Prevention strategies in prostate cancer

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ABSTRACT

Prostate cancer (PCa) prevention has been an exciting and controversial topic since the results of the Prostate Cancer Prevention Trial (PCPT) were published. With the recently published results of the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial, interest in this topic is at a peak. Primary PCa prevention will be unlikely to affect mortality significantly, but the reduction in overtreatment and the effect on quality of life from the avoidance of a cancer diagnosis are important factors to consider.

This review provides a comparative update on the REDUCE and PCPT trials and some clinical recommendations. Other potential primary preventive strategies with statins, selective estrogen response modulators, and nutraceutical compounds—including current evidence for these agents and their roles in clinical practice—are discussed. Many substances that have been examined in the primary prevention of PCa and for which clinical data are either negative or particularly weak are not covered.

The future of PCa prevention continues to expand, with several ongoing clinical trials and much interest in tertiary prostate cancer prevention.

KEY WORDS

Prostate neoplasms, risk, prevention, finasteride, dutasteride, statins, nutraceutical

1. INTRODUCTION

Prostate cancer (PCa) is the most common cancer in men, and there is much debate about treatment approaches and screening for the disease. Recent evidence from the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the European Randomized Study of Screening for Prostate Cancer suggests a high rate of overdiagnosis and overtreatment of this cancer, which carries a low mortality rate relative to the incidence rate [1,2]. Despite the results of the foregoing trials and the success of studies of active surveillance for low-risk PCa, the high intervention rate continues. Prevention of PCa is therefore important. Unfortunately, prevention may have little effect on disease-related mortality. However, many benefits can be conceived as a consequence of alleviating the disease burden:

- Prevention strategies could reduce the detection of clinically insignificant cancers and thereby reduce unnecessary adverse affects on urinary and sexual function associated with radical treatment.
- Prevention could result in cost savings by reducing the number of men needing radical treatment.
- A reduction in the number of patients with clinically insignificant cancer followed on active surveillance protocols could also reduce costs and the psychological impact of living with cancer.

Whether primary PCa prevention is truly primary or tertiary can be debated, given that histologic evidence suggests that microscopic disease lurks in 1 of 3 men in their thirties—well before the average PCa patient is diagnosed [3]; but for the purposes of this review, "primary prevention" refers to the prevention of clinically detectable disease.

Proposed modifiable risk factors for PCa that are potential targets for prevention include prostate inflammation, the endocrine–sex steroid axis, dietary factors, and obesity. Clearly sex steroids are important in the pathogenesis of PCa, with strong evidence for targeting this axis in primary prevention. In many cases, only mixed or low-grade evidence is available for the other potential targets of prevention. This review presents the evidence for successful and potential primary prevention strategies associated with modifiable risk factors for PCa and includes some guidance on how those strategies can be incorporated into clinical practice.

2. DISCUSSION

2.1 Chemoprevention with 5α-Reductase Inhibitors

Androgens help to maintain the normal secretory and metabolic function of the prostate and also contribute

a pathogenic role in the development of PCa and benign prostatic hyperplasia. The enzyme 5α-reductase resides in prostatic tissue to convert circulating testosterone to localized dihydrotestosterone (DHT), a more potent agonist of androgen receptors in prostatic cells. Type II 5α-reductase is the isoform common in benign prostatic tissue; type I predominates in localized PCa[4]. Notably, in older men, DHT levels remain high in the prostate despite a decline in serum levels with age as a consequence of 5α-reductase activity[4,5]. Finasteride is a selective inhibitor of the type II enzyme; dutasteride inhibits both isoforms with a greater degree of measured DHT suppression[6]. As will be evident shortly, a differential impact on clinical outcomes is not clearly defined when both enzymes are inhibited.

2.2.1 PCa Prevention Trials

The Prostate Cancer Prevention Trial (PCPT) was the hallmark study of PCa chemoprevention. Table I summarizes the PCPT trial criteria and outcomes in comparison with the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) trial.

