CHEMOPREVENTION IN CHRONIC PROSTATITIS IN BPH AND IN LOW GRADE CARCINOMA

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Prostate cancer is the most common solid malignancy in men in the United States. As a disease predominantly affecting the elderly and with the continuing aging of the population, the importance of studying and treating prostate cancer will continue to increase. Many factors have been implicated in the development of prostate cancer. It presents a variability of incidences influenced by dietary factors. The administration of substances, such as Lycopene, Polyphenols, Iso-flavonoids, Vitamin D, Vitamin E, Selenium and Zinc have a decisive role in the prevention of anti-apoptotic and pro-angiogenesis processes which are long-term developing properties of cancer cells. In this study, we will provide an overview of the current state of art between dietary habits and risk of prostate cancer.

Prostate cancer is the second form of cancer that causes death in males (1). It is more frequent among the black American population and presents a variability of incidence influenced by dietary factors, which can be protective, such as vegetables or non-protective such as fats (2). Prevention is aimed at finding strategies to reduce the risk of cancer development, such as screening tests, the abolition of substances which may be involved in carcinogenesis (oxidants, diets rich in fats). Administration of chemical mixtures are characterized by the ability to inhibit or to make the cancer regress.(3) Some chemical substances lead to malignant transformation of cells(4). Some carcinogens act inside the cell and produce a DNA lesion which brings gene mutation, acting as initiators of tumor formation.(5). Other substances, such as testosterone, are called promoters of cancer growth. The growth factors, induced by carcinogens and stimulated by promoters, represent the last stage of cancer, blocking cellular apoptosis mechanisms.(6). Chemotherapy acts as anti-initiators, anti-promoters and anti-progression factors (7).

The growth factors are small peptide molecules which stimulate or inhibit cellular division and the differential processes (8). In chronic prostatitis there is an infiltration of plasma cells and macrophages with focal invasion of lymphocytes. These inflammatory cells are a source of growth factors in the prostate human tissue. The T cells, in particular, produce and secrete a great variety of growth factors, including HB-EGF and FGF-2. Therefore the T cells, long-living in the prostatic environment, are able to secrete powerful epithelial and stromal mitogens.(9) The growth factors have an important role in the pathogenesis of benign prostatic hypertrophy. The interactions among growth factors and steroidal hormones can modify the balance between cellular proliferation and cellular death until the production of BPH.(10) The factors in discussion are βFGF (basic fibroblastic growth factor), AFGF (acid fibroblastic factor growth), TGF (cancer growth factor), EGF (epidermal growth factor), KGF (keratinocyte growth factor) and IGF (insulin growth factor) (11). These growth factors, particularly TGF, have been implicated in tumour pathogenesis (11). TGF-β is an inhibition factor of normal epithelial cell proliferation. In prostate cancer models there is

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evidence suggesting that malignant cells lose the growing inhibitory effect due to TGF (11). Many substances, already used in adjuvant therapy in PIN and T1 carcinomas, are able to change the role of growth factors and to reduce the risk of cancer in BPH and chronic prostatitis (12).

The administration of Lycopene, Polyphenols, Iso-flavonoids, Vitamin D, Vitamin E, Selenium and Zinc has a decisive role in the prevention of anti-apoptotic and pro-angiogenesis processes which are long-term developing properties of cancer cells (13).

MATERIALS AND METHODS

Lycopene

Oxidative damage can develop a transformation and promotion process through membrane and DNA per oxidation (13). Lycopene is a carotenoid that is very common in nature (tomatoes, fruits and some vegetables).(14). It dissolves in the blood, through the bilious acids and the pancreatic lipase, where it circulates linked to low density lipoproteins. The antioxidant action takes place through the capture of free radicals and the transfer of excitement energy of O2 to Lycopene. Furthermore, Lycopene is able to interfere with the action of IGF-1 by inhibiting the phosphorylation of tyrosine and hence blocks the baseline signals of cellular cycle progression and therefore the progression of cancer (16). It has been reported that Lycopene reduces the relative risk to developing prostate cancer in subjects that eat tomatoes at least five times a week compared to those that eat them once a week.(17).

Polyphenols

The Polyphenols, particularly the epigallocatechina-3-gallato (EGCG), are contained in tea up to 400 mgs per cup (18). After the assumption of 400 ml of tea, a rapid increase of the reducing power in the serum was observed, with peak activity after 40 minutes (19).

Using TPA in rats, it is possible to induce the production of oxygenated water, which is a powerful oxidant able to induce the synthesis of the ornithine decarboxylase enzyme (DOC). This enzyme is encoded by a testosterone-dependent gene that causes the biosynthesis of the polyamine and it is over-expressed in prostate cancer (20). In this experimental model it was observed that the employment of tea's polyphenols stopped the synthesis of the DOC, interfered with the androgen receptors, decreased the quantity of transcribed mRNA and consequently the enzyme. Besides, it induced the synthesis of enzymatic systems (CAT, GR, GST) able to neutralize the oxygenated water. This double action of the polyphenols leads to cancer regression through the induction of apoptosis in DU 145 prostate cancer cells mediated by the activation of kinases and the fragmentation factor of DNA (21). Finally, the Polyphenols inhibit EGF action by reducing the tyrosine kinases. They also inhibit the liberation of TNF in dose-dependent manner (21).

Iso-flavonoids

Green tea also contains Iso-flavonoids, a subclass of flavonoids, constituted mainly by: Genistein, Daidzein and conjugate. The Iso-flavonoids circulate in the blood, where they expound their antioxidant activity, tied up to the low density lipoproteins (22). Even if the antioxidant effect can contribute to explain the anticancer activity, it is more probable that it derives mainly from the dose-dependent action on the cytosine enzyme and on the increase of beta transforming growth factor. The Genistein, at micro molar concentrations, is able to inhibit the angiogenesis important for growth and cancer metastasis (23).

