PERSPECTIVES

Battling Prostate Cancer with 5-Alpha-Reductase Inhibitors: a Pyrrhic Victory?

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Given the relatively small impact of prostate cancer screening on cancer mortality, experts are now suggesting that chemoprevention with 5-alpha-reductase inhibitors (5-ARI) may be a more effective strategy for cancer control. Two large placebo-controlled randomized trials found that men receiving 5-ARI were about 25% less likely than controls to be detected with cancer. However, most cancers were detected on routine biopsies required by study protocols. The benefit from receiving 5-ARI was minimal among men who underwent biopsy for clinical indications. Additionally, men receiving 5-ARI were more likely than controls to be diagnosed with high-grade cancers, though post-hoc analyses adjusting for biases accounted for the excess risk in one of the studies. A recent guideline recommended that men considering prostate cancer screening also consider chemoprevention. The rationale is that reducing cancer incidence, given the known risks for overdiagnosis and subsequent overtreatment, is sufficient justification for chemoprevention. However, a large randomized controlled trial found that screening was associated with a 70% increase in prostate cancer diagnosis—which chemoprevention would then reduce by 25%. This does not seem an acceptable trade-off especially because the potential increased risk for high-grade cancers could lead to higher cancer mortality.

KEY WORDS: prostatic neoplasms; chemoprevention; finasteride; dutasteride; evidence-based practice.

Abbreviations

PCPT	Prostate Cancer Prevention Trial
REDUCE	Reduction by Dutasteride of Prostate Cancer Events
AUA	American Urological Association
IPSS	International Prostate Symptom Score
PSA	prostate-specific antigen
DRE	digital rectal examination

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"Another such victory over the Romans, and we are undone."

~Attributed to King Pyrrhus of Epirus, after the Battle of Asculum

Despite two decades of widespread prostate-specific antigen (PSA) testing, evidence for the efficacy of screening remains inconclusive. Randomized controlled trials recently reported conflicting results, the U.S. Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) showed no prostate-cancer survival benefit for screening after seven years of follow up¹, while the European Randomized Study of Screening for Prostate Cancer (ERSPC) showed a 20% benefit after nine years of follow up². However, the absolute survival benefit in ERSPC was only 0.7/1000, implying that over 1,400 men would need to be screened approximately twice over nine years to prevent one prostate cancer death. While simulation modeling suggests that screening has accounted for much of the 30% decline in the U.S. prostate cancer mortality rate³, the absolute mortality benefit is small given that the estimated lifetime risk of dying from prostate cancer is only 2.8%⁴. Experts have questioned whether the value of screening has been exaggerated to the American public⁵. Esserman and colleagues argued that screening might be just increasing the burden of low-risk cancers without decreasing the burden of aggressive cancers⁶. These authors called for different approaches to cancer control, including chemoprevention.

In 2009, a joint American Society of Clinical Oncology (ASCO)/American Urological Association (AUA) guideline concluded that men being regularly screened or considering screening for prostate cancer may benefit from prostate cancer chemoprevention with the five-alpha-reductase inhibitors (5-ARI) finasteride or dutasteride⁷. Chemoprevention is an attractive strategy for reducing the burden of cancer because, unlike screening which increases cancer incidence while attempting to reduce mortality, chemoprevention might reduce both incidence and mortality. The guideline advised informing interested men about the potential benefits and harms of chemoprevention. Such

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discussions usually occur in primary care settings. Therefore, primary care physicians should know that the guideline is supported only by trials whose findings suggest that chemoprevention could potentially cause more harm than benefit. Furthermore, by associating chemoprevention with screening, the guideline could paradoxically result in increased cancer incidence.

The rationale for using 5-ARI chemoprevention is that these drugs inhibit the conversion of testosterone to the more potent dihydrotestosterone⁸. Because men with congenital 5- α -reductase deficiency do not develop prostate cancer, a 5-ARI could theoretically protect against androgen-dependent carcinogenesis. Evidence regarding the benefits of chemoprevention comes from two randomized controlled trials, the Prostate Cancer Prevention Trial (PCPT)⁹ and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE)¹⁰ (Table 1). Both studies used prostate cancer incidence rather than mortality as the primary endpoint.

The PCPT randomized 18,882 men age 55 years and older with a normal digital rectal examination (DRE) and PSA ≤ 3 ng/mL to receive finasteride 5 mg daily or placebo for 7 years⁹. Biopsies were recommended if PSA levels exceeded 4 ng/mL (adjusted in the finasteride group) or if the DRE was abnormal; end-of-study biopsies were also offered to men not otherwise meeting biopsy criteria. Prostate cancer was detected in 18.4% of the finasteride group and 24.4% of the placebo group, a 24.8% risk reduction (95% CI 18.6 to 30.6%).

The REDUCE study randomized 8,231 men ages 50 to 75 with PSA levels from 2.5 to 10.0 ng/mL and a single negative biopsy within 6 months of enrollment to receive either dutasteride 0.5 mg daily or placebo for four years¹⁰. Biopsies were performed for clinical indications, but the study protocol also called for routine biopsies at years 2 and 4. Prostate cancer was detected in 19.9% of the dutasteride group and 24.9% of the placebo group, a 22.8% risk reduction (95% CI 15.2 to 29.8%).

