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The Changing Landscape of Prostate Cancer Chemoprevention: Current Strategies and Future Directions

Jason M. Phillips and E. David Crawford
University of Colorado Division of Urology
USA

1. Introduction

Current controversy exists regarding the role of chemopreventative agents for prostate cancer. However, prostate cancer's role in our society remains prevalent. Prostate cancer continues to be the leading cause of newly diagnosed male cancers in the United States. In 2011, the American Cancer Society estimated 241,740 new cases and 28,170 deaths from prostate cancer.[1] Only lung cancer has more male cancer deaths. Current treatment strategies such as surgery, radiation, chemotherapy and hormone therapies have been successful in decreasing prostate cancer related morbidity and mortality. However, the physician's armamentarium is focused on treating existing prostate cancer and not preventing it. Despite the prolongation of life for patients with prostate cancer, each therapy carries a side effect profile.

Due to improved early detection, prostate cancer is now often identified at an earlier stage and grade. Newly diagnosed tumors are often organ confined and slow growing. However, once a patient's PSA laboratory value is abnormal, he will most likely receive a prostate biopsy for diagnosis. Given the fact that less than 10% of Americans select active surveillance, screening starts a snowball effect that usually "buys" a treatment. It is well known that treatment including radical prostatectomy or radiation has been shown to overtreat prostate cancer in as many as 30-50% of patients.[2] Morbidity, including incontinence and impotence can significantly affect a patient's quality of life. In addition, the knowledge of prostate cancer may cause emotional, financial and physical harm.[3,4] Given that the US male population faces a 16.7% lifetime risk of prostate cancer, prostate cancer is an ideal candidate for prevention strategies.

Cancer chemoprevention focuses on the use of natural or synthetic agents to suppress, delay, or prevent the development of tumors. Natural substances have long been utilized with varying results for prostate cancer prevention. More recently in the 2000s, 5-alpha reductase inhibitors (5-ARI) have also been used. These substances have focused on both primary prevention and secondary prevention. Primary prevention focuses on deferring or preventing the presence of cancer prior to cancer formation. Secondary prevention focuses on preventing premalignant lesions from progressing to cancer. For prostate cancer, secondary prevention focuses on preventing the progression of high grade prostate epithelial neoplasia (HGPIN).

In December of 2010, the Federal Drug Administration's (FDA) Oncology Drugs Advisory Committee (ODAC) reviewed 5-ARI's indication for the prevention of prostate cancer in men at increased risk for prostate cancer. This committee ruled against the use of 5-ARI's for the use of prostate chemoprevention. Advocacy groups have since issues statements disagreeing with the FDA's ruling, highlighting the fact that controversy continues to exist. The goal of this paper is to examine the available agents and the current environment.

2. Current chemopreventative agents - pharmaceuticals and micronutrients

The ideal chemopreventative agent should be minimally expensive, nontoxic and effective. Having multiple preventative benefits is considered a plus; however it should not potentiate other causes of morbidity or mortality. Pharmaceutical agents, most notably 5-ARIs, and micronutrients have been studied to better establish their potential role in cancer prevention.

2.1 Pharmaceuticals

Finasteride and dutasteride are both 5-ARI medications used to successfully inhibit prostate growth. These two agents are both currently accepted for treating benign prostatic hypertrophy (BPH). The difference between the two medications is minimal, however potentially significant. 5-α-Reductase has two isoenzymes. Finasteride inhibits the type 2 isoenzyme while dutasteride inhibits both the type 1 and type 2 isoenzymes. Dutasteride thus has more complete inhibition of DHT, roughly 90% as compared to finasteride's 70% reduction of serum DHT.[5,6] It has been proposed that expression of the type 1 isoenzyme is increased with prostate cancer while the type 2 isoenzyme is unaffected with prostate cancer.[7] 5-ARI medications focus on inhibiting androgen receptor (AR) activation. Research on BPH has shown that consistent use of finasteride or dutasteride decreases prostatic volume 30% and reduce PSA levels 50-60%.[8] Both 5-ARI medications have been tested for chemopreventative benefits with multicenter, randomized, double blind, placebo controlled trials. The thrust of this paper will discuss the 5-ARI medications and their current role in prostate cancer prevention.

