Antioxidants and Prostate Cancer

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INTRODUCTION

The prostate is the gland that produces semen (the fluid that carries sperm) and is essential for reproduction. About the size of a walnut, the prostate is located below the bladder and in front of the rectum. Cancer that begins in the prostate is called primary prostate cancer (or prostatic cancer). Prostate cancer may remain in the prostate gland or may spread to nearby lymph nodes. It could also spread to the bones, bladder, rectum and other organs.

Prostate cancer is identified as the second leading cause of cancer-related death in men worldwide. The World Health Report 2002 placed prostate cancer as the fifth most common cancer for males globally. Prostate cancer is accounted for 6.8% of total deaths by malignant neoplasms in males. Substantial variations in incidence of prostate cancer occur across different regions and ethnicity. Developed countries, such as North America, Europe and Australia, have higher incidence rates than developing countries. In America, for example, prostate cancer accounts for 33% of incidence cases for men (Jemal *et al.*, 2004) and in 2004, it is estimated that 230 110 new cases and 29 900 deaths from prostate cancer are to be expected (American Cancer Society, 2004). The highest incidence rates in the world are reported among African-American men and the lowest among men in China (Whelan *et al.*, 1990). Rates are also much lower in Africa than among African-American (Waterhouse *et al.*, 1976).

The etiology of prostate cancer remains largely unknown but it is widely believed to be related to the stimulatory action of testosterone. Symptomatic carcinoma of the prostate is rare in men under 50 years of age but its incidence increases almost exponentially beyond that age. Most prostate cancers are adenocarcinomas which arise from epithelial cells of the ducts or acini.

The incidence rates of prostate cancer have been increasing in recent years in many parts of the world, and while reasons for this increase remains unclear, they are partly related, in the developed world, to widespread screening for prostate cancer (Potosky *et al.*, 1990). Early detection of prostate cancer is carried out using PSA (prostate specific antigen) blood test or digital rectal examination (DRE). The PSA blood test measures a protein made by the prostate cells. The higher the PSA level, the more likely the chance of prostate cancer. With the DRE, physician palpates the prostate to detect the presence of lumps or other abnormalities.

Prostate cancer can be treated surgically and/or non-surgically. Non-surgical treatments for prostate cancer include radiation therapy, hormone therapy and chemotherapy. Hormone therapy is carried out to lower the levels of male hormones or androgens and thereby slow the growth of prostate cancer cells. Various drugs are used in hormone therapy to lower the amount of testosterone or to block the body's ability to use androgens. They are called leutinizing hormone-releasing hormone (LHRH) analogs or agonists. Anti-androgens are drugs used along with LHRH analogs to provide total androgen blockade. An example is flutamide (Labrie *et al.*, 1992).

The majority of research for dietary influence on prostate cancer prevention has focused on antioxidants, namely vitamin A and E. This paper reviews the effects of some of the antioxidants on prostate cancer.

ANTIOXIDANTS AND FREE RADICALS

Antioxidants are biochemical compounds, preventing oxidation, a process which could be damaging to the human body. Oxidation results in the formation of highly charged particles known as free radicals and reactive oxygen species (ROS). A free radical has a missing electron in the outer shell and it reaches its stable state by latching onto or taking electrons from other healthy cells or genes. This may result in a series of damaging

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effects in the human body known as oxidative stress which include cell damage, degradation of collagen (which is responsible for the elasticity of skin), reprogramming of genes and cell replication. Free radicals are known to attack cellular components, damaging lipids, proteins and DNA (deoxyribonucleic acid). This eventually initiate a chain of events resulting in the onset of disease. The main free radicals and ROS that occur in the human body include hydroxyl radical ($OH^{\bar{n}}$), superoxide radical ($O_2^{\bar{n}}$), nitric oxide radical ($NO^{\bar{n}}$) and hydrogen peroxide (H_2O_2).

