Acta Oncologica, 2011; 50(Suppl 1): 127–136

informa
healthcare

REVIEW ARTICLE

Chemoprevention of prostate cancer

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Abstract

Over the past two decades, many more men are diagnosed with prostate cancer then die of the disease. This increase in diagnosis has led to aggressive treatment of indolent disease in many individuals and has been the impetus for finding a means of reducing the risk of prostate cancer. In the past decade, there have been eight large trials of prostate cancer risk reduction using dietary supplements, 5α-reductase inhibitors, or anti-estrogens. The only two trials which have demonstrated efficacy are those involving 5α-reductase inhibitors: the PCPT (finasteride) and REDUCE (dutasteride). This review examines prostate cancer risk reduction, with emphasis on conclusions that can be drawn from these two landmark studies.

Epidemiology

Prostate cancer is a heterogeneous disease. Whereas most prostate cancers behave indolently and are undiagnosed during life, it is still the second most common cause of cancer death in men. Autopsy studies have indicated that as many as 30% of men in their 30s will have microfoci of prostate cancer with the prevalence increasing by about 10% with each decade of life [1]. With the advent of widespread PSA testing, especially in North America, the incidence of prostate cancer diagnosis has greatly increased [2]. At present approximately one in six men will be diagnosed with prostate cancer in regions where PSA testing is widespread, and 3.5% of men will die of the disease. Because up to 90% of men diagnosed with prostate cancer are treated with aggressive therapy (radical prostatectomy, radiation, or androgen ablation) [3], cancers that are considered pathologically insignificant are still clinically significant, once they are diagnosed. Even if PSA screening is conclusively shown to decrease the death rate from prostate cancer, it is unlikely that treating low volume, low-grade prostate cancer will contribute to this reduction. Therefore, reducing the overdiagnosis and overtreatment of low-grade prostate cancer is a key benefit of prostate cancer chemoprevention.

Definition of chemoprevention

The term "chemoprevention" implies that a disease is being prevented. With respect to prostate cancer, "risk reduction" is a more appropriate terminology. Nevertheless, because of its widespread use, "chemoprevention" will continue to be used throughout this manuscript. Primary chemoprevention refers to reducing the risk of cancer development. Secondary chemoprevention involves reducing the risk of progression of cancer that is already present. Because many older men have foci of undiagnosed prostate cancer, chemoprevention involves both primary and secondary cancer risk reduction. This distinction is important, because any successful prostate cancer chemopreventative agent will also need to be a treatment of localized prostate cancer.

Targets for prostate cancer chemoprevention

The two principal targets for prostate cancer chemoprevention have been inflammation and hormonal stimulation of the prostate [4,5]. Inflammation has been associated with the development of lung cancer in smokers, hepatic cancer in chronic hepatitis and bowel cancer in inflammatory bowel disease. In the prostate, inflammation is associated with prostate cancer precursor lesions such as

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(Received 13 September 2010; accepted 17 September 2010)

ISSN 0284-186X print/ISSN 1651-226X online
DOI: 10.3109/0284186X.2010.527367

proliferative inflammatory atrophy (PIA) and is believed to increase genetic instability leading to prostate carcinogenesis. Studies involving rofecoxib (a cyclooxygenase-2 inhibitor) and the antioxidants, selenium and Vitamin E, have all been designed to test whether decreasing inflammation in the prostate would reduce the risk of prostate cancer.

Other trials have involved agents designed to reduce hormonal stimulation to the prostate. Androgens are known to stimulate both benign and malignant prostate growth. Neither benign prostatic hyperplasia nor prostate cancer has been described in eunuchs. However, abolishing androgen production and blocking the androgen receptor are unrealistic methods of chemoprevention, because of the side-effects of hypogonadism. On the other hand, testosterone, the major circulating androgen, must be converted to dihydrotestosterone by the 5α-reductase enzymes in order to be active in the prostate. Both finasteride and dutasteride, 5α-reductase inhibitors, target this pathway and have been the subject of successful chemopreventative trials described below.