Prostate Cancer Prevention Trial: In PCPT, patients were randomized to finasteride or placebo without a baseline biopsy[7]. Men with an abnormal digital rectal exam (DRE) or a prostate-specific antigen (PSA) level rising above 4 ng/mL were recommended for prostate biopsy ("for-cause biopsy") during the study. An end-of-study prostate biopsy was recommended at 7 years. The final endpoint, showing a 24.8% relative risk reduction in PCa with finasteride as compared with placebo, was met early, and the study was closed with 9060 men included in the final analysis. Unfortunately, a 25.5% increase in the diagnosis of high-grade (Gleason score ≥ 7) PCa occurred in the men taking finasteride, creating concern over the use of this medication for PCa prevention.

Today, several years after original publication of the PCPT outcomes, post-hoc analyses and interpretations have been formulated to explain and justify the relative increase in high-grade disease in those treated with finasteride. Briefly, the effects of reduced prostate volume in modelling studies and the increase in PSA/DRE predictive accuracy in the finasteride arm are postulated explanations for the increased detection rate of high-grade disease[8–11]. Moreover, on biopsy, markers of disease extent and aggressiveness (that is, perineural invasion, bilateralism of Gleason 8–10 cancers, and percentage of positive cores) were worse in the placebo group[12]. For subjects who underwent radical prostatectomy in the placebo and finasteride arms of the study, the rates of more aggressive disease were not in concordance with the biopsy results[9,12]. A higher number of patients in the placebo arm than in the finasteride arm displayed high-grade disease (8.2% vs. 6.0%), for a relative risk reduction of 27% in favour of finasteride[9]. Despite those analyses, a causal relationship

between high-grade PCa and finasteride treatment cannot be eliminated.

REDUCE Trial: As As in the PCPT trial, men in the REDUCE trial were randomized to treatment (dutasteride) or placebo, with PCa incidence as the primary endpoint. The REDUCE patients were a higher risk population as indicated by the inclusion criteria (outlined in Table I). Unlike the PCPT trial, the REDUCE trial required subjects to have a negative prostate biopsy [no PCa, high-grade prostate intraepithelial neoplasia (PIN), or atypical small acinar proliferation] within 6 months of starting the trial. This requirement aimed to limit for-cause biopsies (protocol independent). Perhaps one of the most important design features was the plan to require biopsies at 2 and 4 years to further minimize for-cause biopsies as a result of the increased PSA and DRE sensitivity previously noted with therapy using 5α-reductase inhibitors (5ARIS)[8]. In the REDUCE trial, approximately 12% of patients had a for-cause biopsy, compared with 35% of patients in the PCPT trial.

For the most part, the results of the REDUCE trial parallel those of the PCPT trial (Table I). The 22.8% reduction in PCa diagnosis with dutasteride at the end of 4 years was similar to that with finasteride (24.8%) at the end of 7 years. Consistent with the PCPT trial, the diminutive effect of dutasteride on PCa diagnosis occurred in all pre-specified subgroups (classified by age, PCa family history, body mass index, prostate volume, and so on) suggesting good utility in a wide range of men. A side-effect profile similar to that with finasteride was demonstrated, with effects on erectile function, ejaculatory function, and sexual desire. Importantly, those side effects had a minor impact on discontinuation of the medication (Table I), and the observed improvements in urinary symptoms may have provided balance. Of concern was an increase in all types of cardiac events in the dutasteride arm. Nonetheless, when compared with the total number of patients in each arm, the absolute numbers were very small (30 of 4105 in the dutasteride group, 16 of 4126 in the placebo group), and this outcome, a composite of several cardiac-related conditions, was not homogeneous.

