Review Article
International Braz J Urol Vol. 32 (1): 3-14, January - February, 2006

Role of Vitamins, Minerals and Supplements in the Prevention and Management of Prostate Cancer

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ABSTRACT

The authors review the current literature on the complementary and alternative medicines most frequently utilized by prostate cancer patients and those at risk for the disease. Products covered are vitamin E, vitamin A, selenium, zinc, soy, lycopene, pomegranate juice, green tea and omega-3 fatty acids. There is no definitive proof that any of the nutritional supplements discussed can impact the course of prostate cancer or its development. The authors believe that simply taking a standard daily multivitamin should be sufficient to ensure that patients have the appropriate levels of vitamins and minerals without risking the over utilization of vitamins, minerals, and supplements which can lead to numerous negative side effects.

Key words*: prostatic neoplasms; chemoprevention; complementary medicine; dietary supplements; lycopene; omega-3 fatty acids*
Int Braz J Urol. 2006; 32: 3-14

INTRODUCTION

Over the last decade there has been an increase in the awareness and utilization of complementary and alternative medicines (CAM). Population surveys indicate that the increase is due to people's desire to be pro-active in their health management as well as their sense that anything "natural" is inherently safe (1,2). In terms of prostate cancer, the highest utilization of CAM is amongst those who have already been diagnosed and treated for prostate cancer, and patients with progressive prostate cancer were more likely to use CAM than those with stable disease (3). However, the data supporting this over exuberance of usage is contradictory at best. This article will review the current available data of the most frequently utilized CAM products.

VITAMIN E

Vitamin E (actually a group of 4 tocopherols and 4 tocotrienols) is the most popular supplement used by men. It is estimated that 15% to 17% of men are taking this supplement (4,5). As it is a fat-soluble vitamin, good dietary sources tend to be foods rich in plant-derived oils: avocadoes, nuts, eggs, peanut butter, soybeans, and ready-to-eat whole-grain breakfast cereals. Cooking oils tend to be the largest source of vitamin E in the diet (6). The recommended daily allowance (RDA) is 15 mg (22.5 IU). Plasma levels of vitamin E are saturable at approximately 800 IU.

Vitamin E is generally thought to be safe and has not shown mutagenic properties despite years of megadosing. However, high-dosage ($\geq$ 400 IU/day) vitamin E supplements have recently been shown to

increase the risk of cardiovascular events (7). Alpha-tocopherols (the most abundant natural form of vitamin E) also decrease platelet aggregation and thereby increase the risk for bleeding. Patients should be advised to withhold vitamin E intake 10 to 14 days before prostate biopsy, radical prostatectomy, radioactive seeding or any other surgical procedure (6).

Laboratory Studies

Many in vitro studies across a variety of human cancer cell lines have shown that vitamin E can have a beneficial impact on carcinogenesis. The most well known function of vitamin E is as an antioxidant, detoxifying oxidizing radicals that arise as unwanted by-products during normal metabolism. These oxidizing radicals can interfere with many cellular mechanisms important in cell growth and regulation including those mechanisms involved with prostate carcinogenesis (6). Others roles for vitamin E include as an antiprostaglandin; prostaglandins are believed to have some role in prostate carcinogenesis (9).

In vitro studies of prostate cancer cell lines have also shown that vitamin E induces cell cycle arrest in prostate cancer cells at physiological levels as well as up-regulating the expression of p27, a cell cycle regulator (9).

Clinical Studies

The potential impact of vitamin E usage on the development of prostate cancer was first demonstrated in the findings of the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC Study) (10). This was a randomized, double-blind study of 29,133 male smokers who were given vitamin E (50 mg), beta-carotene (20 mg), both substances, or a placebo daily for 5 to 8 years in order to evaluate the impact of these 2 nutrients on preventing lung cancer. While lung cancer incidence was not diminished, the male smokers taking vitamin E had a dramatic 32% reduction in prostate cancer and a 41% reduction in prostate cancer deaths at 7 years (10). The fact that the ATBC Study was not conceived as a prostate cancer prevention trial, leaves open the possibility that the results represent a statistical fluke.