The role of estrogens in human prostate cancer is not well defined. In some rodent models, exogenous estrogens can synergize with androgens to promote prostate cancer [6,7]. In humans the role of estrogens in prostate carcinogenesis is unclear. Clinical trials of estrogens and antiestrogens are difficult to interpret, because of the indirect effect of these agents on testicular and adrenal androgen production.

Prostate cancer risk reduction studies

Nearly all of the major prostate cancer risk reduction studies started in the last ten years are now complete (Table I). The only successful ones have involved 5α-reductase inhibitors: PCPT (finasteride) and REDUCE (dutasteride). The unsuccessful trials will be briefly reviewed in the order of their completion, followed by a more detailed discussion of the PCPT and REDUCE trials.

ViP trial (rofecoxib) (http://www.clinicalstudyresults.org/documents/company-study_783_0.pdf)

Based on an association of COX-2 overexpression with increased angiogenesis and decreased apoptosis in the prostate, the VIP trial planned to enroll 15 000 men at increased risk of prostate cancer based on an elevated PSA (2.5–10 ng/ml), in order to test whether the COX-2 inhibitor rofecoxib could reduce the risk of prostate cancer. The trial was terminated after 4 741 men were enrolled, because rofecoxib was withdrawn from the market due to an excess of ischemic cardiac events in another study. Therefore, the efficacy of this approach to prostate cancer risk reduction was never tested.

SELECT trial (Selenium and Vitamin E Cancer Prevention Trial)

Selenium and Vitamin E had been associated with a reduction in prostate cancer in post-hoc analyses of two large studies [8,9]. Prostate cancer was not a pre-defined endpoint in either study. In SELECT, 35 000 men over age 50 were randomized to receive 200 μg/d selenium, 400 IU/day Vitamin E, both or neither. Among the four groups, 1 758 cancers were diagnosed. After a median follow-up of 5.5 years, the trial was terminated for lack of efficacy [10].

Table I. Prostate cancer prevention studies (in order of completion).

Agent (Trial Name)	Population Studied	Number of Subjects	Date Concluded	Results	Sponsor
Finasteride (PCPT)	Age ≥ 55 PSA ≤ 3.0	18,882	02/2003	24.8% decrease in cancers	Southwest Oncology Group
Rofecoxib (ViP Trial)	Age 50–75 PSA 2.5–10	15,000 planned	09/2004	Trial cancelled (drug toxicity)	Merck
Vitamin E and C (Physicians Health Study II)	Age ≥ 50	14 641	08/2007	No benefit from either agent	NIH Wyeth
SeleniumVitamin E (SELECT)	Age > 50 PSA ≤ 4.0	35 533	10/2008	No benefit from either agent	Southwest Oncology Group
Dutasteride (REDUCE)	Age ≥ 50 PSA 2.5–10	8 231	01/2009	23% decrease in cancers	GlaxoSmithKline
Soy, Selenium, Vitamin E	HGPIN	325	2010	No Benefit	NCI Canada
Selenium	Age ≥ 40 PSA ≤ 10 HGPIN	~435	05/2010	No significant benefit	U.S. National Cancer Institute
Toremifine	Age ≥ 30 PSA ≤ 10 HGPIN	1 590	05/2010	No significant benefit	GTx

Physicians' Health Study II (Vitamin E and C)

In this study, 14 641 male physicians over age 49 were randomized to receive 400 IU Vitamin E, 500 mg Vitamin C or placebo for up to ten (median 7.6) years. There were 1 008 prostate cancers diagnosed on for-cause biopsies, with no difference among the groups [11].

Prostate Cancer Prevention Study for Men with High-grade Prostatic Intraepithelial Neoplasia (toremifene vs placebo; ClinTrials.Gov identifier: NCT00106691)

This trial randomized 1 590 men with high-grade PIN and no cancer on biopsy to 20 mg toremifene, a selective estrogen receptor modulator, or placebo daily for three years [12]. Repeat biopsies were done after one, two and three years. In a press release on May 24, 2010, the sponsor GTx announced that toremifene reduced the incidence of prostate cancer by a non-signficant 10.2% ($p = 0.385$).