Other pharmaceutical agents potentially used for prostate cancer prevention include statins, nonsteroidal anti-inflammatory drugs (NSAIDS), and toremifene. Statins inhibit HMG-CoA, the rate limiting step of cholesterol synthesis. Statin use over 2 years has been associated with a decrease in prostate specific antigen.[9] By inhibiting prostatic cellular growth and promoting apoptosis, statins also decrease cellular growth. No large double blind study has evaluated the effect of statin use on prostate cancer but a meta-analysis did find a protective effect.[10] Further studies are needed to substantiate current evidence.

NSAIDS inhibit cyclooxygenase-2 (COX-2), which is a key enzyme found in prostate cancer which converts arachidonic acid to prostaglandins. Experimental evidence demonstrated a regression of PIN after NSAID use, but the planned trial with rofecoxib was withdrawn after safety concerns.[11,12]

Selective estrogen modulators (SERMs) are best known for their effects on breast cancer. Toremifene has decreased prostate cancer in the TRAMP model. A phase 2b study found that 20mg doses of toremifene resulted in a 48% decrease in prostate cancer at one year.[13] However, the phase III trial demonstrated no significant risk reduction.[14]

2.2 Micronutrients

Micronutrients have long been sought after to provide a chemotherapeutic benefit for the development or prevention of prostate cancer. Antioxidants in vitro can inhibit cellular proliferation, induce apoptosis and modulate genes leading to the suppression of prostatic tumor. [15,16] The largest scale trial on micronutrients was for selenium and vitamin E in the Selenium and Vitamin E Cancer Prevention Trial (SELECT).

The interest in selenium began with the Nutritional Prevention of Cancer Trial, which used oral selenium for nonmelanoma skin cancer. Men were randomized to selenium versus placebo and were found to have a 65% reduction in prostate cancer incidence after a 4.5 year follow up. Vitamin E interest developed after a 32% reduction in prostate cancer in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Trial (ATBC) trial, which was a double blind randomized placebo controlled trial for lung cancer incidence and mortality.

These studies paved the way for the SELECT trial, published in 2009, which was a randomized, placebo controlled population based primary prevention trial focused on the effects of selenium and vitamin E on preventing prostate cancer. SELECT randomized 35,533 men to four treatment arms: selenium with placebo, selenium with vitamin E, Vitamin E with placebo, placebo with placebo. Study supplements included 200 micrograms l-selenomethionine, 400mg racemic alpha-tocopherol and an optional multivitamin containing no selenium or vitamin E. Eligible men were at least 50 years of age for African-Americans, at least 55 for Caucasians, negative DRE, PSA less than 4ng/mL, and normal blood pressure.

The primary endpoint was the presence of prostate cancer found on for cause biopsies. The indications for biopsy were not indicated in the protocol and were at the discretion of the physician.

During the second interim analysis seven years after initiation of the trial, the independent Data and Safety Monitoring Committee recommended discontinuation of the SELECT because the data demonstrated no significant differences between groups. No statistically significant effects were reported on primary or secondary analyses of the data, suggesting no prostate cancer prevention benefits from selenium or vitamin E.[17] Unfortunately, selenium and vitamin E, which initially demonstrated promise, was eventually found to not have a significant effect on preventing prostate cancer. [17-19]

Other chemopreventative micronutrients include lycopene, green tea, soy, DIM and curcumin. Molecular targets these agents affect include nuclear factor-KB, AKt, Wnt, Hedgehog and Notch.[20]

Lycopene is a biologically occurring carotenoid that is a potent antioxidant. It has been shown to be associated with lower prostate cancer risk in a number of epidemiologic studies.[21] Using the preclinical TRAMP mouse model, prostate cancer was significantly decreased 60% vs. 95% (P=.01). However, no correlation was found with prostate cancer in a PLCO trial examining 29,000 men.