ANTIOXIDANT EFFECTS ON PROSTATE CANCER

Most cancers have a latency period of 10 to 20 years, which provides ample time for preventive measures. In most epithelial tissues including the prostate, genetic progression and loss of cellular control functions occur as the cell and tissue phenotype changes from normal to dysplasia [prostatic intraepithelial neoplasia (PIN)] first to increasingly severe dysplasia high grade PIN (HGPIN), then to superficial cancers and finally to invasive disease (Kellof *et al.*, 1999). The high prevalence, long latency, significant mortality and morbidity are important features of prostate cancer that provide the most opportune and promising approach for biological intervention.

In recent years, the role of micronutrients as biological agents for cancer has been the focus of many studies carried out worldwide, including clinical trials and studies of animal carcinogenesis models for cancer-inhibiting potential of these substances (Reddy, 1996). Promising nutrients identified as biological agents in prostate cancer include antioxidants such as vitamins A and E, selenium, carotenoids and lycopene (Albanes

and Taylor, 1998; Heinonen *et.al.*, 1998; Giovannucci, 1999). These antioxidants function by suppressing metabolic pathways, inhibit cellular damage and lower PSA in prostate cancer cell lines (Richards *et al.*, 2003).

TOCOPHEROLS AND TOCOTRIENOLS

These compounds are well-known for their antioxidant properties as free radical scavengers and have the potential to decrease DNA damage, inhibit malignant transformation and induce apoptosis. In addition, tocopherols and tocotrienols affect the immune system, specifically the function of T lymphocytes. Decreased tocopherol intake has been associated with decreased immune function, while high levels have a stimulatory effect on immune function (Burton and Ingold, 1989; Meydani, 1995).

The association of tocopherols with decreased incidence of diseases related to oxidative stress namely atherosclerosis and certain forms of cancer have been indicated in epidemiological studies worldwide (Gey, 1993; Kimmick *et al.*, 1997; Pienta and Olson, 1998). The tocopherols and tocotrienols occur in nature in four forms (alpha, beta, delta and gamma) based on the number and position of methyl groups on the chromanol ring (Meydani, 1995). Tocopherols and tocotrienols differ in their structure with the presence of three double bonds in the carbon side chain of the tocotrienol molecule (Nesaretnam, 2000).

Tocopherols are found most abundantly in the oils extracted from soyabean, cottonseed and sunflowerseed while tocotrienols are found primarily in palm oil and oil fractions of cereal grains such as wheat, barley and rice. Crude palm oil consists largely of tocotrienols (24% α-tocotrienol, 43% γ-tocotrienol, 11% δ-tocotrienol) with the remainder being α-tocopherol (21%).

Commercial red palm olein contains 29% α-tocotrienol, 41% γ-tocotrienol, 10% δ-tocotrienol and 19% α-tocopherol, with a mixture of carotenes. Refined bleached deodorized palm oil on the other hand contains 29% α-tocotrienol, 36% γ-tocotrienol, 10% δ-tocotrienol and 25% α-tocopherol (Bonnie *et al.*, 2000). Both tocopherols and tocotrienols are capable of scavenging and quenching free radicals using different mechanisms. Although α-tocopherol has been considered as a more potent antioxidant for many years, the relative antioxidant effectiveness of tocotrienols compared to δ-tocopherol has been shown to be higher in lipid peroxidation (Nesaretnam *et al.*, 1993; Kamat *et al.*, 1997).

Tocotrienols, namely γ-tocotrienol have also been shown to be very potent inhibitors of human breast cancer growth whilst tocopherols are not. Inhibition of cancer cell growth was observed at very low concentrations of tocotrienols as compared to that of tocopherols (Nesaretnam *et al.*, 1995; 1998; 2004). The effect of tocotrienols on prostate cancer is a new area of research and no information is currently available in the literature. However, we have shown that TRF and γ-tocotrienols have an extremely potent inhibitory effect on the androgen independent prostate cancer cells DU-145 (*Figure 1*) (Teoh *et al.*, 2004). The only other study done on tocopherols and tocotrienols is from Galli *et al.* (2004) and they have showed γ-tocotrienol to be more inhibitory than α- and γ-tocopherol on PC3 cells.

