

# Chemoprevention: A novel approach to prostate cancer

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### ABSTRACT

Prostate cancer is one of the most common visceral malignancies diagnosed in men. Prostate cancer has a high prevalence, long latent period and screening is inadequate. The morbidity and mortality of prostate cancer are significant, making it a good candidate for chemoprevention. Prevention of this disease would have a major impact on disease associated cost, morbidity and mortality for a large segment of population. In this backdrop an intervention that could prevent the cascade of events would indeed be beneficial to the society. Here we review a few of the most promising agents that have been tested for their effect on reducing the risk of prostate cancer and with the advances in understanding the molecular mechanism of their actions and vast amount of epidemiological data in support of chemoprevention of prostate cancer, opportunities to test efficacy and even combination of never agents for synergistic action needs serious consideration. [IJEM 2008;12(8):15-20]

**Key words:** Chemoprevention, prostate cancer, 5-alpha-reductase inhibitor, Selenium, Lycopene, Toremifene

### INTRODUCTION

Prostate cancer is the most common malignancy in US men, with an estimated lifetime risk of disease of 16.6% for Caucasians and 18.1% for African-Americans and a lifetime risk of death of 3.5% and 4.3% respectively(1). With an annual mortality load of approximately 220,000 deaths, it is the sixth leading cause of cancer mortality among men worldwide(2). Although mortality due to prostate cancer has begun to decline, there are some compelling reasons to search for ways to prevent the development of prostate cancer, including the increasing risk of diagnosis during the lifetime of a man. The fact that majority of prostate cancer cases and deaths occur during the later years of life in a man, a delay in diagnosis by one or more years could substantially affect mortality. Moreover, the current approach of early detection and treatment is not only costly, with considerable morbidity but also has failed to demonstrate any decrease in population morbidity and mortality from disease(3). The cumulative cost and mortality of various treatments for early stage disease, treatment related morbidity and treatment of biochemical failures remains substantial attracting increased interest in chemoprevention or better termed as disease risk

reduction of prostate cancer. Cancer chemoprevention is the use of agents to inhibit, delay or reverse carcinogenesis. There is a growing and lengthy list of opportunities for prevention of prostate cancer unlike many neoplasms. The significant public health burden imposed by the incidence and treatment of the disease has generated a lot of interest in leading cancer institutes of the world in identifying agents which prevent at least some proportions of men at risk from developing prostate cancer. Since 2003 when finasteride was first reported to be an effective preventive agent(4), progress in molecular biology has revealed several signal transduction routes in carcinogenesis leading to search for mechanism-based chemopreventive agents in preventing prostate cancer

Various clinical trials have been undertaken to explore the possibility of agents to reduce the risk of prostate cancer. These agents can be studied for reduction of risk of prostate cancer, as it is unlikely to explore the decrease in the risk of cancer deaths in man as it would require a larger study and nearly two decades to complete. For this reason prostate cancer prevalence and incidence is chosen to study the effect of any agent. Before phase III clinical trials (randomized double blind with clinically important study end points) are undertaken, earlier phase studies are required for planning these studies and selection of an appropriate study population(5). These include smaller studies where chemopreventive agents are examined that could have a

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mechanism of actions that can be evaluated in target tissues and also to establish that the proposed agent achieves appropriate concentrations in the target tissues (phase IIA). A phase IIB trial is to determine whether an agent modulates an intermediate end point biomarker. In prostate cancer there is paucity of validated end points that are confirmed to be related to ultimate prostate cancer development. Reasonable end points in case of prostate cancer may include prostatic intraepithelial neoplasm (PIN), angiogenesis and most commonly used end point, the prostate specific antigen (PSA). These preliminary studies establish initial evidence of efficacy and occasionally measure effect size, which would allow for a better understanding of sample size in subsequent studies. Here we summarize few of the most promising agents studied in reducing the risk of prostate cancer along with their probable mechanism of action and the evidence in support of such actions.