Green tea contains several catechins believed to inhibit oncogenesis and provide antioxidants. Epidemiologic studies between Asian men with a high intake of green tea first suggested that green tea may provide a protective benefit against prostate cancer. Three

clinical trials suggest a benefit.[22] A small clinical trial (n=60) using oral green tea catechins (GTC) found that patients with HGPIN randomized to GTC vs. placebo had no change in PSA levels, but did have less progression of prostate cancer: 1 patient vs. 9 patients progress.[23]

Soy, like green tea, was also found to demonstrate lower prostate cancer in epidemiologic studies between diets high in soy versus western diets. The benefit is potentially a 70% reduction of prostate cancer.[24] Soy affects signaling pathways, specifically Wnt and Hh signaling. Randomized studies are currently being performed.

DIM (the dimeric product of indole-3-carbinol) is found in a variety of plants and has been shown to inhibit alpha reductase suggesting that it may have an inhibitory role in prostate cancer. Curcumin is a bioavailable agent in turmeric and is also an alpha reductase inhibitor. Other regulators along the tumor pathway are inhibited by these two substances. Clinical trials are required to evaluate their effects.

Currently no biologically available micronutrients have been proven to provide chemoprevention benefits of prostate cancer. As such, current patient recommendations are to eat healthy foods and pursue healthy lifestyle changes.[25]

3. Review of 5-ARI chemoprevention trials

We reviewed the multicenter randomized double blind studies focused on 5-ARI usage versus placebo for prostate cancer chemoprevention including the Prostate Cancer Prevention Trial (PCPT) and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE). Table 1 compares their study design.

Trial	Population	Risk Category	Agent	Target	Reported
Prostate Cancer Prevention Trial (PCPT)	n = 18,882	PSA <3.0 ng/mL DRE Normal	Finasteride (Merck)	Type 1 5-ARI	2008
Reduction by Dutasteride of Prostate Cancer Events Trial (REDUCE)	n = 8,229	PSA 2.5-10 ng/mL DRE Normal	Dutasteride (GlaxoSmithKline)	Type 1,2 5-ARI	2009

Table 1. Comparison of PCPT & REDUCE trials.

3.1 Prostate Cancer Prevention Trial (PCPT)

The Prostate Cancer Prevention Trial was the first large multicenter randomized double blind prostate prevention trial using a 5-ARI. In 2003, 18,882 men, 55 years or older with a PSA level less than 3.0ng/mL and a normal digital rectal exam (DRE) were randomized for seven years to finasteride 5mg daily or placebo.

Of the men who participated, 48%, or 9060 men were included in the final analysis. Enrollment criteria included men 55 years or older who were free of prostate cancer, no other significant co morbidities, and an American Urological Association symptom score (AUA-SS) of less than 20. Eligible participants were required to have a PSA less than 3.0ng/ml, normal DRE, adherent to the study protocol and no side effects during placebo. Men were contacted every three months for medical event evaluation and were seen by the

study site every six months for side effect evaluation and medication refills. Annual PSA and DRE were performed. Biopsy was recommended if the DRE was abnormal or PSA was greater than 4.0ng/ml in the placebo arm or 2.0 times PSA (adjusted to 2.3x in year 4) in the finasteride arm. At the completion of the trial in year seven, all participants were recommended to undergo an end of study prostate biopsy with at least six cores. All biopsies were reviewed by a blinded pathologist.