The major outcome difference between PCPT and REDUCE was the effect on high-grade cancers. Dutasteride did not significantly affect the diagnosis of Gleason 7–10 PCas: 220 men were diagnosed in the dutasteride arm, and 233 in the placebo arm. When the high-grade cancers were narrowed to Gleason 8–10 cancers, no difference in incidence was found at the 2-year mark, and a significant difference was found from 2 years onward in favour of the placebo arm (1 case for placebo, 12 cases for dutasteride). However, given the known variability between Gleason 7–10 biopsy pathology and final surgical pathology and the small number of Gleason 8–10 biopsy cases during years 3–4, the potential for a false positive result should limit any conclusions at this point. In addition,

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TABLE I   Comparison of prevention trials in prostate cancer: PCPT (Prostate Cancer Prevention Trial) and REDUCE (Reduction by Dutasteride of Prostate Cancer Events)

Variable	PCPT	REDUCE
	(both multicentre double-blind placebo-controlled RCTS)	
Agent used	Finasteride	Dutasteride
	(type II 5ARI)	(type I and II 5ARI)
Patients analysed at conclusion (*n*)		
Total	9060	6729
Placebo	4692	3424
Treatment	4368	3305
Inclusion criteria		
PSA (ng/mL)	≤3.0	2.5–10
		(or 3.0–10.0 if age > 60)
Age (years)	≥55	50–75
Others	Normal DRE	1 Prior negative biopsy
	AUASS<20	Prostate volume ≤80 mL
		IPSS<25
Follow-up (years)	7	4
Primary outcome	PCa detection	PCa detection
Biopsy		
For cause (*n* 5ARI/*n* placebo)	1476/1667	344/466
End of study	Yes at 7 years	Yes at 2 and 4 years
	(6 cores)	(6–12 cores)
PCa rate (%)		
Placebo	24.4	25.1
5ARI	18.4	19.9
Relative risk reduction for PCa (%)	24.8[a]	22.8[a]
High-grade PCa rate (%)		
5ARI/placebo	6.4/5.1[a]	6.7/6.8
Discontinuation for adverse effects (%)		
5ARI/placebo	36.8/28.9[a]	4.3/2.0[a]
	(only temporary reported)	(only permanent reported)

[a] $p < 0.01$.
RCT = randomized controlled trial; 5ARI = 5α-reductase inhibitor; PSA = prostate-specific antigen; DRE = digital rectal exam; AUASS = American Urological Association symptom score; IPSS = international prostate symptom score; PCa = prostate cancer.

the REDUCE authors noted that, by 2 years, 141 more patients with Gleason 5–7 disease were removed from the placebo arm than from the dutasteride arm as a consequence of PCa diagnosis. Conceivably, an appreciable proportion of those patients could advance to Gleason 8–10 if continued in the study for another 2 years, thereby offsetting the higher number of Gleason 8–10 patients in the dutasteride arm. Moreover, other markers of disease extent (number of positive cores, volume of disease) were similar between the placebo and dutasteride arms, even when subdivided by Gleason score.

The rationales for increased high-grade PCa detection bias in the PCPT trial may also apply to the REDUCE trial, and although as stated earlier, REDUCE was designed to minimize such biases, they may in part explain the differential outcomes between the two trials.

Despite the lack of effect for dutasteride on overall high-grade PCa, the evidence is insufficient to claim superiority of dutasteride over finasteride, because the two study populations and follow-up protocols are not congruent. Extending the REDUCE follow-up to 7 years could potentially uncover findings similar to those in the PCPT study, particularly when considering that Gleason 8–10 cancers became more pronounced in the latter half of that study. Alternatively, if finasteride were to be tested in a higher-risk population with application of the REDUCE inclusion criteria and more frequent per-protocol biopsies, the possibility exists that high-grade tumours might occur at a lower rate with finasteride than with placebo.

The findings of the PCPT trial culminated in the combined 2009 American Urological Association and American Society of Clinical Oncology guidelines and

a systematic review on PCa prevention with 5ARIS [13]. The message from the expert guideline panel was that 5ARIS can be considered in PCa prevention contingent on a patient discussion conveying these points:

- The 5ARIS do not eliminate the risk of PCa, they reduce the incidence.
- Uncertainty remains about an increased risk of high-grade disease.
- The effect on mortality is unknown.
- Treatment holds a significant chance for sexual-related side effects.
- Well-documented beneficial effects accrue to men with symptoms of benign prostatic enlargement.