### **5 $\alpha$ reductase inhibitors**

In the early 1990's, finasteride was approved for the treatment of lower urinary tract symptoms in men. Prostate cancer prevention trial (PCPT) was initiated to test a chemopreventive strategy in men with risk of prostate cancer(4). It was based on the observations that intraprostatic androgens have a key role in prostatic carcinogenesis and men with congenital deficiency of type 2 5 $\alpha$  reductase are unaffected by benign prostatic hyperplasia and prostatic cancer(6). Finasteride induces an acquired deficiency of type 2 5 $\alpha$  reductase, lowering the intra prostatic dihydrotestosterone levels and modulate prostate cancer risk. PCPT was initiated in 1993; a total of 18,882 men 55 years or older with a normal digital rectal examination (DRE) and a prostate specific antigen (PSA) level of 3.0ng/mL or below were assigned to treatment with finasteride 5mg/d or placebo for 7 years(4). Prostate biopsy was recommended if the annual PSA level adjusted for the effect of finasteride exceeded 4.0ng/mL or if the DRE was abnormal. The primary end point was the prevalence of prostate cancer during the 7 years of study as diagnosed by biopsy either for abnormal DRE or increased PSA or at the end of the study. The trial was stopped 15 months before planned closure due to overwhelming evidence that primary end point (25% risk reduction) was reached. The prevalence of prostate cancer was reduced by 24.8% from 24.4% to 18.4% in those taking finasteride compared to placebo(4). The risk reduction associated with finasteride occurred to the same degree among all risk groups. Sexual side effects were more common with finasteride, whereas urinary symptoms were more common with placebo. The prevalence of Gleason grade 7-10 tumors was higher in finasteride group than placebo (6.4% vs. 5.1%). The men diagnosed early in the study due to increased PSA or abnormal DRE were more likely to have high grade cancers, while those diagnosed after 7 years on study after the greatest period exposed to the drugs had a similar rate of diagnosis of high grade disease

demonstrating that finasteride significantly improved the sensitivity of PSA for cancer overall and for high grade cancer. Finasteride treated glands were 25% smaller than those in the placebo arm. Since the number of tissue cores taken at the end of study was similar the smaller glands in the finasteride arm were over sampled suggesting the possibility of an even greater risk reduction with finasteride than previously observed. There is no argument to suggest that long term finasteride may promote the development of highly aggressive cancer as recent analysis of data has shown that the high grade cancers on total prostatectomy specimens were not more aggressive in the finasteride arm than in the placebo arm(7). Additional important observations included a 25% risk reduction in finasteride arm in both clinically apparent and end of the study biopsies. There were equal numbers of deaths (five) in each study arm. In this scenario it was estimated that estimated that 316,760 person-years would be saved due to finasteride in the United States alone(8). There was 24.4% prevalence of prostate cancer in placebo arm which was four times higher than the 6% assumed in the trial design on basis of epidemiological evidence, highlighting that many more men have prostate cancer than are destined to die from it and that there was a need to develop markers that can distinguish indolent tumors from biologically significant ones.

There are two isoenzymes of 5 $\alpha$  reductase. There is an increased expression of 5 $\alpha$  reductase type 1 from benign prostatic hyperplasia to high grade prostatic intraepithelial neoplasia (HGPIN) to prostate cancer; the expression of 5 $\alpha$  reductase type 2 also increases from HGPIN to prostate cancer(9). Finasteride competitively inhibits the activity of type 2 isoenzyme, while dutasteride affects both type 1 and 2 and lowers serum dihydrotestosterone by more than 93%(10). In a recent study, men scheduled to undergo radical prostatectomy were treated with 3.5 or 0.5 mg of dutasteride or placebo. It showed that dutasteride treatment was associated with small tumors and prostate volumes but did not affect the tumour grade(11). In another study, a total of 4325 men with benign prostatic hyperplasia but without a history, or evidence, of prostate cancer, and a serum prostate-specific antigen level of 1.5 to 10 ng/mL, were randomized to 0.5 mg/day dutasteride or placebo for 24 months. Dutasteride treatment has shown to significantly reduce the risk of prostate cancer at 24 months (1.1% vs 1.9%) and at 27 months (1.2% vs. 2.5%) as compared to placebo(10). Due to these encouraging results REDuction by Dutasteride in prostate Cancer Events (REDUCE) trial was initiated in 2003, it includes those who are at a generally greater risk for prostate cancer. Approximately 8,000 men, 50 to 60 years old with PSA between 2.5 to 10ng/mL and 60 to 75 years old with PSA between 3 and 10 ng/mL all having had a negative biopsy before study were enrolled. The study will randomize men to 0.5 mg dutasteride vs. placebo and followed up with prostate biopsy at 2 and 4 years. Results from this study are awaited(12).