The answer to the question of whether or not the result was a coincidence is now being tested in the Selenium and Vitamin E Cancer Prevention Trial (SELECT). The SELECT trial is testing vitamin E (400 mg of racemic alpha-tocopheryl acetate) and selenium (200 mcg from L-selenomethionine) in 32,400 American men. Randomization will be equally distributed among 4 study arms (selenium, vitamin E, selenium and vitamin E, and placebo). The study is designed to allow detection of a 25% reduction in the incidence of prostate cancer from the combination of selenium and vitamin E compared to either nutrient alone. The combination effect of the selenium and vitamin E could be synergistic, as was demonstrated in in vitro experiments where the 2 supplements together achieved greater cell growth inhibition than either alone (11). The SELECT trial reached their full complement of men in April 2004. Initial data is anticipated in 2006 with final results in 2013 (12).

VITAMIN A

Vitamin A is a very versatile fat-soluble vitamin that has roles in several body processes. The recommended dietary allowance (RDA) for men is 900 mcg and it is estimated that approximately 3% of men are taking this vitamin as a supplement(s).

According to epidemiological and clinical research, vitamin A is not associated with prostate cancer risk (13). The relationship was hypothesized based on the role retinoids play in regulating the growth differentiation and apoptosis of normal and malignant cells. In the Beta-Carotene and Retinol Efficacy Trial (CARET), a 7-year, randomized, double-blinded, placebo-controlled chemoprevention trial that tested the combination of beta-carotene (30 mg) and retinyl palmitate (vitamin A) (25,000 IU) taken daily against placebo in 12,025 men and 6,289 women at high risk of developing lung cancer, there was no difference in prostate cancer incidence among those men receiving vitamin A and a placebo (14). While that study's primary endpoint was the reduction of lung cancer incidence in a population at high risk of that disease, the data is compelling that vitamin A is most probably not going to be a chemopreventive agent for prostate cancer.

SELENIUM

Selenium is a trace element that occurs in both organic and inorganic forms. The organic form enters through the food chain via the consumption of plants grown in soil containing the inorganic form. It is found in seafood, meat and grains and the amount varies depending on the amount present in the soil. It is estimated that 9% to 10% of men are taking this supplement (4,5).The RDA is 55 mcg and the Tolerable Upper Intake Level (UL) for adults is 400 mcg. An excess of selenium can impair natural killer cell activity, impact the synthesis of thyroid hormones and the metabolism of growth hormone and insulin-like growth factor-1, and also has dermatologic effects, such as nail and hair loss and dermatitis (15).

Anticancer Properties of Selenium

The exact method whereby selenium affects carcinogenesis is unknown, but its role as an antioxidant (both alone and incorporated as a cofactor in antioxidant enzymes) has been an area of research focus. Other potential effects include antiproliferation, induction of apoptosis, modulation of androgen levels, and effects on immune function (16,17).

Clinical Studies

While many epidemiologic studies have shown evidence of a link between low selenium levels and higher cancer incidence, it was the Nutritional Prevention of Cancer (NPC) Trial that highlighted its relationship to prostate cancer. The NPC Trial of 1,312 men and women was a randomized trial of 200 mcg of daily selenium designed to test whether such supplementation could reduce the risk of recurrent non-melanoma skin cancer (18). While the selenium supplementation did not have an effect on skin cancer, at the end of the trial, an analysis of the 457 men receiving supplementation showed a significantly lower incidence of prostate cancer than those 470 men receiving a placebo (with a mean follow-up of more than 7 years). Among men with baseline PSA values of less than or equal to 4 ng/mL, the results showed a significant 65% reduction in prostate cancer incidence with selenium supplementation. Those participants with PSA values in excess of 4 ng/mL showed no reduction in incidence. When the data from the NPC Trial is evaluated based on baseline selenium levels, those men in the lowest and middle tertiles (≤ 123.2 ng/mL) showed significant reductions in incidence of 86% and 61%, respectively. Researchers have also evaluated a cohort from the Health Professionals Follow-Up Study of 51,529 men over 8 years that showed that when the 181 case subjects with advanced prostate cancer were segregated into five groups based on baseline selenium levels, those men in the study in the highest quintile of selenium level had a 51% lower risk of advanced prostate cancer than those men in the lowest quintile of selenium level (19). Until the results of the SELECT Trial are available, it seems that only those with low levels of selenium (this should be tested first) are appropriate candidates for supplementation with the mineral.