The primary endpoint of the study was the prevalence of prostate cancer as diagnosed by biopsy for cause or end of study biopsies. Prostate cancer was found in 24.4% of the placebo group (1,147/4,692) and 18.4% of the finasteride group (803/4,368), representing a 24.8% risk reduction (CI 19-31, $p<0.001$). Finasteride's relative benefit was found across all groups including age, race/ethnicity, family history and entry PSA. In addition, Finasteride also reduced the risk of HGPIN compared to placebo.

Interestingly, tumors with a Gleason grade of 7-10, high grade tumors, were found to be more prevalent in the finasteride group (37%), 280 of 757 graded tumors, as compared to the placebo group (22%), 237 of 1,068 graded tumors. This was statistically significant ($P<.001$). The increased prevalence of high grade tumors in the treatment group has generated tremendous speculation and sub-analysis. Forty of the excess high grade tumors were found in the "for cause" biopsies, clinically indicated due to increasing PSA or changes in the DRE.

Secondary analyses have found a detection bias demonstrating a net reduction in high-grade cancers and a 53% reduction in low grade cancers.[26] However, due disagreement in the medical community regarding finasteride's effect on high-grade cancers, it was not given a new indication for prostate cancer prevention.

3.2 The Reduction by Dutasteride of Prostate Cancer Events (REDUCE)

Published in the *New England Journal of Medicine* in April of 2010, the REDUCE trial, was a 4-year multicenter, randomized, double-blind, placebo-controlled, parallel-group study. 8,231 men were randomized equally to dutasteride 0.5mg daily versus placebo. This trial was begun prior to the completion of the PCPT trial. Eligible patients were randomized to receive either Dutasteride or placebo. There has never been a large randomized trial comparing finasteride to dutasteride for the prevention of prostate cancer.

An important distinction between dutasteride and finasteride is the effect on 5-alpha reductase. Unlike finasteride, dutasteride affects the expression of both type 1 and type 2 isoenzymes of 5-alpha reductase inhibitors. Animal studies demonstrate that compared to finasteride, dutasteride has an increased reduction in both DHT and tumor growth.[27] Dutasteride, then, theoretically could enhance the anti-tumor effect.

Eligible participants were required to be 50-75 years old, have a serum PSA between 2.5ng/mL-10mg/mL for men aged 50-60 years or 3.0-10ng/mL for men aged >60 years, and had undergone a prostate biopsy within six months of enrollment. Men were excluded if they had more than one biopsy, had prostate cancer of any grade, HGPIN, atypical small acinar proliferation, or a prostate volume of more than 80 grams, had previous prostate surgery of any kind, or had an international prostate symptom score (IPSS) of 25 or higher.

During the trial 6726 men (82.6%) underwent at least 1 biopsy and 1516 men (22.5%) were diagnosed with prostate cancer. The primary endpoint was the presence of prostate cancer

detected on biopsy 2 or 4 years after treatment. Biopsies performed out of the protocol were considered protocol independent biopsies. Other important endpoints included Gleason score, tumor volume, percent of positive biopsy cores, presence of HGPIN, and presence of small acinar proliferation. BPH endpoints were also evaluated.

The dutasteride arm represented an absolute risk reduction of 5% and a relative risk reduction of 23% (857 in the placebo arm versus 659 in the dutasteride arm, P<.001). This benefit was across all subgroups including age, family history, PSA level, prostate volume, or body mass index. The odds ratio for prostate cancer, detected on biopsy, with dutasteride as compared with placebo was 0.60 for all tumors (P<.001) and 0.62 for Gleason scores of 7 to 10 (P<.001).

Low grade tumors (Gleason 5, 6) were statistically higher in the placebo group (617 in placebo vs. 437 in dutasteride, P<0.001). The evidence of premalignant lesions was also decreased. HGPIN had a relative risk reduction of 39% (p<0.001) and small acinar proliferation (ASAP) had a relative risk reduction of 21% (p=0.04).