Comparing the detection rates across intervention and placebo groups in these trials is problematic because analyses combined data from men who underwent biopsy for cause with those who underwent a routine, protocol-directed biopsy. In PCPT, the prostate cancer status was known for only 59.6% of intervention group subjects and

63.0% of placebo group subjects, thus creating a potential selection bias. When outcomes were restricted to subjects with cancers detected for cause, a more clinically relevant cohort, the absolute effect of the 5-ARI was less impressive. The cumulative incidence of prostate cancer diagnosed for cause (or other procedures such as transurethral resection of the prostate) was 7.2% in the placebo group and 5.8% in the finasteride group. The REDUCE trial reported similar proportions of subjects with cancers detected for cause (1.2% in the dutasteride group and 1.9% in the placebo group). However, these estimates are difficult to interpret because men who underwent biopsy for clinical indications near the time of the scheduled biopsy were classified as per-protocol biopsies.

A worrisome finding from the trials was the apparent increased risk for high-grade disease among men assigned to a 5-ARI. The PCPT found that men in the finasteride group were more likely to have tumors of Gleason grade ≥ 7 , 6.4% vs. 5.1%, $P=0.005$. Subjects undergoing for-cause biopsies accounted for nearly all of the excess risk for high-grade tumors. While the REDUCE trial reported similar proportions of tumors with Gleason grade ≥ 7 for the two groups, 12 tumors of Gleason grade 8 to 10 were detected in the dutasteride group during years 3 and 4 compared with only 1 in the placebo group. Additionally, among men undergoing biopsy for cause, those in the dutasteride group were more likely than the placebo group to have a Gleason grade 7 to 10 tumor, though the difference was not statistically significant.

A number of post-hoc analyses have addressed the increased risk for high-grade cancer in the PCPT. Lucia and colleagues compared tumor grade at biopsy and prostatectomy in the 489 subjects with cancer grading available on both specimens¹¹. The increased relative risk for high-grade disease observed with finasteride in biopsy specimens (RR=1.68, 95% CI 1.30 to 2.17) was not found to be significant in prostatectomy specimens (RR = 1.20, 95% CI 0.97 to 1.49). Compared to the placebo group, men in the finasteride group had smaller prostates and were more likely to have biopsies that detected the high-grade disease found at prostatectomy, 69.7% vs. 50.5%, $P=0.01$. Investigators concluded that the increase in high-grade cancers was more likely attributable to increased

Table 1. Prostate Cancer Randomized Placebo-Controlled Chemoprevention Trials Using 5-Alpha Reductase Inhibitors (5-Ari)

	PCPT	REDUCE
Drug	Finasteride	Dutasteride
Inclusion criteria	Age 55+ PSA < 3 ng/mL Normal DRE AUA symptom score < 20	Age 50–75 PSA 2.5–10 ng/mL (ages 50–60) PSA 3.0–10 ng/mL (ages 60+) Negative prostate biopsy within previous 6 months IPSS < 25 (< 20 on alpha-blocker)
Sample size: 5-ARI vs. Placebo	9423 vs. 9459	4105 vs. 4126
Follow-up duration	7 years	4 years
Biopsy indications	Clinical (PSA > 3 , abnormal DRE) Protocol: end-of-study (if not previously diagnosed with prostate cancer)	"Clinical indications" Protocol: end of years 2 and 4 (if not previously diagnosed with prostate cancer)
Prostate cancer detection		
Overall (all biopsies) 5-ARI vs. Placebo (%)	18.4% vs. 24.4%	19.9% vs. 24.9%
Biopsies for clinical indication 5-ARI vs. Placebo (%)	5.8 vs. 7.2*	1.2 vs. 1.9
High-grade prostate cancer detection† 5-ARI vs. Placebo (%)	6.4% vs. 5.1%	6.7% vs. 6.8%

*Includes men who underwent another procedure such as transurethral resection of the prostate †Gleason score 7–10

cancer detection and the selective inhibition of low-grade cancer than induction of high-grade cancer.

Pinsky and colleagues also used prostatectomy grading data to model the true rates of high-grade disease in order to estimate misclassification rates of biopsies¹². Among subjects undergoing prostatectomy, investigators observed an absolute risk reduction of 0.7 percentage points for high-grade disease in the finasteride group (relative risk 0.84, 95% CI 0.68 to 1.05). Redman and colleagues further adjusted for the selection biases introduced because 21% of subjects declined the end-of-study biopsy and only 25% of men with early-stage cancer underwent radical prostatectomy¹³. Adjusted analyses found that finasteride was associated with a 2.2 percentage points absolute risk reduction (relative risk 0.73, 95% CI 0.56 to 0.96) for high-grade disease. However, when "high grade" was defined as Gleason 8 to 10, the adjusted analyses actually found a non-significantly increased risk associated with finasteride.