ZINC

Zinc is an essential mineral that acts as a cofactor for more than seventy enzymes. The RDA for men is 11 mg per day and approximately 7% to 8% of men report taking it (4,5). Zinc at high levels can be toxic; intakes of 150 to 450 mg per day have been associated with low copper status, altered iron function, reduced immune function, reduced levels of high-density lipoproteins, and hair loss (20). Low copper status, in turn, can cause a sideroblastic anemia, leukopenia, and neutropenia (21). More importantly, usage of a dosage greater than 100 mg/day seems to increase the likelihood of advanced prostate cancer (22).

Much of the interest in zinc as an agent for prostate cancer treatment and prevention is due to studies that have shown a marked reduction in prostate tissue zinc levels in prostate cancer cells versus normal prostate cells (23). In normal prostate tissue, zinc acts as an inhibitor of an enzyme (m-aconitase), which is part of the Krebs cycle. With the inhibition removed by the low levels of zinc, the malignant cells are now able to complete the Krebs cycle and go from energy-inefficient secretory epithelial cells to energy-efficient cells (24).

Unfortunately, replacing this intracellular prostatic zinc is not as simple as ingesting it: exces-

sive intestinal zinc levels downregulate zinc absorption and therefore, oral zinc supplements have little or no effect upon zinc levels in the prostate (25). The zinc is actively transported across the prostate cell membrane and there is evidence that the downregulation of the transporters involved is a cause of the reduced zinc uptake and this change in gene expression may be a factor in the development of prostate cancer. Research has shown that the hormones testosterone and prolactin can increase zinc uptake in prostate cells, but no human studies of this effect have been undertaken (24).

Epidemiological Studies

The studies on zinc and prostate cancer have been inconclusive (26). Some studies have suggested that high intraprostatic zinc levels may protect against prostate carcinogenesis, while other studies show that it may increase risk by facilitating enzymes thought to be responsible for the unlimited proliferation of tumor cells (22)

In an analysis of 14 years of data on a cohort of 46,974 men from the Health Professionals Follow-Up Study, it was observed that supplemental zinc intake at doses of up to 100 mg/day was not associated with an increased prostate cancer risk (22). However, men who consumed more than 100 mg/day did have a relative risk of advanced prostate cancer of 2.29 greater than nonusers. Thus, zinc supplementation could promote the development of prostate cancer. Zinc obtained from food sources was not associated with prostate cancer risk (22).

SOY

The role of soy and the beneficial effects that the phytoestrogens (specifically the isoflavonoids) it contains have on prostate cancer have been a focus of recent research. Only 4% to 8% of men are estimated to use soy as a supplement (4,5). Much of the research has focused on two isoflavones specifically, genistein and daidzein.

Epidemiological Studies

The research is seeking to provide understanding of epidemiological studies that have shown lower incidence of prostate cancer in populations with diets rich in soy products (27). It has been reported that while Chinese and Japanese men had a lower incidence of prostate cancer than U.S. born males, the incidence in the population of Asian immigrants to the United States are in line with U.S. incidence rates (28). Soy is of interest as a possible reason, as the average Asian diet includes ten times the amount of soy products consumed in the typical American diet (27). Isoflavone consumption is approximately 50 mg/day in Asia versus 2 to 3 mg/day in the United States (27). A study of the dietary habits of 12,395 American Seventh-Day Adventists, demonstrated a 70% reduction in the risk of prostate cancer in those men who consumed soy milk more than once a day (29).

Laboratory Studies

Genistein, daidzein and their metabolites, with their mild estrogenic activity, have been shown to inhibit benign and malignant prostatic epithelial cell growth (30), down-regulate androgen-receptor genes (31), and reduce tumor growth in some animal models. In addition, genistein inhibits the growth of both androgen-dependent and androgen-independent prostate cancer cells in vitro (12). No large-scale clinical trials using soy or soy products as chemoprevention or therapy have been reported, so current opinion must rely on epidemiologic studies, in vitro studies, and in vivo studies in animal models.