For high grade tumors, REDUCE demonstrated no significant overall increase in Gleason score 7 to 10, high grade, cancers. This was different from the PCPT, which alarmingly showed an increase in high grade cancer. Overall, there were 220 tumors with a Gleason score of 7 to 10 among 3299 men in the dutasteride group and 233 among 3407 men in the placebo group (P=0.81).

For the Gleason grade 8-10 tumors, there was no overall statistical difference looking at biopsies from all four years: 19 in placebo vs. 29 in dutasteride (P = .15). However, focusing on the second round of biopsies during years 3 and 4 of the study demonstrated a statistical increase in high grade tumors as compared to placebo. There were 12 tumors with a Gleason score of 8 to 10 in the dutasteride group, as compared with only 1 in the placebo group (P=0.003).[28] The authors speculate that this was caused by more frequent early detection of low grade tumors in the placebo group that might have progressed if left untreated. As expected, dutasteride also demonstrated improved outcomes with BPH. Prostate volume, acute urinary retention and BPH related surgery, and urinary tract infections were all significantly reduced in the dutasteride group.

The REDUCE trial, like the PCPT, demonstrated a significant effect on low grade cancers (Gleason 5, 6), but did not appear to alter the prevalence of high grade cancers. Overall it was well tolerated but did have significant effects on libido, erectile dysfunction, and semen volume.

3.3 Controversy: high grade tumor risk and generalizability

The effects of 5ARI's on low grade cancer is consistent across both the PCPT and the REDUCE trials. However, each trial demonstrates a trend towards high grade disease. Initially, the authors from the PCPT concluded that the risk of finasteride on high grade tumors was uncertain. They recommended finasteride not be used as a chemopreventative agent.[29]

Secondary analyses based on the PCPT data were then performed to better understand the conclusions drawn from the data. These authors concluded that biases due to prostate specific antigen (PSA), digital rectal exam (DRE), and prostate volume detection were

responsible for a trend towards increased detection of higher grade tumors found in the "for cause" biopsies for the finasteride arm of the PCPT trial. Consequently, the "end of study" biopsies showed no increased risk of high grade tumor.[30] The increased sensitivity of digital rectal exam performed while a patient is on finasteride has also been shown to increase sensitivity for detecting nodules. Detection increased from 16% to 21% (P=.015).[31]

Finally, PSA sensitivity for detecting prostate cancer increased with the use of 5-ARIs. Both finasteride and dutasteride reduce the PSA laboratory value by approximately half. Consequently, PSA performs better (is more sensitive) in detecting high grade tumors.[32] For the PCPT, for cause biopsies due to a higher PSA level artificially selected for more biopsies to be taken from the treatment group. Prostate volume decreases with finasteride use thus allowed for a larger percentage of the gland to be sampled due to the ratio of the needle to the prostate. The PCPT did not stratify on prostate volume size and it is unclear if this theoretical bias altered the trend towards high grade tumors.

A reevaluation of the PCPT data adjusted for prostate sampling density and baseline PSA levels found that the finasteride group actually had a small net reduction in high grade cancers and a 53% decrease in low grade tumors.[26] A subsequent analysis of the PCPT data using end point prostatectomy instead of prostate biopsy demonstrated a 16% reduction in high grade tumor. At the time of prostatectomy, significant upstaging of cancer was detected in the placebo group but not in the treatment group. In fact, the misclassification of true high-grade disease (to low-grade disease on biopsy) was significantly lower for finasteride (34.6%) than for placebo (52.6%).[33] Finally, another study looking at 500 patients who underwent prostatectomy demonstrated a high-grade cancer rates of 8.2% (placebo) versus 6.0% (finasteride), a 27% risk reduction (RR, 0.73; 95% CI, 0.56-0.96; P = 0.02) with finasteride.[34] The authors concluded that it finasteride probably does not cause high grade cancers, and may in fact improve the detection of them.