Tocopherols, alone or in combination with other supplements has shown promising evidence as a preventive agent for prostate cancer. Case control studies (Ripoll *et al.*, 1986; Hayes *et al.*, 1988; Hsing *et al.,*1990; Chan *et al.*, 1999; Kristal *et al.*, 1999) examining the connection
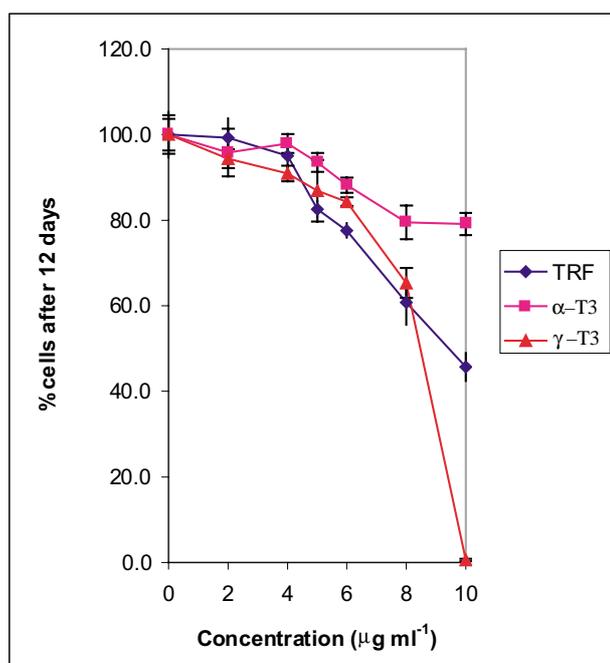
Figure 1. Effect of TRF and tocotrienol fractions on DU-T45 cell growth.

between pre-diagnostic levels of alpha-tocopherol and incidence of prostate cancer showed conflicting results. While three of the studies (Ripoll *et al.*, 1986; Hayes *et al.*, 1988; Kristal *et al.*, 1999) demonstrated decreased occurrence of prostate cancer, the other two (Hsing *et al.*, 1990; Chan *et al.*, 1999) showed no statistical reduction in prostate cancer cases. In the Finnish Trial, Heinonen *et al.* (1998) showed that 50 mg of alpha-tocopherol per day reduced prostate cancer incidence by 32% and prostate cancer deaths by 41% in a group of male smokers in Finland. This Alpha-Tocopherol, Beta-Carotene Cancer (ATBC) Prevention Study was a randomized, double-blind, placebo-controlled primary-prevention trial, designed primarily to explore the prevention of lung cancer among 29 133 male smokers aged between 50-69 years by supplementation with 50 mg α-tocopherol, 20 mg β-carotene, both, or a placebo for an average of 6.5 years (Heinonen *et al.*, 1998). In this study, a reduction in clinically evident cancers appeared soon after the onset of supplementation, suggesting that α-tocopherol

influences the transformation phase of cancer from latent to clinical. However, it had no effect on advanced prostate cancer as the time from diagnosis of clinical prostate cancer to death was not lengthened compared to non-recipients of the supplements. In recent studies, supplemental tocopherol was reported to be beneficial in inhibiting growth of human prostate cancer cells induced by a high-fat diet in a mouse xenograft model (Fleshner *et al.*, 1999). The study suggests that oxidative stress is important in the genesis of clinical prostate cancer and raises the possibility of the role of antioxidants as preventive agents.

