.[42]

Several experimental and epidemiological studies have focused on the possible role of catechins and other tea polyphenols against PCa in humans.[43] In a study, the authors did notice that green tea consumption was associated with a dose-dependent decrease in the risk of advanced PCa (RR = 0.52, 95% CI 0.28-0.96).[44] In an RCT, 60 volunteers with high-grade PIN randomized to receive either green tea catechins or placebo and followed with two saturation biopsies within a year. Green tea catechins supplementation was associated with an almost 80% reduction in PCa diagnosis, from 53% to 11%.[45] Recently, a meta-analysis revealed that drinking green tea of more than 7 cups/day can reduce the risk of PCa. In addition, the green tea catechins were found to be effective in preventing PCa (RR = 0.38, P = 0.02).[46]

Vitamin E

Findings regarding the possible preventive role of Vitamin E supplementation are conflicting.[47] While some studies endorse beneficial role of Vitamin E as a preventive agent,[32,48] others reject this notion or are inconclusive. The early report of the SELECT showed that Vitamin E had no effect on PCa development.[49] However, with longer follow-up, the study revealed that dietary supplementation of Vitamin E significantly increased the risk of PCa among healthy men.[31]

Several studies claimed that the effect of Vitamin E supplementation on PCa risk could be varied based on the smoking history of the patients. As such, SELECT trial has shown that Vitamin E may help prevent PCa in smokers as opposed to nonsmokers; possibly due to the high oxidative stress conditions in smokers. In fact, in nonsmokers, Vitamin E excess could enhance PCa risk.[31] Likewise, the prostate, lung, colorectal, and ovarian (PLCO) study showed a significant decrease in PCa aggressiveness among smokers following Vitamin E supplementation (doses in excess of 400 IU/day led to 71% reduction in risk of advanced PCa).[50] In general, Vitamin E supplementation may only exert a protective effect against PCa in high-risk groups like smokers.

Vitamin C

Animal studies showed that Vitamin C alone or in combination with Vitamin E inhibits PCa cell growth.[51] A study claimed that higher intakes of fruits-including citrus fruits rich in Vitamin C-were associated with the higher incidence of PCa (OR = 1.51, 95% CI = 1.1–-2.01 for 4th quartile).[52] This finding appears to contradict the hypothesis of the protective effects of Vitamin C. Moreover, an RCT showed that a daily intake of 400 IU Vitamin E and 500 mg of Vitamin C was not associated with a decrease in PCa risk.[53] Vitamin C in doses higher than recommended dietary levels might have therapeutic effects in some cancers.[54] A study showed that the administration of high-dose intravenous Vitamin C led to PSA reduction in 75% of prostatic cancer patients.[55] However, this finding was no reproduced in another trial.[56]

Vitamin A and β-carotene

Beta-carotene is a precursor of Vitamin A and is responsible for the orange pigment in plants and vegetables. In a case–control study, higher intake of carotene and beta-carotene was associated with a decline in PCa risk (OR = 0.70 and 0.72, respectively).[57] A nested case–control study in the PLCO trial showed that higher concentrations of serum retinol were associated with a 42% reduction in aggressive (GS >7) PCa risk.[58] In contrast, in carotene and retinol efficacy trial, the risk of PCa did not differ by taking a daily dose of β-carotene (30 mg) and retinyl palmitate (25,000 IU). However, when other dietary supplements accompanied this combination,

the risk of aggressive PCa increased (RR = 1.52).[59] Nevertheless, a recent study showed that daily intake of carrot (>3.2 g/day) might be associated with decreased PCa risk (OR: 0.35, CI: 0.21–0.58).[60]

Vitamin D

Vitamin D receptor signaling has been found to play role in the development and prognosis of PCas.[61] Moreover, it has been reported that Calcitriol is able to inhibit the proliferation of PCa cell lines.[62] A study conducted by John *et al*. showed that residential sunlight exposure is associated with lower PCa risk; the result which indirectly points to the protective effect of Vitamin D on PCa.[63] Likewise, higher circulating 25(OH) D has been shown to be associated with a 57% reduction in the risk of lethal PCa.[64] It has been proposed that Vitamin D binding protein may modulate the association between serum Vitamin D levels and the risk of advanced and lethal PCa.[65]

However, some studies have put this effect into question as higher serum levels of Vitamin D were not associated with decreased PCa risk. In fact, it might be associated with the greater risk of aggressive PCa.[66,67]

Resveratrol

Resveratrol known as a superior cancer chemopreventive agent is a stilbenoid with potential antioxidant properties which is found in high amounts in grapes skin.[68] The results of pre-clinical studies in animals and cell lines led to the hypothesis that this agent may exert a preventive effect on cancers including PCa.[69] In a recent study, researchers assessed the synergic effect of resveratrol and cisplatin on PCa cells viability and apoptosis. Resveratrol has been shown to promotes apoptosis in PCa cells and sensitizes these cells to cisplatin.[70] Thus, despite the scarcity of clinical data, it seems worthwhile to consider resveratrol as a potential cancer-preventive agent in future clinical studies.

Indoles and isothiocyanates

Indoles are found in Brassica vegetables such as cabbage, broccoli, and Brussels sprouts. An *in vitro* study revealed that Indole-3-carbinol has anti-proliferative effects on PCa cells. Thus, it deserves to be considered as a potential chemotherapeutic agent and warrants further study.[71] A study showed that higher consumption of cruciferous vegetables-as the main source of Isothiocyanates-is associated with reduced risk of PCa.[72] Nevertheless, this association was not replicated by another trial.[73]

CONCLUSION

The relatively indolent course of PCa provides us with the opportunity to intervene with the intention of preventing the disease using a variety of nutritional and lifestyle modifications. So far, many dietary and nutritional interventions have been studied such as calorie restriction and supplement consumption. Calorie restriction has been shown to be associated with the decreased likelihood of aggressive PCa. Supplements like pomegranate may improve PCa treatment outcomes. In addition, antioxidant products found in green and black tea seems to decrease the risk of advanced PCa. Furthermore, genistein in soy products and lycopene in tomatoes are associated with a decreased risk of PCa. However, minerals such as zinc and selenium are not proved to have a preventive effect on PCa. Regarding vitamins, data related to the preventive role of Vitamin A and Vitamin C are inconsistent and results are rather controversial. However, Vitamin E has a reportedly positive effect on preventing PCa in high-risk groups particularly smokers. Furthermore, it seems that Vitamin D deficiency is associated with an increased risk of PCa. Though, more aggressive phenotype of the disease is noticed with higher serum levels of this vitamin. In the nutshell, there are no conclusive evidence regarding the positive effect of nutritional interventions on PCa development and progression. Nevertheless, the majority of these instructions and protocols could be followed by the patients with the intent of living a healthy lifestyle.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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