While it may seem that a reduction in risk could be achieved by increasing soy intake, a recent study showed that the situation could be more complicated (30). In that study, equol, a metabolite of daidzein, demonstrated inhibitory effects. Not all individuals consuming daidzein produce equol. It is the habitual diet that determines the bacterial strains in the gastrointestinal tract, which in turn determines whether the individual converts daidzein to equol. This study only focused on one metabolite, but demonstrates the difficulty in applying results in one population to another as local intestinal flora as well as diet can influence the presence of biologically active metabolites.

Administration of soy products may not be without risk, as one animal study demonstrated when

it showed an enhancement in androgen-independent tumor growth in vivo when the rats were fed a diet high in an isoflavone-rich soy protein isolate (32).

Clinical Studies

The clinical data collected to date has been limited and equivocal. Studies have had small numbers of participants or were limited in duration. Some have shown no impact on PSA levels or PSA velocity in healthy men or in prostate cancer patients (33-35), while others have demonstrated the exact opposite in a group of men with prostate cancer (36,37). Clinically, these studies are inconclusive because they have focused on imperfect markers of prostate cancer and not the disease itself. Studies of soy supplementation in humans have not been performed and are needed in order to assess clinical impact (38).

LYCOPENE

Similar to selenium and vitamin E, lycopene is a potent antioxidant. It is a carotenoid found primarily in tomatoes and tomato-derived products. There is no recommended daily allowance for lycopene since it is not an essential nutrient. Miller et al recommend the consumption of one serving per day or five servings per week of tomato products as part of a healthy diet (39).

Epidemiological Studies

Epidemiological studies have suggested that tomato products might be potential protective agents against prostate cancer (39-42). An analysis of diet data collected from a cohort of 14,000 Seventh-Day Adventist men showed a 40% reduction in the risk of prostate cancer in those who consumed tomatoes more than 5 times per week when compared to those consuming less than one serving per week (39). These observations were expanded upon by Giovannucci et al. in their 1995 prospective study of a cohort of 47,894 men from the Health Professionals Follow-Up Study (HPFS) (39,43). In that analysis, the only fruit and vegetable items to be associated with a lowered prostate cancer risk were raw tomatoes, tomato sauce, pizza, and strawberries. When the tomato groups are combined, consumption in excess of ten servings per week compared with less than 1.5 servings per week reduced the risk of prostate cancer by 35% (39). A more recent analysis of 450 incident prostate cancer cases versus 450 controls from the HPFS data suggested that tomato products may have a stronger protective role in preventing sporadic prostate cancer rather than prostate cancer with a strong familial/hereditary component (44).

Laboratory Studies

While lycopene can be taken as a supplement, a recent animal study showed a protective effect from tomato powder but not pure lycopene, indicating that compounds in addition to lycopene are influencing prostate carcinogenesis (45). Other animal and in vitro studies have demonstrated that taking vitamin E (which is present in tomatoes) along with lycopene led to synergistic inhibition of prostate cancer (46,47).

As with other antioxidants, lycopene may have a role in limiting oxidative damage to cellular macromolecules. In vitro laboratory studies suggest that lycopene is the best natural carotenoid for quenching singlet reactive oxygen. The actual ways in which lycopene works with other antioxidants and biologic systems that protect against oxidative damage is poorly understood (39). Lycopene has also been shown in vitro to impact insulin-like growth factor 1 (IGF-1) signaling, cell cycle progression and cellular proliferation. High levels of IGF-1 have been associated with an increased risk of prostate cancer (48).

Clinical Studies

A 2002 study of 26 men newly diagnosed with prostate cancer, demonstrated that supplementation with a lycopene preparation (which included 30 mg lycopene as well as a mixture of tomato carotenoids and other phytochemicals, including vitamin E) 3 weeks prior to radical prostatectomy resulted in decreased plasma PSA levels as well as reduced the diffuse involvement of the prostate gland with HGPIN, a precursor to prostate cancer (49). No prospective controlled clinical study of lycopene supplementation has been performed to date.

POMEGRANATE JUICE

Pomegranate juice is a strong antioxidant that has recently been receiving increased research attention. It is a rich source of polyphenolic flavonoids, which are believed to be the reason for its potent antioxidant and anti-atherosclerotic properties. The most abundant of these polyphenols is punicalagin and is responsible for more than 50% of the juice's potent antioxidant activity (50).