L-Selenium Based Chemoprevention of Prostate Cancer Among Men with High-grade Prostatic Intraepithelial Neoplasia (ClinTrials.Gov identifier: NCT00030901)

This trial recruited approximately 465 men aged 40–80 with high-grade PIN on biopsy, who were treated with 200 μg selenium or placebo for three years. End-of-study biopsies were performed on any man not diagnosed with prostate cancer on for-cause biopsy during the study. This study showed similar incidences of prostate cancer in the two study arms, as reported during a plenary session at the 2010 Annual Meeting of the American Urological Association.

5α-reductase inhibitors for prostate cancer chemoprevention

Rationale. Testosterone is the principal circulating androgen, but it must be converted to dihydrotestosterone (DHT) in the prostate to stimulate prostate growth. DHT is intrinsically about twice as potent as testosterone, and it binds more tightly to the androgen receptor [13,14]. There are two enzymes responsible for conversion of testosterone to DHT, Type 1 and 2 5α-reductase [15]. Type 2 5α-reductase predominates in benign prostate tissue, and men born with Type 2 5α-reductase deficiency have small prostate glands and have never been reported to develop prostate cancer [16]. Type 1 5α-reductase is upregulated in prostate cancer, especially in high-grade or advanced disease [17,18]. Both finasteride, a selective type 2 5α-reductase inhibitor (5ARI), and dutasteride, a dual 5ARI, have proven effective in the treatment of benign prostatic hyperplasia by reducing androgen stimulation to the prostate [19]. Based on the knowledge that prostate cancers have not been reported in eunuchs or men with 5α-reductase deficiency, finasteride and dutasteride have both been considered logical candidates for prostate cancer chemoprevention.

Finasteride and the Prostate Cancer Prevention Trial (PCPT)

The PCPT was funded by the U.S. National Cancer Institute and coordinated by the Southwest Oncology Group. It was initiated in 1993 at over 200 sites in USA and concluded in 2003. The key inclusion criteria were men $\geq$ 55 years old, PSA $\leq$ 3.0 ng/ml, a normal digital rectal examination (DRE), and no suspicion of prostate cancer [20]. There were no baseline biopsies.

Men were randomized to 5 mg finasteride/day or placebo for seven years. Annual PSA measurements and digital rectal examinations (DREs) were done and a prostate biopsy ($\geq$ 6 cores) was recommended for a PSA $>$ 4.0 ng/ml or a suspicious DRE. PSA values were doubled in the finasteride arm in Years 1–3, and multiplied by 2.3 after Year 3 to compensate for the mean decrease in serum PSA with finasteride in an attempt to equalize for-cause biopsies in the two groups. An end-of-study prostate biopsy was recommended at Year 7 for any man not diagnosed with prostate cancer during the study. For-cause biopsies were defined as biopsies that occurred in any man with a PSA $>$ 4.0 ng/ml or an abnormal DRE, whether they were done as an interim or end-of-study biopsy.

Ultimately, 18 882 men were randomized, and 9 060 men (48%) were included in the final analysis (Table II) [21]. The analysis included all men who had an interim biopsy for prostate cancer or who had an end-of-study biopsy (modified crude rate). For-cause biopsies were done in 39% of the participants, and 52% of the cancers were diagnosed on for-cause biopsies. There were 15% fewer for-cause biopsies in the finasteride group. Finasteride demonstrated a 24.8% reduction in the primary endpoint, the prevalence of prostate cancer during the seven-year period (18.4% vs. 24.4% of participants, $p < 0.001$). Looking only at for-cause biopsies, there were 10% fewer cancers in the finasteride group (26.5% vs. 29.5%; p = NS). The reduction in overall cancer incidence was entirely due to a reduction in low-grade cancers (Gleason score $\leq$ 6), and there was an increase in moderate to high-grade cancers: 280 (6.4%) in the finasteride group and 237 (5.1%) in the placebo group ($p = 0.005$). The increase in Gleason 7-10 cancers was almost entirely due to their increased detection in for-cause biopsies. In the end of study

Table II. Summary of subjects, biopsies and cancers in the PCPT.

