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Prophylaxis and Treatment of Prostate Cancers by Nutrition Supplements: A Clinician's View of Facts and Hope After the SELECT Study

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ABSTRACT

The well-known Selenium and Vitamin E Cancer Prevention Trial (SELECT) published in 2009 seems to show that prevention of prostate cancer by nutrition supplements is ineffective. Many opposing studies have found that various vitamins, minerals, and other over-the-counter (OTC) drugs show measurable effects in prostate cancer prevention and treatment. One purpose of the present review is to discuss some possible causes for the negative results in the SELECT study. For example, it is possible that unknown intake of vitamin C influenced their results, because vitamin C alters the effect of selenium. A second purpose of this review is to present evidence from other literature that an effective prophylaxis of prostate carcinoma is possible. Protective evidence from the literature is shown for selenium, lycopene, lignane, vitamin D, and vitamin E; vitamin C and vitamin B are not protective. Supplement combinations are preferable to single agents. Other substances with preliminary data are discussed. In conclusion, there is substantial evidence in the literature that daily use of protective supplements can be beneficial, and that these benefits should not be dismissed based on a single study that did not control all of the baseline variables.

KEYWORDS: Prostate cancer; Vitamin D; Vitamin E; Selenium; Lignane; Lycopine; Nutrition supplementation

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INTRODUCTION

In 2009, Lippman et al [1] published the results of the Selenium and Vitamin E Cancer Prevention Trial (SELECT). The results showed that prevention of prostate cancer by nutrition supplements is ineffective. However, there are many other well-designed studies that have provided measurable effects showing a reduced risk of developing prostate cancer in patients taking nutritional supplements. The purposes of the present review are to: (1) discuss some possible causes for the negative results in the SELECT study, and (2) present evidence from other literature that an effective prophylaxis of prostate carcinoma is possible. In particular, there is evidence from a randomized controlled trial that selenium has a positive protective effect [2]. Furthermore, a few weeks after the SELECT study was published, an American paper was published which pointed out that there are several drugs and nutrition supplements that reduce prostate cancer development [3].

It is well known that the so-called western lifestyle is related to a higher incidence of cancer development when compared with others. A diet high in cooked and grilled meat, large amounts of fat intake, and alcohol consumption is known to be dangerous [4]. The negative lifestyle effects are mediated by oxidative processes. The original molecular damage [5-7] cannot be healed over a long period of time. Thus, over years or decades, a malignant cell that neglects apoptosis may be growing [6].

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review

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There is evidence to indicate that by engaging in regular sports or other exercise (30 minutes per day), eating a meat-reduced diet, and taking vitamin E (400 units), selenium (200 µg), fish oil (3 mg) and vitamin C (2g) daily, the prostate-specific antigen (PSA) level is reduced. Even manifest prostate cancer can be reduced, an effect which also takes place in cell cultures contaminated with blood samples of those men [8].

In summary, nutritional supplementation must have some effects which cannot be negated by a single study such as SELECT. The purpose of the present review is to report only natural substances available by nutrition. The well-known prostate cancer protective effects of finasteride, dutasteride (PCPT and REDUCE trials), and statins depend on other molecular processes inside the cells and will not be discussed.

Selenium: Risk or Protection?

Selenium is one of the most important drugs in tumor prevention due to its effect on the glutathione peroxidase. Geographically, selenium is unequally distributed with areas of high and low content in soil. For example, Japan has a high concentration in its soil and the incidence of prostate cancer development in Japan is very low when compared with other countries such as Europe. Europe is a continent with a low concentration of selenium; the USA is in between [9,10].

Differences in selenium concentrations in various locations are important to interpreting the outcome of the SELECT study. In a former National Cancer Institute (NCI) study [11] the mean baseline selenium was 113 ng/mL; in the SELECT study [1] the baseline PSA was higher at approximately 135 ng/mL. Furthermore, it is known that the tumor-protection effect of selenium is best between serum levels of 150 and 180 ng/mL [12]. The increase of the selenium serum level in the SELECT study by 200 mg supplementation daily was limited. However, this result should be interpreted with caution because the natural baseline selenium level that is present through normal nutrition was neglected when considering the baseline statistics of the SELECT study.