Epidemiological Studies

Epidemiological studies have shown that consuming fruits and vegetables with high phenolic content correlates with reduced cancer mortality. Pomegranate juice has been marketed as being high in antioxidants and laboratory research has been focusing on its potential to impact prostate cancer. Interestingly, studies have shown commercial juice to be high in punicalagins because industrial processing extracts some of the tannins present in the fruit rind (50). Thus, any benefit from pomegranate is likely to come from consuming juice and not fruit - and specifically juice that includes some processing of the fruit rind.

Laboratory Studies

Studies in breast cancer have demonstrated the juice to have significant potential for the down-regulation of angiogenesis. Certain fractions, especially the seed oil, are known to have estrogenic activity. In addition, as with vitamin E, the punicic acid in pomegranate seed oil inhibits prostaglandin formation (51). In vitro studies have also shown a synergistic inhibition of prostate cancer cell invasion from the application of a combination of pomegranate extracts (52,53). Recent research has shown the beneficial effects of the various extracts of pomegranate juice are enhanced when combined with the other polyphenols found in the juice (54).

Clinical Studies

A recent 2-year, single center clinical trial was completed for 48 men with rising PSA levels after surgery or radiotherapy (55). Patients drank eight ounces of pomegranate juice daily. Mean PSA doubling time significantly increased with pomegranate juice supplementation, from a mean of 14 months to 26 months. These findings suggest that further testing is warranted in a multi-center, randomized, placebo controlled study (55).

GREEN TEA

Next to water, tea (made from the leaves of Camellia sinensis) is the most widely consumed liquid in the world. Green, oolong and black tea are all made from the leaves of the same plant. However, their chemical content and flavors are very different due to their fermentation processes. Green tea contains several polyphenolic compounds, including its primary polyphenol, and the one that has received the most research focus, epigallocatechin gallate (EGCG). Consumption is generally considered safe. One study of 49 patients with solid tumors concluded that a dose equivalent to 3.5 to 4 cups (28 to 32 fl. oz.) of green tea 3 times a day could be easily tolerated and could be taken safely for at least 6 months (56). Estimates are that green tea is used by 6% to 8% of men as complementary/alternative medicine (4,5).

Epidemiological Studies

Epidemiologic studies have shown that men who regularly consume green tea have a lower incidence of prostate cancer (57-59). This fact may contribute to the observation that Asian men, with their far higher consumption of green tea, have lower rates of prostate cancer then their western counterparts (60).

Laboratory Studies

Research has focused on the role of the polyphenols contained in green tea, but their mechanism of action has not been determined. Proposed antineoplastic effects observed include: the inhibition of proteolytic enzymes to prevent metastases, alterations in cell communication, and antiangiogenesis. These antitumor mechanisms require prolonged exposure to the green tea (61). EGCG has been shown in both animal and in vitro studies to induce apoptosis and cell-growth inhibition (62-64). In a TRAMP mouse (which spontaneously develops metastatic prostate cancer) model, a polyphenolic fraction iso-

lated from green tea (green tea polyphenols or GTP) at the human equivalent of six cups of green tea per day, caused significant inhibition of prostate cancer and increased survival. GTP seemed to completely inhibit distant site metastases (65).

Clinical Studies

Several clinical studies have shown no effect by green tea on androgen independent prostate carcinoma. However, in those studies the patient populations' cancers may have been too advanced to benefit from this intervention (61,66).

FISH OIL (Omega-3 fatty acids)

Omega-3 fatty acids can be found naturally in the oil of cold-water fish, such as mackerel, salmon, sardines, anchovies, and tuna, or as extracted oils from plants, such as flaxseed, canola, or soybean. Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are found mainly in fatty fish and are often referred to as marine fatty acids. Both can be synthesized in humans from a precursor (alpha-linolenic acid). However, the conversion of alpha-linolenic acid to EPA or DHA is inefficient, direct dietary consumption is a more effect method of increasing serum levels of fatty acids (67). Blood or adipose tissue levels of omega-3 fatty acids are correlated to intake of fatty fish rather than to the intake of alpha-linolenic acid (68). The FDA recommends that the consumption of fish oils be limited to 3 grams or less per day because higher doses may increase the risk of bleeding (69).