The REDUCE data would probably update the statement regarding high-grade PCa to read "The risk of high-grade PCa is unlikely to be increased with 5ARI use." In short, 5ARIS lower the detection rate for cancers that are less likely to harm patients and most likely do not increase the risk of more aggressive cancers, but they possibly improve detection of the more aggressive cancers by PSA and DRE. Therefore, 5ARIS are indicated in men with enlarged prostates and lower urinary tract symptoms and, with the recent REDUCE results, may be considered in men who are asymptomatic with risk factors for PCa.

Any benefits must certainly be weighed against the costs of the medication and the development of side effects that (fortunately) are usually reversible on cessation of the drug. Notably, a recent cost–benefit study does not, in terms of mortality outcomes, support the use of these medications for prevention of PCa, but it does show merit with respect to quality-of-life outcomes that reflect living with or being treated for cancer [14].

2.3 Chemoprevention with Other Agents

2.3.1 Selective Estrogen Receptor Modulators
The prostate contains both estrogen α and β receptors, which in laboratory and preclinical studies have been implicated in PCa pathogenesis [15]. Using the transgenic adenocarcinoma of the mouse prostate model, a preclinical study showed that, as compared with animals receiving placebo, those treated with the selective α estrogen receptor antagonist toremifene showed a 60% reduction in PCa [16]. That finding prompted a double-blind phase IIB randomized placebo-controlled trial using various doses of toremifene in 514 patients with high-grade PIN [17]. At 12 months, participants taking toremifene 20 mg daily demonstrated a 21.8% decreased cumulative risk of PCa as compared with those taking placebo, without any effect on Gleason score or prostate volume, and with no increase in adverse events. A concern in the toremifene treatment group was a minor increase in levels of other serum hormones such as testosterone.

Whether an additive or synergistic effect would arise if 5ARIS were to be taken in combination with toremifene can only be speculated. No recommendation on the use of toremifene for PCa prevention can be issued until the anticipated results of an ongoing phase III study (see NCT00106691 at www.ClinicalTrials.gov) of men with high-grade PIN are available.

2.3.2 Statins
Statins inhibit the 3-hydroxy-3-methyl-glutaryl-CoA reductase enzyme early in cholesterol signalling, thereby reducing the synthesis of cholesterol and many of its metabolically active precursors involved in cell proliferation. The role of a high-fat diet and cholesterol in PCa is complex. Likewise, the anti-cancer effects of statins are complex, with evidence for inhibition of inflammation, angiogenesis, cell proliferation, adhesion, and invasion, not to mention promotion of apoptosis [18]. Most data investigating a link between statins and PCa came from post-hoc analyses of randomized controlled trials designed to assess cardiovascular outcomes. Three meta-analyses reviewed those studies and found no association between statins and overall PCa risk [19–21].

In 2007, three large prospective cohort studies and one case–control study changed that perception by uncovering a reduction in advanced PCa with no effect on overall cancer in men taking statins [22–25]. Although several biases were noted in the studies, the main problem in terms of assigning a new clinical indication for these medications is that very few patients present with advanced PCa in the PSA era. The number needed to treat to prevent one advanced cancer is therefore excessively high. Furthermore, as noted by Hamilton and Freedland [18], designing a randomized controlled trial would be futile with the high number of men already taking these medications for cardiovascular reasons. Perhaps the future direction of emphasis with statins will be in tertiary prevention for men with advanced disease or on active surveillance.

2.3.3 Nutraceuticals and Micronutrients
The term "nutraceutical" refers to "natural" or "holistic" unmodified compounds, usually derived from plant matter, with demonstrated benefit against chronic disease or cancer. A high percentage of patients at risk for or already diagnosed with PCa seek alternative therapies in this form [26]. In laboratory studies, nutraceutical compounds most commonly show antioxidant properties combined with other anti-neoplastic actions [27].