	Total	Finasteride	Placebo
Subjects randomized	18 882	9 423	9 549
Included in analysis	9 060 (48%)	4 368 (46%)	4 692 (50%)
For-cause biopsies (% of men biopsied)	3 573 (39%)	1 639 (38%)	1 934 (41%)
Total cancers	1 950	803	1 147
Cancers diagnosed for cause	1 006 (52%)	435 (54%)	571 (50%)

biopsies, there were 92 and 89 Gleason 7-10 cancers in the finasteride and placebo groups, respectively.

These results indicate some limitations of the PCPT trial. Less than 50% of randomized men were included in the final analysis, and over half of the prostate cancers were detected on for-cause biopsies. There were fewer for-cause and end-of-study biopsies in the finasteride arm, suggesting that finasteride affected the decision to be biopsied. Subsequent analyses have demonstrated that finasteride improved the sensitivity of both PSA and DRE to detect prostate cancer, including high-grade cancers [22,23]. Furthermore, if high-grade cancers were present at radical prostatectomy, they were more likely to be detected in the finasteride arm than the placebo arm [24]. Also, finasteride decreases prostate volume (24% lower in the finasteride arm at the time of biopsy), improving the detection of both low and high-grade cancers [25,26].

Based on the increased utility of PSA for prostate cancer detection and prostate volume reduction, one would predict that finasteride would increase cancer detection rates, especially on for-cause biopsies. Four separate post hoc analyses have now been conducted to attempt to account for these factors in determining the true effect of finasteride on overall and high-grade cancer [27–30]. The results have ranged from a 0.88 odds ratio for high-grade cancer with finasteride when prostate volume changes were included to a 27% relative risk reduction when the results from subsequent radical prostatectomies were used instead of prostate biopsies. Because these analyses were retrospective in nature and involved many assumptions, they must be considered hypothesis generating rather than providing definitive answers. Although these analyses suggest that finasteride did not cause a net increase in high-grade cancers, they also suggest that it was less effective in reducing the risk of high-grade cancer, compared to low-grade cancer.

In summary, in the PCPT finasteride causes a highly significant reduction in overall and low-grade prostate cancers. Although induction of high-grade cancer cannot be excluded, the literature suggests instead that finasteride likely led to an earlier detection of high-grade cancer, which was less extensive than in the placebo group [24]. Some authors have challenged the efficacy of finasteride in the PCPT by focusing on the non-significant 10% reduction in prostate cancer in for-cause biopsies only [31]. To do so ignores the factors discussed above. The PCPT was never designed or powered to assess the effect of finasteride in a situation where cancers are only detected on for-cause biopsies.

Dutasteride and the Reduction by DUtasteride of prostate Cancer Events (REDUCE) trial

The initial interest in dutasteride for prostate cancer risk reduction came from two observations.

The first was the finding that the ratio of type 1 to type 2 5α-reductase was increased in prostate cancer, suggesting that inhibition of both isoenzymes might be important [18]. The recent observation that both isoenzymes are increased in localized high-grade prostate cancer compared to low-grade cancer or benign tissue emphasizes the potential relevance of dual 5α-reductase inhibition [32]. The second observation came from Phase 3 dutasteride trials for benign prostatic hyperplasia, in which the incidence of prostate cancer was 51% less in the dutasteride arm compared to placebo (27 vs 55 cancers) [33]. Although this was a post-hoc observation of adverse event data, such a decrease had not been seen in similarly designed trials with finasteride [34,35].

The REDUCE trial was designed in 2002, and the first patient was enrolled in early 2003 [36]. It was a multinational, randomized, placebo-controlled trial designed to test the ability of dutasteride to reduce the risk of biopsy-detectable prostate cancer in men at high risk of being diagnosed with the disease. The key entry criteria were men aged 50–75, PSA 2.5–10.0 ng/ml, prostate volume < 80 ml, and a single, negative prostate biopsy of 6–12 cores done independent of the study and taken within six months prior to study enrollment. After a one-month placebo run-in to assess symptoms of benign prostatic hyperplasia and prostatitis, 8 122 men were randomized to dutasteride or placebo for four years and took at least one dose of study drug [37]. Repeat, study-mandated prostate biopsies were taken after two and four years; for-cause biopsies could be done at any time. For-cause biopsies during Months 19–24 and 43–48 replaced the Year 2 or 4 study-mandated biopsies, and hence did not increase a subject's chance of being diagnosed with prostate cancer. Protocol-independent prostate biopsies were those for-cause biopsies done during Months 1–18 and Months 25–42. Key differences between the REDUCE and PCPT trials are shown

in Table III. Because the trials had different study designs and involved different patient populations, they should be viewed as providing complementary results.