The REDUCE investigators explained their disconcerting Gleason findings as a consequence of the study protocol, where subjects were withdrawn from the study at the time of cancer diagnosis¹⁰. The authors speculated that if the men in the placebo group who were diagnosed during years 1 and 2 had remained in the study, a proportion of their cancers would have been upstaged to Gleason 8 to 10. Unlike with PCPT, REDUCE investigators did not find that adjusting for potential confounders reduced the estimated risk for high-grade disease and conceded that the increased risk for cancers with Gleason score of 8 to 10 could result in part from dutasteride therapy.

The ASCO/AUA chemoprevention guideline, published in 2009⁷, was based on a meta-analysis of six randomized studies showing a 26% reduction in overall cancer detection (95% CI 2 to 44%), with the PCPT contributing by far the largest number of patients (REDUCE results had not been published). The guideline recommended initiating a discussion about taking 5-ARIs with men who are already—or anticipating—undergoing annual PSA screening for early detection of prostate cancer. However, the panel of guideline experts considered available data to be insufficient for determining whether chemoprevention would have greater impact for high-risk groups such as African Americans or men with a family history of prostate cancer. In describing the meta-analysis, the panel acknowledged that, "The summary relative risk of prostate cancer-specific mortality was 1.00 with wide 95% CIs (0.29 to 3.47)." The panel argued that chemoprevention was still justified because they "...judged that even if 5-ARI treatment never translates into reduced overall or prostate cancer-specific mortality, reduction in risk of prostate cancer diagnosis with the consequent morbidity of treatment is a clinically beneficial end point in and of itself."

The goal of reducing overdiagnosis is commendable because 23 to 42% of screening-detected cancers are estimated to be clinically unimportant tumors for which any treatment would present unnecessary risk¹⁴. However, the guideline seems inconsistent by targeting men who have selected a screening strategy that potentially raises their risk of prostate cancer diagnosis by 70%, as documented in the European screening trial², in order to prescribe a daily medication for up to 7 years to mitigate that increase by about 25%. This potential for overdiagnosis was confirmed in the chemoprevention trials, where subjects were required to undergo annual screening.

Subjects in the intervention groups of both PCPT and REDUCE had a cumulative risk of prostate cancer detection over just 4 to 7 years that exceeded the estimated 16% lifetime risk for prostate cancer in the United States⁴.

Whether men would even take a daily medication for many years to prevent cancer is also uncertain. Although finasteride adherence in PCPT was estimated to exceed 85%⁹, rates may be much lower among average-risk men in a non-study setting. Registry data from Canada showed that just over 70% of women with breast cancer and a BRCA mutation completed 4 years of tamoxifen chemoprevention therapy¹⁵.

The guideline authors also addressed the elevated risk for high-grade disease seen in the intervention group, and their bottom line was: "Although the majority of the Panel judged the observed higher incidence of high-grade (Gleason score 8-10) cancer in the finasteride group is likely due to confounding factors, the increased incidence of high-grade cancer as a result of induction by the drug cannot be excluded with certainty." This conclusion is troubling because the ultimate goal of chemoprevention is reducing disease-specific mortality. Both PCPT and REDUCE relied on the surrogate endpoint of cancer detection, so that the potentially deleterious effect of the increased risk of high-grade cancers on survival is unknown. However, given that the absolute mortality benefit for chemoprevention would likely be quite minimal, even a small increase in high-grade disease could negate any benefit. Walsh has further argued that the 5-ARI agents merely shrink low-grade tumors and, by lowering PSA levels, may delay cancer diagnosis until tumors have become high-grade and less curable¹⁶.

These issues call into question the utility of chemoprevention trials. The principal investigator of the PCPT has noted that the size, cost, and time required to conduct a chemoprevention trial with a mortality endpoint is unachievable¹⁷. Another problem in conducting large-scale chemoprevention trials is that placebo arms will be readily contaminated when the intervention can be obtained outside of the study setting, either prescribed for another indication or available over the counter. If rigorously assessing the ultimate consequences of chemoprevention is not feasible, then perhaps we should question the value of conducting—and funding—such trials. And if the real health benefit of 5-ARI chemoprevention is too small to be detected in even a large clinical trial, then perhaps we already know the answer to the question of whether the benefit is sufficiently large to be clinically important.

The impact of the PCPT study so far appears to be minimal, at least based on VA patient and physician data¹⁸. VA investigators evaluated physician knowledge and use of finasteride for chemoprevention following the 2003 publication of the PCPT results, but before publication of REDUCE or the chemoprevention guideline. Finasteride prescribing patterns did not appear to change through 2007, and over 80% of primary care physicians reported never prescribing finasteride for prostate cancer chemoprevention—with 52% not even aware of this indication. Meanwhile, although more likely to prescribe finasteride chemoprevention, urologists were concerned about inducing high-grade tumors. These reservations seem prudent. Chemoprevention has not been proven to reduce—and may possibly increase—prostate cancer mortality. While the guideline panel rigorously assessed the available evidence, we would argue that this evidence is insufficient to recommend chemoprevention (a position recently supported by the Food and Drug

Administration¹⁹). If reducing prostate cancer incidence without regard to mortality is the desired outcome, forgoing PSA screening in the first place would be a much more effective strategy.

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