## Lycopene

Lycopene is a red orange carotenoid found primarily in tomatoes and tomato derived products like tomato sauce, tomato ketchup and paste and other red fruits and vegetables notably watermelon. Lycopene is a highly unsaturated acyclic isomer of  $\beta$  carotene. It is the predominant carotenoid in the human plasma and possesses potent antioxidant activity. There is epidemiological evidence that lycopene consumption is associated with a lower risk of prostate cancer with some study results showing a significant decrease in risk while as others have shown no risk reduction(13). Lycopene inhibits the growth of benign and malignant prostatic epithelial cells in vitro(14). In an in-vivo model in which rats were treated with N-methyl-N-nitrosourea and testosterone to induce prostatic cancer, a protective effect was observed for calorie reduction and tomato powder but not for pure lycopene suggesting that tomato products contain compounds in addition to lycopene that modify prostate carcinogenesis(15).

The most compelling positive analysis of role of lycopene in preventing prostate cancer was from Health Professional Follow up Study in which prostate cancer cases were ascertained in more than 47,000 subjects, identifying 2,481 men with prostate cancer(16). Lycopene intake was associated with a decreased risk of prostate cancer(RR 0.84, 95% CI.  $p=0.003$ ) Intake of tomato sauce, the primary source of this agent was associated with a greater reduction of risk(RR 0.77.  $p<0.001$ ) and an even greater reduction of risk for extra prostatic disease(RR 0.65). In Prostate, Lung, Colorectal and Ovarian cancer study of the National Cancer Institute, after analysis of 1,338 prostate cancer cases intake of tomato products and lycopene showed some protective effect in individuals with a family history of disease but no overall protective effect of lycopene intake(17). A recent study suggested that serum beta-carotene along with alpha-tocopherol modify the family history and prostate cancer association to some degree(18). A diet rich in tomato products may be more beneficial in reducing the risk of prostate cancer in humans, even though there is unclear evidence and ongoing clinical trials, patients still prefer lycopene supplements presumably to decrease the risk of disease(19).

## Vitamin E

Vitamin E is a family of naturally occurring essential fat soluble vitamin compounds which act as the major anti oxidants in cell membranes. The most biologically active form of vitamin E is  $\alpha$ -tocopherol. It is the most abundant and widely distributed predominant form in human tissues. Preclinical data is supportive of its potential as preventive agent for prostate cancer(20, 21). Its possible mechanism of action in modulating prostate cancer cell growth is suggested by the fact that  $\alpha$ -tocopheryl succinate causes G1 cell cycle arrest by decreasing expression of the cell cycle regulating proteins cyclin D1,D3,E and cdk2 and 4(22). PMCol, the chromanol moiety of vitamin E has anti androgen activity.