Overall, prostate cancer was diagnosed in 858 men in the placebo group (25.1%) and 659 men in the dutasteride group (19.9%) with a relative risk reduction of 23% ($p < 0.0001$) (Table IV) [37]. Gleason 7-10 cancers were diagnosed in 220 men in the dutasteride group (6.7%) and 233 men in the placebo group (6.8%) ($p = 0.81$). In the subset of Gleason 8-10 cancers, there were 29 cancers in the dutasteride group and 19 cancers in the placebo group ($p = 0.15$). During Years 1–2 there were 17 and 18 Gleason 8-10 cancers in the dutasteride and placebo groups, respectively. However, during Years 3–4 there were 12 Gleason 8-10 cancers in the dutasteride group and only one in the placebo group (of 2 343 biopsies). Although induction of high-grade cancer cannot be excluded, one possible explanation for the paucity of Gleason 8-10 cancers in the placebo arm in Years 3–4 was the fact that 141 more Gleason 5-7 cancers were diagnosed in the placebo arm during Years 1–2. Because men with cancer were removed from treatment, there was no opportunity for those cancers diagnosed during Years 1–2 to be reclassified or upgraded during Years 3–4. Support for this hypothesis comes from an active surveillance study in which 105 men with Gleason 4-7 cancers entered into an active surveillance study [38]. Eight (8%) were upgraded to Gleason 8 cancers on re-biopsy a median of 22 months later. A similar rate of upgrading of lower grade cancers diagnosed during Years 1–2 in the REDUCE trial could explain the "missing" Gleason 8-10 cancers in the placebo group during Years 3–4. Futhermore, in the CombAT study [39], a 4 800-patient, 4-year BPH study comparing dutasteride and tamsulosin monotherapies with the combination of the two, in which all biopsies were done for cause, there was no evidence of an increase in high-grade cancers in the two dutasteride arms compared to the tamsulosin monotherapy arm (Roehrborn CR, Nickel JC, Andriole GL, Gagnier RP, Black L, Wilson TH, Rittmaster RS. Dutasteride improves the outcomes of benign prostatic hyperplasia when evaluated for prostate cancer risk reduction: a secondary analysis of the REduction by DUtasteride of prostate Cancer Events (REDUCE) trial., In Press, European Urology, 2010).

Table III. Key differences between the PCPT and REDUCE study designs.

	PCPT	REDUCE
Drug	Finasteride	Dutasteride
Duration (years)	7	4
Age range	≥ 55	50–75
Entry serum PSA (ng/ml)	≤ 3.0	2.5–10.0
Baseline biopsies	No	Yes (6–12 cores)
Study-mandated biopsy timing	Year 7	Years 2 and 4
Study-mandated biopsy cores	≥ 6 (6 cores in ~80%)	10

Other benefits of 5α-reductase inhibitors in men at risk of prostate cancer

Regardless of the etiology of the increase in high-grade cancers in the PCPT and REDUCE, it is important that such cancers be rapidly diagnosed when they occur. Both finasteride and dutasteride have been shown to enhance the utility of PSA for the diagnosis of high-grade prostate cancer [22,40]. Both medications increase the area under the receiver operator characteristics (ROC) curve for PSA detection of prostate cancer. In the REDUCE trial, any rise in PSA after six months of dutasteride treatment characterized a group of men with an increased likelihood of cancer overall, high-grade cancer and pathologically significant cancer (modified Epstein criteria), compared with men whose PSA was stable or continued to decrease [40]. This relationship was markedly attenuated in the placebo arm. The combination of a reduction in the diagnosis of low-grade cancer and enhanced detection of high-grade cancer should lead to a reduction in the overdiagnosis and overtreatment of indolent prostate cancers.