The REDUCE trial proved that there was no overall difference for high grade tumors between dutasteride and placebo during the entire study. However subgroup analyses demonstrated a trend towards Gleason 8-10 tumors in the dutasteride group study (19 in placebo vs. 29 in dutasteride, P = .15). In addition the statistically significant increase of high grade tumors in years 3 and 4 was alarming (1 in placebo vs. 12 in dutasteride, P = .003). The authors of the study concluded that the increased number of high grade tumors was due to the increased detection bias in the dutasteride arm as well as removal of low grade cancer in years one and two in the placebo arm. Post hoc analyses similar to the ones performed on the PCPT are pending.

3.4 Current political environment of 5-ARI

In December of 2010, the Federal Drug Administration's Oncology Drugs Advisory Committee (ODAC) reviewed 5-ARI's indication for the prevention of prostate cancer in men at increased risk for prostate cancer. GlaxoSmithKline submitted an application to add prostate cancer prevention as an indication for dutasteride, and Merck submitted an application to alter the labeling for finasteride to reflect a more favorable safety profile with regard to preventing prostate cancer.

ODAC analyzed the results from the PCPT and REDUCE trials. They concluded that the majority of cancers prevented were low risk, thus providing no evidence of prostate cancer

mortality reduction. Also, the controversy with the potential increase in high grade cancers could not be overlooked. Their conclusion was based on the fact that the risks of high-grade cancer were potentially real and could not be explained entirely by volume grade bias, increased sensitivity of PSA and DRE or removal of low-grade cancers. Finally, since the both REDUCE and the PCPT trials utilized end-of-study biopsies, the trial results were not yet generalizable to the US population. ODAC voted against the new indication for dutasteride (yes = 2, no = 14, abstain = 2) and against the new labeling for finasteride (yes = 0, no = 17, abstain = 1).

Due to ODAC's ruling, the FDA does not currently support the use of 5-ARIs for prostate cancer chemoprevention. After the decision made by ODAC, a publicly funded clinical trials cooperative group, SWOG (Southwest Oncology Group), released a statement disagreeing with ODAC's decision to not use 5-ARIs for the prostate cancer prevention.[35]

Clearly, disagreement remains after the publication of the two trials. GlaxoSmithKline has subsequently announced that it is withdrawing applications for similar approval in other countries.[36] More long term data is needed to help experts agree on a consensus although we doubt that any further trials will be done with these agents to prevent prostate cancer. And likely because the other trials mentioned above have been negative, future trials for chemoprevention of prostate cancer will be rare.

3.5 Economic impact of prostate chemoprevention

Current economic assessments for chemoprevention are based on varying assumptions that take into account data from the PCPT, treatment costs, and life expectancy. In addition, variations on the model include how the PCPT data is integrated into the model. For example, PCPT high grade disease can include projections based on the actual data set or based on a data set adjusted for biases.

To be effective, chemoprevention for cancer should cost roughly $100,000 or less per life year (LY) saved due to low adoption rates when cost is greater than $100,000/yr and high when cost is less than $20,000/yr .[37] Svatek *et al* used SEER data to estimate real world incidence and analyzed the cost-effectiveness of finasteride. Their group concluded that finasteride was too expensive at $578,000 to $1,107,000 USD per LY saved.[38]

Subsequent studies supported that chemoprevention was too expensive and estimated the expense per LY saved at up to $1.6 million.[39] However, an analysis on quality adjusted life-years (QALYs) based on PCPT prevalence rates showed a lower cost per LY due to higher PCPT prevalence rates. This analysis demonstrated $122,000 per QALY saved.[40] If finasteride is assumed to not increase the incidence of high grade cancers, then the analysis demonstrated $112,000 per QALY saved. Thus more patients benefit from chemoprevention. These analyses were based on the current price of finasteride at $66/month. If finasteride becomes less expensive, then the cost per QALY has the potential to drop significantly. Similarly, one study evaluated dutasteride based on the REDUCE study data and concluded that it too was not cost effective as a general chemopreventative agent.[41]

Currently chemoprevention with either finasteride or dutasteride is not cost effective. The identification of a high risk subgroup would potentially decrease the cost to benefit ratio thus making chemoprevention feasible from an economic standpoint. In addition, decreasing the cost of either 5-ARI has the potential to make chemoprevention feasible.