The PMCol-induced growth shift was similar to that produced by the androgen receptor antagonist bicalutamide. It inhibits PSA secretion and androgen induced promoter activation but does not affect androgen receptor protein expression levels(23). As it is widely believed that inflammation may also be related to prostate cancer carcinogenesis so cancer prevention can partly be due to the anti inflammatory effect of vitamin E. In a large scale cancer prevention trial for lung cancer, Alpha Tocopherol Beta Carotene Cancer prevention trial (ATBC) there was a statistically significant 32% reduction in prostate cancer incidence and a 41% lower mortality in those receiving  $\alpha$ -tocopherol (50mg dL- $\alpha$ -tocopherol/d)(24). Long term use for population at risk is important as the beneficial effect of  $\alpha$ -tocopherol disappear during post intervention follow up suggesting that it acts in real time and its effect washes out after discontinuation. Analysis of serum micronutrients in Beta Carotene and Retinol Efficacy Trial (CARET) demonstrated that low levels of  $\alpha$ -tocopherol was associated with higher risk of prostate cancer(25). Similar observations have been made in other studies(26). Some studies have shown that intake of supplements of  $\alpha$ -tocopherol is related to increased risk of heart failure in patients at risk of cardiac disease(27).

## Selenium

Selenium is an essential trace element; this micronutrient is found in soil incorporated into forage crops and thereby into animals. Selenium is widely distributed in body tissues and is an important constituent of many antioxidant enzymes, most notably glutathione peroxidase and due to this antioxidant effect there is evidence that selenium may significantly reduce the risk of prostate cancer(28). There is considerable epidemiological evidence in support of its global cancer prevention effect. In a study in men with normal pretreatment serum selenium levels, it was demonstrated that oral selenium accumulates preferentially in prostate substance(29). The strongest evidence for a protective effect of selenium comes from the National Prevention of Cancer trial, where after a mean follow up at 4.5 years, the incidence of prostate cancer reduced in selenium arm by two thirds compared to placebo(30). The effect was strongest for those with a PSA level below 4ng/mL and those with lowest serum selenium levels at study entry. A less powerful autopsy study among Inuit, whose diet is rich in omega-3 polyunsaturated fatty acids and selenium found only one prostate cancer and no latent cancers in 61 males dying of other causes(31). Selenium, as is the case with vitamin E has effect on cell growth suppression primarily by augmenting apoptosis as has been demonstrated in the PC3 human prostate cancer cell line(32). Methyl selenic acid (MSA), a rapidly metabolized precursor of methyl selenol (active form of selenium at cellular level) induces cell cycle arrest mediated in part by up regulation of p19INK4d and p21WAF1 and down regulation of CDK1, CDK 2 and cyclin A. It also modulates many androgen-regulated genes and

suppresses androgen expression.

Currently a large scale study is going on to examine the effect of selenium in men with HGPIN and to evaluate any reduction in the risk of subsequent diagnosis of prostate cancer(33). It has been suggested that vitamin E and selenium combination may be more effective than either of these agents alone. Selenium and Vitamin E Cancer prevention Trial (SELECT) is to explore the prevention in general risk population (those at low risk with PSA 4.0 ng/mL or less and a normal DRE), results being applicable to healthy, aging population(34).

### **Soy**

Legumes play an important role in the traditional diet of eastern countries where prostate cancer incidence is low. Several studies have shown that major isoflavone components of soy, including genistein, daidzein and their metabolites inhibit benign and malignant prostatic epithelial cell growth, down regulate androgen regulated genes and reduce tumor growth in some animal models(35). The chemical similarity of the isoflavones in soy to estrogenic substances has led to the speculation that the preventive activity of soy may be hormonally mediated(36). Recent work suggests that these effects are mediated in part by the inhibition of insulin like growth factor I resulting in cell cycle arrest and induction of apoptosis(37).

### **Toremifene**

Toremifene is a selective estrogen receptor modulator and is approved for management of breast cancer. It has been found to decrease prevalence of prostate cancer through non androgen pathways in a mouse model of prostate cancer(38). Toremifene has been tested in 514 men with high grade prostatic intraepithelial neoplasia (HGPIN) and randomized to receive placebo or 20, 40, 60 mg of toremifene daily(39). The 20mg dose as opposed to 40 or 60mg was seen to be associated with 48% decrease in the risk of prostate cancer at 12 months after initiation of study. This agent is currently undergoing phase III trials.