Because most men over age 50 harbor foci of prostate cancer, one could argue that the main effect of 5ARIs is to reduce the risk that biopsy-undetectable cancer will grow to biopsy-detectable cancer. 5ARIs also reduce the incidence of high-grade PIN, considered to be a marker of increased risk of prostate cancer on a subsequent biopsy. In the PCPT finasteride reduced the incidence of high-grade PIN without cancer by 15% [41]; in REDUCE dutasteride reduced the incidence of high-grade PIN without cancer by 39% [37]. This data suggest that 5ARIs reduce the stimulus to prostate cancer formation and will decrease the need for follow-up biopsies.

Whether or not 5ARIs have a beneficial effect on some high-grade cancers, clearly the greatest effect is the reduction in low-grade cancers. Although some authors have called such cancers "insignificant", up to 90% of prostate cancers undergo some form of aggressive treatment [3]. For example, in the REDUCE trial, there were 32% fewer treatment interventions for prostate cancer in the dutasteride arm [42].

Men with an elevated PSA are at increased risk not only for prostate cancer, but also for BPH and its complications. In the finasteride arm of PCPT, urinary retention occurred 33% less often, there were

47% fewer transurethral prostate resections, and 29% fewer urinary tract infections, compared to the placebo arm [21]. In the dutasteride arm of REDUCE acute urinary retention was reduced by 77%, BPH-related surgery by 73%, and urinary tract infections by 41% [37]. Because men in REDUCE had higher baseline PSA levels than those in PCPT, they were at a higher risk of BPH complications, and hence these results are not directly comparable between the two studies.

Side-effects of 5ARIs

Dutasteride and finasteride have similar side-effect profiles, the most common drug-related adverse events being related to sexual function. In a one-year comparative trial, new instances of impotence were noted in 9% of the finasteride group and 8% of the dutasteride group; new instances of decreased libido were noted in 6% of the finasteride group and 5% of the dutasteride group [43]. In the PCPT, erectile dysfunction occurred in 67% of the finasteride group and 61% of the placebo group. Decreased libido occurred in 65% of the finasteride group and 60% of the placebo group [21]. Age had a much greater effect on sexual dysfunction in the PCPT than did finasteride use, with sexual function deteriorating in both groups over the seven years of the trial [44]. In the four-year REDUCE study, new instances of decreased libido occurred in 5.1% of the dutasteride group and 2.9% of the placebo group [37]. New instances of erectile dysfunction occurred in 9.0% of the dutasteride group and 5.7% of the placebo group. Four point three percent of the dutasteride group and 2.0% of the placebo group dropped out due to drug-related side-effects. Gynecomastia occurred in 4.5% of the finasteride arm of the PCPT over seven years and 1.9% of the dutasteride arm of REDUCE over four years, with placebo rates being about half those of the 5ARIs. If decreased libido or erectile dysfunction is going to occur due to 5ARIs, it usually happens within the first six to 12 months of treatment, with rates in the active and placebo groups being similar thereafter [45]. On the other hand, new instances of gynecomastia with 5ARIs occur at a low, but steady rate in excess of placebo.

There have been no life-threatening or serious side-effects proven to be related to either finasteride or dutasteride. Both can occasionally be associated with allergic-type skin reactions. In REDUCE, there was an excess of events in the composite term "heart failure" in the dutasteride vs. the placebo group (30 vs. 16; 0.7% vs. 0.4%); such an increase has not been seen with dutasteride in other studies.

Balancing the benefits and risks of 5ARIs for prostate cancer risk reduction – Who should be treated?

Neither dutasteride nor finasteride has yet to be approved in the EU or USA for reducing the risk of prostate cancer. The PCPT and REDUCE trials indicate that both drugs are effective in reducing biopsy-detectable prostate cancer, although the populations in which each was tested were different. Although the rates of prostate cancer in the placebo groups of the PCPT and REDUCE were similar, the likelihood of a prostate cancer diagnosis in the REDUCE population is much greater outside of a clinical trial. Men with serum PSAs less than 3.0 ng/ml are biopsied infrequently, and biopsying such men yields a low rate of detection of potentially lethal cancers [46]. On the other hand, men with a negative biopsy and elevated PSA are men that are followed closely, often have a rising PSA, and are likely to be re-biopsied. In REDUCE, 72% of men in the placebo group had a rising PSA after Month 6 [40]. Hence, this is a population at high risk of a prostate biopsy and resultant prostate cancer diagnosis and most likely to benefit from prostate cancer risk reduction.