It takes many years or even decades before a benign cell will become a cancer cell [5,6,9]. At that point, the cellular DNA repair mechanisms no longer are sufficient to prevent cancer development. Therefore, it cannot be expected that a relatively short period of taking selenium as an antioxidative medium (as was the study design of the SELECT study) will be effective in cancer protection. The median intake time of selenium in the SELECT study was only 5.5 years. Furthermore, participants were relatively old when entering the study. Participants with African American racial background were > 50 years old; Caucasian participants were > 55 years old. Thus, decades of DNA damages may have occurred before taking the first selenium supplementation dosage. It can be hypothesized that the fatal DNA damage had already occurred.

It was appropriate to end the SELECT study before following the participants for a longer period of time, because it is known that selenium in higher dosage by additional supplementation on top of a relatively high natural serum level might be toxic [13]. Similar problems may be encountered when taking vitamin E. Therefore, it is not surprising that the SELECT study failed to show a reduction in prostate cancer development during the study period.

The SELECT study showed that a schematic regime of supplementation of selenium and vitamin E was not beneficial. However, individual administration should consider the area where the man is living and what he is eating. For example, in Germany there is different content of selenium in the soil, with a minimum of 74 µg/kg in Bayern and a maximum of 194 µg/kg in Schleswig-Holstein [14]. Depending on diet and baseline levels, a man living in Bayern may need more supplements than a man living in Schleswig-Holstein.

At the same time that the SELECT study was published, the NCI published a study to show the tissue effects of selenium and vitamine E in prostate cancer [15]. The conclusion was: "Dietary or nutrient supplement prevention of cancer may be best achieved by lifelong healthy eating habits." Additionally, the study by Whitley et al [16] supports this conclusion. They demonstrated that nutrient habits in childhood influence prostate cancer development in later life.

In another NCI study [4], it was shown that selenium and vitamin E had positive effects on prostate cancer even in the histology specimen. Selenium also reduced the risk of progression and metastases [17]. The activity of p53 was significantly increased, thus indicating that antitumor effects took place; in 39 men the result was close to statistical significance. Furthermore, selenium induces apoptosis in cells [18].

Selenium is available as selenite and as selenomethionine and selenocysteine. The organic selenium influences the glutathione peroxidase enzyme directly. The anorganic version first must be transformed to the organic form, but this happens in the cell.

Glutathione peroxidase is an enzyme that hinders the enrichment of H_2O_2 and lipid-hyperoxids, which easily react and destroy cell compounds. These oxidation processes are highly responsible for development of cancers, inflammations, and

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coronary artery sclerosis. This helps to explain how selenium is tumor-protective. The serum levels should be adjusted between 130 and 180 ng/mL [12]. Therefore, selenium supplementation should not be performed without serum controls. Furthermore, selenium must not be combined with vitamin C because this combination reduces the efficiency of the selenium.

Vitamins and Other Nutritional Supplements

Multiple studies have shown that there are substances that are protective against prostate cancer when taken regularily. Vitamins A, C, D, and E and selenium and lycopines have been shown to be protective [19-22]. A positive secondary effect is protection against cardiovascular diseases [17,23]. The authors of both of the latter studies point out that it is mandatory to start nutrition supplements early in life. Besides vitamins and selenium, there are other tumor-protective substances available in daily nutrition.

The protective mechanisms can be understood by considering the molecular cascades of DNA damage in tumor development [7]. If this destroying cascade is blocked by antimutagenic substances that repair DNA, cancer can be prevented [4]. In prostate carcinoma, such DNA damage (hypermethylation in the promoter region) is well known [4]. Another study showed similar effects [8].

Vitamin E

Vitamin E is transported by 2 different gene forms (SEC14L2). The gene forms influence the vitamin E serum level to the extent that they likely influence the protection effect of vitamin E [24]. Vitamin E has an effect on the proliferation of prostate cancer cells through high regulation of IGFBP-3. This protects against tumor progression [10].