Table II presents the most notable nutraceutical compounds examined in PCa prevention, including vitamin D, vitamin E, selenium, lycopene, soy, and green tea [28]. Aside from data originating from the well-designed SELECT (Selenium and Vitamin E Cancer Prevention Trial) protocol, evidence for these compounds is largely retrospective and in many cases contradictory. For that reason, many of the compounds

TABLE II   Primary prostate cancer prevention with selected nutraceuticals

Compound	Origin	Proposed mechanism	Strength of evidence	Outcomes	Selected references
Vitamin D (calcitriol)	Sunlight, meats, fish	Vitamin D receptor activation: cancer homeostasis, cell proliferation and differentiation	Case–control and cohort studies	Conflicting when levels are normal; modest evidence when levels are low	Trottier et al., 2010[28], Schwartz et al., 2006[29]
Vitamin E (tocopherols and tocotrienols)	Nuts, vegetable oils, palm oil, oats, rye, wheat, rice bran	Antioxidant, proapoptotic	Cohort studies, 2 RCTs[a]	No difference from placebo in RCTs	Gaziano et al., 2009[30], Lippman et al., 2009[31]
Lycopene	Tomatoes	Carotenoid antioxidant	Case–control and cohort studies, meta-analysis	Positive meta-analysis, but negative results from the PLCO screening trial	Etminan et al., 2004[32], Kirsh et al., 2006[33], Peters et al., 2007[34]
Soy and isoflavanoids	Soybeans	Phytoestrogens and tyrosine kinase inhibition causing apoptosis, limited cell growth, reduced inflammation	Case–control and cohort studies, meta-analysis	Positive effect noted with non-fermented soy and mainly in non-Western men	Yan and Spitznagel, 2009[35]
Green tea	Camellia sinensis plant	EGCG is the likely active ingredient: antioxidant polyphenol and 5ARI activity	Case–control and cohort studies, 1 RCT	Conflicting for overall PCa diagnosis; possible positive effect on advanced PCa diagnosis	Kurahashi et al., 2008[36], Brausi et al., 2008[37]

[a] SELECT (Selenium and Vitamin E Cancer Prevention Trial) and Physician's Health Study II.
RCT = randomized control trial; PLCO = Prostate, Lung, Colorectal, and Ovarian Cancer; EGCG = epigallocatechin-3-gallate; 5ARI = 5α-reductase inhibitor; PCa = prostate cancer.

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have been disregarded as effective agents against PCa risk in spite of adequate negative evidence.

Of the foregoing compounds, soy derived from soybeans has the best evidence for PCa prevention, as summarized in a meta-analysis of case–control and cohort studies showing a relative risk or odds ratio of 0.74 ($p = 0.01$) in favour of soy [35]. However, many of the other compounds should not be completely neglected based on contradictory low-quality retrospective studies riddled with biases. Despite the lack of high-level clinical evidence for efficacy, these compounds appeal to the natural side of medicine, with the added benefits of low cost and exceedingly rare adverse effects. Several clinical trials are ongoing in this area of PCa prevention.

3. SUMMARY

Primary prevention of PCa is complex, and no clear strategies apply in all patients. For example, 5ARIS clearly show benefit in typical patients over 50 years of age, but they carry significant sexual side effects that may be of more concern to the younger patient population that may benefit most. Recall that PCa probably starts its growth during a man's fourth decade. With the results of the REDUCE trial resolving some of the controversy over the increased risk of high-grade disease, the questions now are these: Who outside of the symptomatic benign prostatic hyperplasia population should be considered, and when should they start these medications?

Active prevention will remain an area of contention, although most would agree that patients with risk factors and anxiety would be a good target population. With respect to other areas of prevention, toremifene and statins will remain investigational until further evidence is available. The same can be said for nutraceutical compounds; however, most of those compounds are dietary in nature and have no adverse effects. Although the evidence for their use is modest at best, this paradigm may appeal to many as a consequence of the naturopathic revolution.

The future of PCa prevention is far from over— many trials are ongoing—but the focus seems to be shifting to tertiary prevention in men already diagnosed with the disease.

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