### **Green tea**

There has been epidemiological evidence of low incidence of prostate cancer among native Asians with a high dietary intake of green tea. Polyphenols, which occur in high concentrations in green tea, are widely regarded to reduce the risk of cancer(40). Epigallocatechin-3-gallate (EGCG) the major polyphenol constituent of green tea, induces apoptosis, cell growth inhibition and cyclin kinase inhibitor mediated cell cycle dysregulation in prostate cancer cell culture(40). Additionally it leads to induction of growth inhibiting gene that belongs to G-protein signaling network and it also induces apoptosis by inhibiting fatty acid synthesis(41). In a study from Italy reported in 2006, a total of 60 men with HGPIN were randomized to green tea vs. placebo, it was seen that 1 out of 30 patients treated with green tea compared to 9 out of 30 treated with placebo were found to have cancer after one year(42). These encouraging results from small trials should provide the necessary impetus for larger studies

to avoid errors due to small sample size.

### **Vitamin D**

Prostate cancer cells express vitamin D receptors and several studies have demonstrated an antiproliferative effect of vitamin D on prostate cancer cell lines(43). Active vitamin D exerts its antiproliferative activity predominantly by inducing cell cycle arrest, mediated by induction of insulin like growth factor binding protein-3 expression which in turn increases the levels of the cell cycle inhibitor p21(44). Calcitriol exhibits anti-inflammatory actions that may contribute to its inhibitory effects in prostate cancer(45). Their hypercalcemic effects limit use of Vitamin D analogs in humans but newer analogs with more tolerable toxicity are currently being tested.

### **Dietary intake of red meat and fat**

An increased intake of animal fat and possibly red meat has been associated with an increased risk of prostate cancer. The difference of risk of prostate cancer between western and Asian countries is as great as 20 fold, and this is attributed partly to the low percentage of animal protein in the diet of Asian countries(46). The postulated mechanisms include an increased androgen levels with high fat diets(47). In recent animal models high fat and caloric intake was associated with up-regulation of prostate 5 $\alpha$ -reductase-2-gene expression(48). Despite these interesting observations, the complexity and problems with adherence of dietary intervention prevents this kind of intervention to be studied at a large scale.

### **Cyclooxygenase 2 inhibitor**

Non-steroidal anti-inflammatory drugs (NSAIDs) function by non-selective inhibition of both cyclooxygenase (COX)-1 and COX-2 isoforms. COX-2 is an inducible enzyme mediating inflammation, pain and cellular repair mechanism. Increased expression of COX-2 is known to correlate with increased angiogenesis, decreased apoptosis, increased tumor invasiveness and immunosuppression in various tumors(49). Prostate cancer expresses more COX-2 than benign prostatic epithelium. Evidence is present suggesting that NSAIDs and COX-2 inhibitors cause apoptosis in prostate cancer cells and may significantly decrease the risk of prostate cancer(50). Inhibition of COX-2 reduces expression of several androgen inducible genes, represses androgen receptor mediated activation of PSA and represses androgen receptor protein expression(51). With the withdrawal of rofecoxib from market the study of its role in prostate cancer reduction was closed. Due to the risk of cardiovascular disease this class of agents is unlikely to be included in further studies.

## **CONCLUSION**

Prostate cancer is an attractive target for chemoprevention because of its late onset, long latency period and treatment related morbidity. Since PCPT gave first firm evidence that cancer can be prevented by relatively non-toxic

oral agent, many agents have been identified that may decrease the risk of prostate cancer. These agents can be categorized for evaluation in three different scenarios, general population (finasteride, a tocopherol and selenium), increased PSA with negative biopsy (dutasteride) and prostatic intraepithelial neoplasia (toremifene and selenium). It requires careful study of the agents in specific populations to determine whether the risk is reduced, the magnitude of risk reduction and their side effects. Newer opportunities involve use of combination of agents which may have additive action and the use of such agents that modulate metabolic processes affecting more than a single disorder at different levels, prime example being inflammation which is implicated in neoplasm including prostate cancer and cardiovascular diseases and aging. Thus, physicians who care for men at the risk of prostate cancer because of their age or otherwise must be aware of these preventive opportunities.

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