High natural tocopherol serum levels are protective against prostate cancer [25]. In men with high risk of developing prostate carcinoma, the incidence is reduced [26]. The Alpha-Tocopherol-Beta-Carotene (ATBC) studies [27,28] also showed that vitamin E is tumor-protective. However, this conclusion is not true for every man because protection depends on SEC14L2-gene polymorphism. Thus, there are vitamin E responders and nonresponders [29]. Interestingly, gamma-tocopherol in combination with docetaxel showed synergistic antitumor effect by downregulation of NF-kappa B and EGF-T [30].

Vitamin E seems to be more effective in combination with other supplements. Selenium is the most commonly used partner. Together, advanced tumors are reduced [31]. The combination also induces apoptosis in prostate cancer cells by increasing the relationship between Bax and Bcl2 [32]. Another study showed that the concentration of selenium was antiproportional to prostate cancer risk [33]. Even in small dosage, the protective effect is obvious [34].

Many questions still remain. The NCI published a study in which gamma-tocopherol was tumor-protective, whereas alpha-tocopherol was not [27]. In other American studies, alpha-tocopherol was highly protective [35,36]. In Germany, only alpha-tocopherol is available. It has been shown to be tumor-protective in an animal experiment [37] and in vivo [38]. Further investigations are needed to resolve the discrepancies in these reports.

Vitamin D

Vitamin D (calcitriol) is important in the treatment of malignant tumors. It has been known for 25 years that the vitamin D receptor (VDR) influences cell proliferation and differentiation [39,40]. Therefore, active form 1alpha,25-dihydroxy-vitamin D (1alpha,25 (OH)2D) hampers proliferation of prostate cancer cells and induces their differentiation [41]. These actions are accomplished by reduction of c-Myc-mRNA in the tumor cell [42].

The PCLO study showed an increased risk for prostate cancer development in men who had a low vitamin D serum level [43]; these results were confirmed by others [44]. Vitamin D itself does not have side effects when given as supplementation [44].

Calcitriol hampers the synthesis and activity of proinflammatory prostaglandins by hampering the cyclooxygenase (COX-2) [45]. Thus, inflammatory processes are reduced. This also explains the tumor-protective effect of vitamin D, because it is proposed that prostatitis triggers prostate cancer development. Therefore, the VDR can be used as genetic marker for prostate cancer risk.

Lycopene

Mediterranian food is known as a main cause for reduced tumor incidence in this geographic region, most likely due to tomatoes and tomato products. Epidemiologic data confirm this conclusion. The main active substances are lycopenes [46].

It has been shown that high lycopene levels are associated with low prostate cancer risk [47], because lycopenes are enriched in prostatic tissue [48]. There, they influence the insulin-like growth factor (IGF) system and induce cell apoptosis in cancer cells. The IDF-I-level is reduced and the content of the binding protein (IGFBP-3) is increased [49-51]. Therefore, cell cycle arrest occurs [52] and the PSA level is lowered. Interestingly, a new study showed that chemically isolated lycopenes seem to

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be less effective than those extracted from tomatoes [53].

Lignanes

The tumor-protective activity of soy products is also well known from epidemiologic studies. The active substance is lignane. Lignane hampers prostate cancer cell growth by triggering the apoptosis [54]. In a Swedish study, the isolated substance was less effective when compared with the nutritional soy phytoestrogens [55]. Another study showed that soy-containing food protects against prostate cancer [56]. Men with a specific type of gene polymorphism can profit the most from this protective effect [57], which is mediated by suppression of androgen signalling and induction of apoptosis [58,59].

Combinations of Minerals and Vitamins

Although it is mandatory to proof all single substances for their protective activity, it is obvious that there is no single prophylactic or therapeutic agent. This is supported by the fact that a tumor cell progresses through many different developmental steps and there are many repair mechanisms that can influence the development.

It is clear that the combination of minerals and vitamins shows synergistic effects [60]. For example, intracellular genome activity and repair were shown for selenium and vitamin D [61]. However, some combinations are not without problems, as the SELECT study [1] demonstrated. Furthermore, artificial and natural source substances are not exactly similar, as previously described [58]. However, it should be noted that the healthy mediterranian food diet is a mixture of different single agents.