Epidemiological Studies

It is unclear that the consumption of marine fatty acids can reduce the risk of prostate cancer (68). An analysis of the diet of 47,882 men enrolled in the Health Professionals Follow-up Study showed that eating fish more than three times per week versus less than twice per month translated into a negligibly reduced risk of prostate cancer (7% reduction), of advanced prostate cancer (17% reduction), and a somewhat reduced metastatic cancer risk (44%) (70). This same study found no association between the risk of prostate cancer and the consumption of fish oil supplements (70). In Lancet, Terry et al. analyzed the association of fish consumption and the risk of prostate cancer in 6,272 Swedish men over 30 years (71). Those who ate no fish had a two to three times higher frequency of prostate cancer than those who ate either moderate or high amounts, as defined on a four point scale, of fatty fish. In an autopsy study of 27 Inuits (Eskimos), no latent noninfiltrative-type carcinoma was found; only one of the Inuit prostates showed malignant cancer, and that was in a 73-year old who had a low omega-3 polyunsaturated fatty acid concentration (0.9% of all fatty acids in adipose tissue compared with 1.79% for the entire autopsy group). The absence of latent noninfiltrative-type carcinoma was unexpected when compared with incidences of 25-35% that are usually reported in other comparable populations, including Asians. The authors suggested that the low incidence of prostate cancer was due to the high selenium and omega-3 fatty acid levels (72). These results are strongly contradicted by other epidemiological studies that show no association between prostate cancer risk and total fish consumption nor intake of EPA or DHA (73-75).

Laboratory Studies

In contrast to the epidemiological studies, in vitro results have been more promising. Omega-3 fatty acids have been shown to inhibit cell growth and PSA protein expression (68). In animals, a recent study of human prostate cancer in xenograft mice showed an inhibitory effect of dietary fish oil (76).

EPA and DHA have both been shown to inhibit the biological activity of eicosanoids and androgens, which are both known to have a stimulating effect on prostate cancer cell growth (70).

Clinical Studies

Although numerous studies have been done for cardiac disease prevention and management, none are available concerning prostate cancer (77).

CONCLUSION

Patients with prostate cancer or those at high risk for developing the disease are faced with volu-

minous and often conflicting advice about nutritional supplementation. Any advice to the patient must be tempered by the fact that there is no definitive proof that any of the nutritional supplements discussed can impact the course of prostate cancer or its development.

Dietary fat seems to have the greatest impact on prostate cancer (78). It is clear that patients should keep their weight within 10% of their ideal body mass index (BMI). There seems to be a positive correlation between BMI and the risk of prostate cancer (79,80). The consumption of red meat has been shown to increase the risk of prostate cancer (78). Following a "heart healthy" diet of non-red meat protein (including fatty fish) could possibly benefit those at risk for developing prostate cancer (81).

In terms of supplement usage, the data is unclear. Our belief is that simply taking a standard daily multivitamin should be sufficient to ensure that patients have the appropriate levels of vitamins and minerals. Clearly, overutilization of vitamins, minerals, and supplements can lead to numerous negative side effects such as the increased risk of heart attack and stroke (vitamin E), bleeding (vitamin E, vitamin A), decreased mental acuity (zinc, selenium), anemia (zinc), and hair and nail loss (selenium).

Supplementation is also cautioned when looking at the history of PC-SPES (82). In 2002, approximately 10,000 patients with prostate cancer were using this supplement. Patients utilized the product without close medical supervision and, in those patients, estrogenic side effects (e.g. gynecomastia) were frequent and there were reports of deep vein thrombosis. PC-SPES was found in several subsequent tests to be contaminated with diethylstilbestrol (DES), ethinyl estradiol and warfarin, among other contaminants. The contamination varied by lot examined. The product was recalled in early 2002 and the company manufacturing it ceased operations later that year, but not after the adverse events described (83).

Physicians must be aware of what their patients are taking because these supplements can interfere with the absorption and efficacy of conventional medications. However, studies have shown that patients using CAM usually do not inform their physician (3). Physicians must proactively inquire about CAM usage. Patients must be educated about the limitations and safety concerns when using CAM. More data from rigorous new clinical trials is needed to answer the question of the efficacy of all of these products.

CONFLICT OF INTEREST

None declared.

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Accepted:
September 12, 2005

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