Several studies have also reported synergistic effects of tocopherols with other vitamins, supplements or chemotherapeutic agents (Ripoll *et al.*, 1986; Eichholzer *et al.*, 1996). In the study by Ripoll *et al.* (1986), tocopherols were found to enhance the chemotherapeutic effects of adriamycin (a drug used successfully in treatment of advanced adenocarcinoma of the prostate) *in vitro* and to have a protective effect on the side effects of adriamycin.

Recent advances in the field of molecular biology had shed some light on the mechanisms, which contributed to the anti-proliferative effects of tocopherols and tocotrienols. Briefly, tocopherols triggered apoptosis effectively in prostate carcinoma cells but not normal prostate cells *in vitro* (Israel *et al.*, 2000). Subsequent studies proved that at least three separate signaling pathways are involved comprising of transforming growth factor-β (TGF-β), Fas/Fas ligand and the c-Jun N-terminal kinase (JNK) mitogen activated protein kinase (MAPK) signaling pathway (Yu *et al.*, 1997; 1998; 1999). It is important to note that in the progression of prostate carcinogenesis, these pathways are somehow inactivated, rendering cells incapable of undergoing apoptosis. Astonishingly, prostate tumour cells responsiveness to these pathways are somewhat restored after treatment with tocopherols. Ongoing studies are still being carried out to investigate intrinsically the effects of tocopherols and tocotrienols on these signaling pathways.

CAROTENOIDS

Carotenoids are fat-soluble compounds and exist as a class of yellow to deep-red pigments in plants and fruits. Crude palm oil is the richest natural source of carotenes made up primarily of α-carotene (35.1%), β-carotene (56.0%), lycopene (1.3%) and other carotenoids (7.6%) (Choo, 1994). Commercial red palm olein contains 41.3% α-carotene, 41% β-carotene, 1.0% lycopene and 16.7% of other carotenoids (Bonnie *et al.*, 2000). Carotenoids play an important role as an antioxidant, radical scavenger and as pro-vitamin A precursor (Goodman, 1984; Willett *et al.*, 1984). While carotenoids are the plant sources of vitamin A, the alcohol or the aldehyde forms of vitamin A and their esters are

found in animal sources (Thomas, 1999).

Numerous dietary studies have shown that a low intake of vitamin A and/or β-carotene may be associated with increased risks of various cancers (Shekelle *et al*., 1981; Graham, 1983; Eichholzer *et al*., 1996). The effect of dietary β-carotene on prostate cancer occurrence has been estimated in several retrospective and prospective studies. While some interesting trends were noted, the evidence of a protective effect of β-carotene on the incidence of prostate cancer was weak and inconsistent (Thomas, 1999). Similarly, Hennekens *et al*. (1996) reported lack of effect of β-carotene on prostate cancer. In three investigations of vegetable intake, with special emphasis on β-carotene intake, no association with prostate cancer was observed (Talamini *et al*., 1986; Giovanucci *et al*., 1993; Le Marchand *et al*., 1994). However, inverse associations were reported in two other studies (Hirayama, 1979; Mettlin *et al*., 1989; Hsing *et al*., 1990). In some case control studies (Graham *et al*., 1983; Kolonel *et al*., 1988; Talamini *et al*., 1992), positive association of vitamin A or β-carotene intake and the risk of prostate cancer was observed, particularly among men in the older age group (70 years and above). Likewise, the Physicians' Health Study, reported that men with low baseline blood β-carotene concentrations at the beginning of the study experienced a decreased risk of developing prostate cancer when supplemented every other day with 50 mg β-carotene (Cook *et al*., 1999).

In the ATBC Study in Finland by Heinonen *et al*. (1998), it was found that rates of prostate cancer were lower among non-drinkers who received β-carotene supplements, compared to non-drinkers who received a placebo. In non-drinkers, the risk in the β-carotene group was 32% lower than that in the placebo group. In contrast, the incidence of prostate cancer among all subjects assigned to β-carotene treatment was 23% higher than that for placebo subjects. When subjects were categorized by alcohol intake, the risks were higher than that of the placebo group, although the effects were not significant (Cooper *et al*., 1999). The inconsistency observed in the effects of β-carotene on prostate cancer suggest that further studies are needed in order to establish a better understanding of the role of β-carotene and cancer.