It is known that there are some interferences between selenium and vitamin C and between vitamins C and E; these combinations not only eliminated effectiveness [61] but also increased mortality risk [29]. Knowing these side effects and the widespread use of vitamin C, it is possible that one or more of these supplements could have contributed to the negative result of the SELECT-study. Over-the-counter drugs (OTC) were not noted. Problematic combinations of nutritional supplements or other OTC-drugs must be controlled or avoided in future investigations.

In conclusion, there is clear evidence that some nutritional substances are antitumor-active in prostate cancer. However, schematic administration and prescription could be problematic. These protective agents have to be prescribed with the same clear caution that is exercised for all pharmaceutical drugs. Furthermore, there are some agents (eg, vitamin K, boron, folic acid and B-vitamins) for which protective activity is not as clear or even disproven.

Vitamin K2

In principle, vitamin K has some influence on tumor cells. Recently, the Heidelberg study group [62] demonstrated that vitamin K1 is not active whereas vitamin K2 (menaquinon) is active. This was also shown in prostate cancer [63], but this preliminary result has to be confirmed by further study.

Boron

Boron influences steroid hormone levels. Therefore, it was thought that it might be protective in prostate cancer. However, a pilot study [64] could not show this clearly, and boron seems to be coactive in combination with selenium [65].

Folic acid and B-vitamins

In an NCI placebo-controlled study that took place over 10 years, men receiving folic acid had an incidence of prostate cancer that was about 1/3 less than men receiving a placebo [66,67]. Data are contradictive for B-vitamins. Vitamin B12 in combination with folic acid seems to increase tumor progression in aggressive cancer [68]. Further studies support these data [69,70]. Other B-vitamins can also increase tumor growth [70]. Thus, most men should avoid this vitamin group. They should be reserved only for patients with clinical signs of vitamin deficiency.

Target Groups for Nutritional Supplementation

Patients with familial risk for prostate cancer development seem to be the optimal target for protective supplementation. In addition to finasteride and dutasteride, which both reduce cancer risk by approximately 25% (see both PCPT [71] and REDUCE [72] studies), some nutritional supplementations seem to be worth taking as described in this review and other articles.

Patients with atrophic cells in their prostate biopsy might profit from the apoptotic activity and cell and gene repair mechanisms offered by nutritional supplements. Although these atrophic cells are not yet cancer, they can be an early stage in what may later manifest as cancer. The risk for cancer development averages approximately 50%, as shown in studies [73,74]. The atrophic cell area that is a precursor of later cancer can be detected very early by 3D-CDI-TRUS [75]. Therefore, it seems attractive to offer these patients protective drugs such as 5-alpha-reductase inhibitors and nutrition supplements to support genetic repair mechanisms. Results of an unpublished study written by the present author showed that it was possible to decrease PSA level and bring atrophic lesions inside the prostate into regression using this combination. These results are supported by another recently published study [3]. Additionally, 2 study groups using a wait-and-see-regime

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for patients with prostate cancer demonstrated that tumor progression could be slowed by a change to healthy nutrition and lifestyle [8,76]. Healthy nutrition included the above-mentioned minerals and vitamins.

SUMMARY

Cancer prevention and treatment by nutritional agents is complex, and studies are just beginning to show what is possible with their use [77-81]. Schematic administration should be avoided, as the SELECT study result demonstrated [82]. However, evidence from molecular medicine and results from many series of studies demonstrate that prostate cancer protection is possible through correct selection of substances. Individual needs [83] and baseline nutrition should be the basis on which a patient's supplements can be prescribed, in order to compensate for shortage of substrate. Overdosage must be avoided. Even individual genomic analysis might lead to better supplementation. Furthermore, negative interactions must be considered.

In conclusion, further studies are mandatory to avoid overlooking a variable that may contribute to the results. In the SELECT study, the authors did not consider baseline serum levels and OTC drugs. Although considering nutritional supplements and OTC drugs may negatively influence the number of men that can form a study group, future studies must deal with this topic because individual baseline differences may have a large effect on measured outcomes.

Conflict of Interest: none declared

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