4. Discussion

Currently the only proven chemopreventative agents for prostate cancer are finasteride and dutasteride with up to a ~24% reduction in prostate cancer (24% PCPT, 23% REDUCE). However, as discussed earlier, the perceived risk of high grade cancers and the unclear long term benefit for low grade cancers has caused the ruling against the use of 5-ARI's for chemoprevention. Reanalysis of the Prostate Cancer Prevention Trial (PCPT) does not support this ruling and suggests that high-grade cancer is not associated with finasteride therapy and that prostatectomy is the only definitive diagnosis for the evaluation for prostate cancer.[42] In addition, the effects of PSA, DRE and prostate volume bias will continue to make interpretation of the data difficult.[43]

It is important to note that as many of 30% of clinically insignificant cancers on first biopsy are then upstaged on second biopsy to become significant cancers. Consequently, the long term benefits of preventing low grade disease are uncertain.[44] Also, by reducing the incidence of low grade disease, the potential for decreasing the "burden of treatment" is uncertain. But in the US environment where greater than 90% of men diagnosed with prostate cancer seek treatment, it is clear that individuals who have low grade cancer prevented will benefit.[45]

Despite evidence from the PCPT and REDUCE trials, there does not appear to be a trend towards prescribing 5-ARIs for the prevention of prostate cancer. Approximately 64% of Urologists and 80% of primary care providers never prescribe finasteride for prostate cancer chemoprevention. Over half of Urologists reported concerns for inducing high grade tumors. In addition, half of the primary care physicians were not aware 5-ARIs could be used for chemoprevention.[46] With the current ruling by ODAC, it is likely that physicians will trend away from prescribing 5-ARI medications for chemoprevention.

Further analyses are required to pinpoint the subgroup population that will benefit most and the timing that is required to be effective. The PCPT revealed a high prevalence of prostate cancer, but no reliable markers were available to determine who would benefit most from biopsy or treatment. REDUCE prospectively collected samples to retrospectively analyze potential biomarkers but has not yet identified a subgroup that would yet benefit from dutasteride prevention.[47]

In the current political environment, the adoption of 5-ARI medications is slim due to the uncertainty surrounding finasteride and dutasteride. Further analysis into subgroups of patients may reveal that 5-ARIs are clinically significant and economically available for at risk individuals. Maybe then, the benefits of 5-ARI medications will outweigh their uncertainty regarding high risk disease. In the meantime, investigations into new biomarkers, nutritional supplements and other pharmacologic agents may elicit a potential solution to the perplexing problem of primary prevention.

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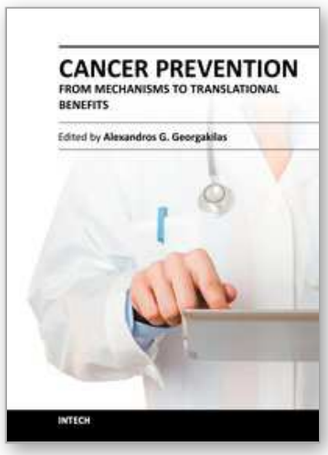

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This unique synthesis of chapters from top experts in their fields targets the unique and significant area of cancer prevention for different types of cancers. Perspective readers are invited to go through novel ideas and current developments in the field of molecular mechanisms for cancer prevention, epidemiological studies, antioxidant therapies and diets, as well as clinical aspects and new advances in prognosis and avoidance of cancer. The primary target audience for the book includes PhD students, researchers, biologists, medical doctors and professionals who are interested in mechanistic studies on cancer prevention and translational benefits for optimized cancer treatment.

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
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Phone: +385 (51) 770 447
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InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
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