Vitamin D

Vitamin D physiologically arrives at the organism through diet or by ultraviolet irradiation, starting from a precursor contained in the skin. The concept that the prostate represents a target organ for Vitamin D is confirmed by the presence of specific receptors for Vitamin D (VDR) in the epithelial cells of the prostate and by the ability of calcitriol, the active form of Vitamin D, to regulate the expression of many genes (24). Vitamin D induces cell differentiation, inhibits cellular growth and promotes the phenotypic differentiation of cells expounding on different steps: the arrest of cellular cycle, the regulation of androgenic receptors, the inhibition of invasion and metastasis and induction of cellular death by apoptosis(25).

The arrest of the cellular cycle is caused by the increased expression of P21 inhibitor of cyclin-dependent kinase. It prevents the hyper-phosphorylation of retinoblastoma, which is responsible for the passage from the G1 to S phase of the cellular cycle. The stimulation of programmed cellular death happens through suppression of anti-apoptotic Bcl2 protein expression, normally over-expressed in the prostate cancer cells. The androgens have a critical role in prostate growth and the differentiation process. Vitamin

D, in dose-dependent way, stimulates the level of mRNA for the androgenic receptors (26). The inhibition of invasion and metastases is modulated through inhibition of synthesis alfa6 and beta4 integrate, necessary for anchorage processes active in the migration of cancer cells (27).

Vitamin E

Vitamin E, or α-tocopherol, is a powerful antioxidant membrane; it is abundant in plant seeds and is involved in the protection of genetic material (28). Nitrogen dioxide is a molecule which reacts with the membrane of unsaturated lipids causing serious lesions of the membranes. During many cellular reactions, a lethal concentration of nitrogen dioxide can be produced. Tocopherols are able to seize the nitrogen dioxide, produce oxidation-derived tocopherolquinone, and protect cells from the mutagen effect of oxidant agents (29). Another effect of the vitamin is the anti-proliferate action, mediated by the direct inhibition of protein kinase C, which is activated by many elements that promote cellular growth, including hormones, neurotransmitters and growth factors. It has been shown that Vitamin E is able to inhibit the proliferation of human prostate cancer cells LNCap in dependent-dose manner and in a range of concentration that is easily found in human plasma. It is of interest to note that Vitamin E induces the apoptosis only in cancer cells, while it doesn't have this effect in normal cells (30).

Selenium

The human organism is not able to absorb the Selenium at the metallic state but assimilate it in selenium-methionine or selenium-cysteine form that are synthesized by plants such as the garlic, rich in selenium-cysteine. Selenium has been shown to possess antioxidant activity, with consequent neutralization of peroxide-nitrites, and protection against the action of free radicals from the moment that it is incorporated in glutathione peroxidase. This enzyme is the key enzyme for the maintenance of cellular oxide-reduction system (31). Selenium is able to stop the growth of the prostate cells of rats in culture and the proliferation of human prostate carcinoma DU-145 cells (32).

Zinc

Zinc, essential component of all the cells, has a central role in some proteins that act as transcription factors of the gene, the so-called "finger Zn proteins" or finger proteins of zinc. The fingers of zinc are small protuberances on the protein surface, formed by the refolding of a polypeptide portion able to penetrate in the furrows of the DNA helix. The refolding is stabilized by an zinc ion that ties four amino acids, two cystines and two histidines (33). The human prostate has the distinctive characteristic to accumulate zinc at concentrations more elevated than any other tissue of the organism. The prostate carcinoma cells have a drastic reduction of zinc concentration. The addition of zinc to these cells blocks the cellular cycle in the G2/M

Chemotherapeutic agent	Where?	Mechanism
Lycopene	fruit, tomatoes, vegetables	1. antioxidant (captation of free radicals) 2. block IGF-1 action
Polyphenols	tea (400 mg for cup)	1. antioxidant (stops the synthesis of DOC) 2. activation of enzymatic systems (CAT, GR, GST) 3. inhibition of EGF action and TNF liberation
Iso-flavonoids	green tea	1. antioxidant 2. increase of Cytosine enzyme and TGFβ 3. inhibit the angiogenesis
Vitamin D	carotenoid, tomatoes, fruit, ultraviolet irradiation	1. cell differentiation 2. inhibits cellular growth 3. induction of cellular death by apoptosis
Vitamin E	Plant seeds	1. antioxidant 2. anti-proliferate action
Selenium	plants	1. antioxidant 2. inhibits cellular growth
Zinc	water, fruit	1. induction of cellular death by apoptosis

phase. The cells, blocked by the presence of high zinc concentrations , express the factor pro-apoptosis p-21 that brings them to apoptosis (34).

The quoted substances, if added to the diet, can help the adjuvant treatment of prostate carcinoma. In our therapy these substances have been administered in the patients affected by prostatitis, in association with antibiotic and/or anti-viral; in the patients affected by BPH in association with inhibitors of 5-alpha reductase and/or alpha blockers and in the patients with prostate cancer in total androgenic block.

In conclusion, incorrect nutrition plays an important role as a risk factor not only for colon carcinoma. Prostate cancer is influenced by eating habits. In support of such theory, there are data from the studies performed on the populations that have emigrated to the USA from Asia. In these populations the incidence of prostate cancer has increased, becoming similar to the autochthonous population in just a few generations. In patients with BPH and chronic prostatitis there is a greater risk of cancer (35-42). In these patients and in the initial forms of cancer, adding antioxidants and modulators of growth factors to the diet is the choice nearest to the traditional therapy.

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