How about men with a high PSA but below the biopsy threshold? Schroder et al. have shown in the ERSPC prostate cancer screening study that men with a baseline PSA $\geq$ 1.5 ng/ml were 3.6 and 7.1 times more likely to be diagnosed with high-grade and low-grade cancer, respectively, than men with a baseline PSA $<$ 1.5 ng/ml [47]. Treatment with a 5ARI in this population will likely reduce the number of men in whom a biopsy is indicated and will reduce the overdiagnosis and overtreatment of low-grade prostate cancers. Such men would already be candidates for 5ARI treatment if they have symptomatic BPH, and prostate cancer risk reduction would be

Table IV. Summary of subjects, biopsies and cancers in REDUCE.

	Total	Dutasteride	Placebo
Subjects randomized	8 122	4 049	4 073
Subjects Biopsied	6 729 (83%)	3 305 (82%)	3 424 (84%)
Number of biopsies	12 024	5 956	6 068
Protocol-independent biopsies (percent of biopsies)	810 (6.7%)	344 (5.8%)	466 (7.7%)
Total cancers (% of men biopsied)	1 517 (22.5%)	659 (19.9%)	858 (25.1%)
Cancers diagnosed on protocol-independent biopsies	98 (6.5%)	41 (6.2%)	57 (6.6%)

an added benefit. Fewer men would undergo aggressive treatment for prostate cancer, reducing the frequency of radical prostatectomy, radiation therapy and androgen ablation.

5ARIs not only decrease the incidence of low-grade cancer, but enhance the detection of high-grade cancer. It is likely that 5ARIs remove some of the background noise in PSA levels, by suppressing PSA production from benign prostate tissue and indolent prostate cancers. In both the PCPT and REDUCE trials, men whose PSA rose while taking a 5ARI were more likely to have a clinically significant prostate cancer [40,48]. One could hypothesize that dutasteride and finasteride may serve as bioassays for clinically significant prostate cancer (cancers whose growth is no longer being controlled by the 5ARI] with PSA being the readout. On the other hand, the percent decrease in PSA with dutasteride during the first six months of REDUCE did not predict overall or high-grade cancer detection during the study. To monitor PSA in men taking a 5ARI, reasonable guidance is to wait six months to establish a new PSA baseline. Confirmed PSA rises from a new baseline should prompt consideration for a prostate biopsy. Continued PSA monitoring is essential in any man taking a 5ARI, if the benefits of increased PSA utility are to be realized.

While it cannot be ruled out, it is unlikely that either dutasteride or finasteride induces the growth of high-grade cancer. In the PCPT, where PSA drove many biopsies, there was an increase in detection of Gleason 7-10 cancers, but only in the for-cause biopsies. In REDUCE, where PSA-driven biopsies were uncommon, there was no overall increase in Gleason 7-10 cancer detection. These results are consistent with the increased utility of PSA for detecting high-grade cancer. Both agents reduce prostate volume, making cancers easier to detect. When prostate volume at the time of biopsy was included in a logistic regression in the PCPT, the odds ratio for Gleason 7-10 cancers in the finasteride arm was 0.88 [27]. When this same adjustment was done in REDUCE, the odds ratio for Gleason 7-10 cancers in the dutasteride arm was 0.62 [49]. Nevertheless, it is clear that both 5ARIs are more effective at reducing the risk of low-grade cancer than high-grade cancer.

One concern is that use of 5-ARIs will cause more high-grade cancers to be missed by preventing PSA increases in such men [50]. There is little evidence to support this hypothesis. In REDUCE, if only men with a rising PSA are biopsied, there will be about twice as many men with Gleason 7-10 cancers who would not be biopsied in the dutasteride arm, compared to the placebo arm. However, normally a rise of 0.35–0.75 ng/ml/year is required for rebiopsy according to most guidelines in men not taking a 5ARI. In REDUCE, if one required a 1 ng/ml rise in PSA from Month 6 to the final PSA before biopsy in the placebo arm, the number of Gleason 7-10 cancers that would not be diagnosed would be similar in both arms [40]. In the dutasteride arm these are presumably cancers whose growth is being controlled, preventing a rise in PSA.