LYCOPENE

Lycopene, unlike other major carotenoids, does not have pro-vitamin A activity but plays an important role as an antioxidant. It has the most potent singlet oxygen-quenching activity (Sies, 1989) and is considered to be due to the interaction of the isoprenoid tail with certain receptors that somehow managed to suppress the expression of HMG-CoA reductase activity. This suppression, in return, slowed down cancer induction and cellular growth (Keyomarsi *et al*., 1991).

Lycopene has been shown to have anti-proliferative effects against breast cancer cells in culture (Levy *et al*., 1995) and tomato oleoresin-treated rats developed fewer 7,12-dimethyl-benz[a]anthracene-induced mammary tumours (Sharoni *et al*., 1997). Gann *et al*. (1999) reported that an increased serum level of lycopene, the most abundant serum carotenoid, is associated with a decreased relative risk of prostate cancer. Epidemiological findings on lycopene have been inconsistent thus far. Case-control studies conducted by Le Marchand *et al*. (1991), Hayes *et al*. (1999) and Kolonel *et al*. (2000) did not find association between lycopene intake in relation to prostate cancer risk. However, a study conducted in New Zealand reported a suggestive albeit statistically insignificant inverse association between total lycopene intake and prostate cancer risk (Norrish *et al*., 2000). In the largest and most significant prospective study to date, high intake of lycopene-rich tomatoes and tomato products, was associated with a 35% lower risk of total prostate cancer and a 53% lower risk of advanced prostate cancer (Giovannucci *et al*., 1995). Clinical studies conducted on men with localized prostate cancer just before prostatectomy revealed that, after three weeks of supplementation with lycopene, mean plasma PSA levels decreased by 18% in intervention group but increased by 14% in control group over the study period (Kucuk *et al*., 2001).

The same study also investigated protein expression of bcl-2 and bax between the two groups. Increased expression of bcl-2 is believed to contribute the resistance of prostate cancer to chemptherapy. Bax, on the other end of the spectrum, served as a pro-apoptotic protein by inducing apoptotic and necrotic cell death. Although, no significant difference in protein expression of bcl-2 and bax in both groups, but, bax protein levels were found to be higher in intervention group when compared to control group.

OTHER ANTIOXIDANTS

Other antioxidants that may prevent prostate cancer include vitamin C (Kristal *et al.,* 1999), genistein (Giovannucci *et al*., 1995), selenium (Yoshizawa *et al*., 1998), retinol, lutein, epigalloca-techin-3-gallate (EGCG) a flavanol found in green tea (Gupta *et al*., 2000) and proanthocyanidin in grape seed extract (Cos *et al*., 2004). Studies have been and are being carried out to investigate the anti-cancer activities of these chemopreventive agents either on their own or in combination (Gunawardena *et al*., 2004) including the ongoing Select study by NIH which is a 12-year (2001-

2013) project to examine the effects if selenium and Vitamin E (tocopherols) on prostate cancer incidence and progression. Research findings at this point indicate an inverse association between consumption of these antioxidants with prostate cancer risk. However, these are only the tip of the iceberg, in actual fact, the information amassed so far would have been too broad to be covered in this paper.

In conclusion, the development of prostate cancer is a slow and debilitating progress. It is accompanied by significant loss of quality life and substantial mortality risk for the individuals involved. Therefore, the possible prevention of prostate cancer through dietary factors is indeed very appealing. The role of antioxidants in decreasing prostate cancer risk cannot be disputed even though epidemiological data seems to be conflicting. In depth investigation of the actual mechanisms and the synergistic effect these antioxidants have on prostate cancer progression is definitely worth pursuing.

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