Neither the PCPT or REDUCE were of sufficient duration to assess whether 5ARIs reduce deaths from prostate cancer, because of the prolonged natural history of biopsy-detected prostate cancer. However, aggressive prostate cancers eventually escape even total androgen ablation, and there is no reason to suspect that such cancers would be controlled by 5ARIs. On the other hand, there is also no reason to suspect that cancers that progress during 5ARI therapy would not respond to more aggressive androgen ablation. Even advanced prostate cancers often respond to more complete androgen ablation after GnRH agonists alone have failed.

In addition to the beneficial effects of 5ARIs in reducing the risk of prostate cancer and high-grade PIN, both finasteride and dutasteride are effective treatments for men with symptomatic benign prostatic hyperplasia (BPH). They not only improve urinary symptoms related to an enlarged prostate, they reduce the risk of acute urinary retention and the need for BPH-related surgery.

Although only 10–15% of men taking 5ARIs are likely to experience new or worsening sexual adverse events, the high prevalence of sexual dysfunction in elderly men makes this issue more challenging. It is one thing to tell a man with an elevated PSA and a negative biopsy that his risk of needing another biopsy, and potentially being diagnosed with cancer, will be reduced by taking a 5ARI. It is a more difficult proposition to expect an asymptomatic man with a mildly elevated PSA to take a medication to reduce the risk of a disease he would prefer not thinking about.

In summary, both finasteride and dutasteride have been shown to reduce the risk of biopsy-detectable prostate cancer. The concern over induction of high-grade cancers and lack of regulatory approval have prevented their widespread use for this indication. Dutasteride is now being submitted for approval worldwide for prostate cancer risk reduction. In the near future we will learn if it meets the strict benefit:risk balance required for a cancer risk reduction indication.

Future directions

There have been many epidemiological or retrospective studies suggesting that different dietary factors, supplements or medications may reduce the risk of prostate cancer [51]. For example, there has been

increased emphasis on statins as a potential class of drugs for prostate cancer risk reduction. However, the data on primary prevention of prostate cancer with statins has been less convincing than their effects on reducing the risk of prostate cancer progression or advanced prostate cancer [52,53]. Complicating the interpretation of these studies is evidence that statins suppress PSA. It is impossible to be certain whether this represents a primary effect on prostate cancer or a primary effect on PSA leading to an ascertainment bias in identifying disease occurrence or progression. The stakes are high, because appropriately designed and powered studies on prostate cancer risk reduction are expensive and take many years to achieve definitive results.

If 5α-reductase inhibitors are going to be widely accepted for prostate cancer risk reduction, they will need the approval of regulatory agencies. Continued research is also needed on the issue of high-grade cancers. With respect to dutasteride, the 3-year REDEEM study, comparing dutasteride to placebo in 302 men with low volume, Gleason 6 cancers being followed by active surveillance [54], will provide data on the rate of upgrading to higher Gleason scores, as well as the utility of dutasteride in an active surveillance setting. This results of this study are scheduled to be published in early 2011. There still remains many unanswered questions regarding 5α-reductase inhibitors, such as whether they can be safely used in men who have never had a biopsy in order to better select men for biopsy, the ideal age at which such therapy should be initiated for prostate cancer risk reduction, and whether they should be continued indefinitely or stopped after a man reaches a certain age.

Prostate cancer can now be counted among the few cancers whose risk can be lowered through dietary or medicinal means. The prospects are excellent for improved management of this disease, especially with respect to the overdiagnosis and overtreatment of indolent prostate cancers that are unlikely to cause death or disability in the absence of treatment.

Declaration of interest statement. Dr. Rittmaster is an employee of GlaxoSmithKline, Inc. GlaxoSmithKline is the manufacturer of dutasteride. Dutasteride and finasteride are approved for the treatment of benign prostatic hyperplasia. Neither medication is approved for prostate cancer risk reduction.

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