Prostate Cancer Chemoprevention: Update of the Prostate Cancer Prevention Trial Findings and Implications for Clinical Practice

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This article updates the findings of the Prostate Cancer Prevention Trial (PCPT) based on recent publications and reviews of the PCPT. New evidence shows that finasteride reduces the overall risk of prostate cancer by 30% and reduces the risk of clinically significant prostate cancer, including high-grade tumors. For tumors with Gleason scores of ≤ 6, men in the finasteride arm had a relative risk reduction (RRR) of 34% (RR, 0.66; 95% CI, 0.55–0.80; $P \leq 0.0001$); tumors with Gleason scores of ≥ 7 had an RRR of 27% (RR, 0.73; 95% CI, 0.56–0.96; $P = 0.02$). The effect of finasteride on sexual function appears to be minimal as men on finasteride had an average 3.21 point increase on the 100 point Sexual Activity Scale compared with men on placebo. With an excellent safety profile and minimal side effects, men aged 55 years or older should be informed of the opportunity to reduce their risk of prostate cancer with finasteride.

Introduction

Prostate cancer continues to be the most common noncutaneous cancer in men. According to the American Cancer Society, 186,320 men will be diagnosed with prostate cancer in 2008. Although there have been recent advances in the treatment of prostate cancer, 28,660 men are predicted to die of prostate cancer this year. Despite efforts to improve treatment, there is little definitive evidence that overall mortality has been significantly affected; a man's lifetime risk of death from prostate cancer has changed little in the past 20 years and is currently about 3%. Other advances have had only modest survival benefits. For example, the use of docetaxel-based chemotherapy has resulted in only a 2- to 3-month survival improvement in advanced, hormone-refractory prostate cancer. However, the economic and quality of life costs associated with treatment of prostate cancer, especially in the last year of life, are considerable. Even more burdensome may be the additive cost and morbidity of treatment of early stage prostate cancer, much of which may be due to overtreatment of indolent cancers. Therefore, prostate cancer is an ideal tumor to target for prevention. It has significant repercussions on overall health and quality of life, and because it is a disease that most often occurs in later years, any reduction in the incidence of prostate cancer could have a significant impact on mortality. As a result, strategies to reduce the risk of prostate cancer offer distinct advantages to individuals and society. The Prostate Cancer Prevention Trial (PCPT) evaluated the role of finasteride in prostate cancer prevention; this review updates the findings of this study.

Summary of the PCPT

The PCPT was conceived in 1992 to test the hypothesis that the type 2 5α-reductase inhibitor finasteride could prevent prostate cancer [1]. On activation of the study in 1993, more than 24,000 men aged 55 years or older without a history of prostate cancer were recruited. From this group, 18,882 men with normal digital rectal examinations (DRE) and a prostate-specific antigen (PSA) of ≤ 3.0 ng/mL were randomly assigned to placebo or 5 mg of finasteride daily for a period of 7 years with annual examinations. Prostate biopsies were performed for cause (elevated PSA ≥ 4.0 ng/mL or an abnormal DRE) and at the end of the 7-year study period in cancer-free men. The goal was to determine the 7-year period prevalence of prostate cancer as determined by a combination of the "for-cause" biopsies and "end-of-study" biopsies for the placebo and finasteride arms. The basic study

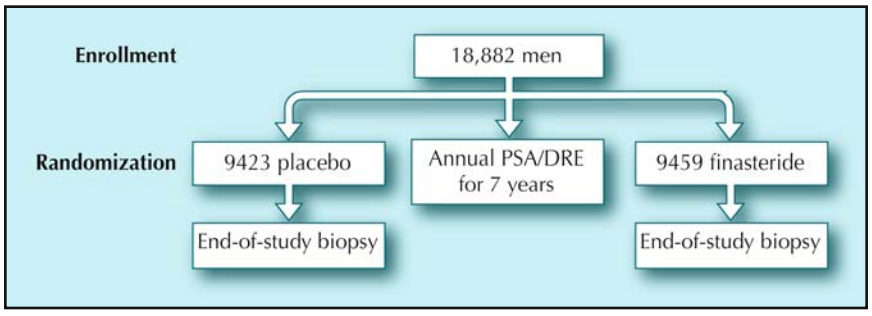

Figure 1. Design of the Prostate Cancer Prevention Trial. DRE—digital rectal examination; PSA—prostate-specific antigen.

design is shown in Figure 1. The trial was stopped 15 months early by an independent Data and Safety Monitoring Committee because there was a 24.8% reduction of prostate cancer in the finasteride arm and a sensitivity analysis demonstrated that further prostate biopsies would not change the outcome. Results also indicated a higher incidence of high-grade (Gleason ≥ 7) tumors in the finasteride arm (6.4% vs 5.1%) compared with placebo, leading to a general lack of enthusiasm in adopting finasteride as a preventive agent. Furthermore, there was a higher than expected overall prevalence of prostate cancer among men with no clinical suspicion of cancer (ie, PSA ≤ 4.0 ng/mL and normal DRE). As expected, there were improved urinary symptoms but increased sexual dysfunction in the finasteride group.

A number of biases, recognized and quantified after study closure and inherent to the use of finasteride, could have affected the outcome. The effect of finasteride on PSA and DRE were two of the most significant biases [2]. Other biases included the biopsy technique, adherence and contamination, and the number of participants undergoing transurethral resection of prostate for obstructive urinary symptoms secondary to benign prostatic hyperplasia [2]. Numerous strategies were incorporated into the design of the PCPT to compensate for these biases, such as PSA indexing, standardized biopsy techniques, and pill counting. Because of these biases, the interim cancer rate as determined by for-cause biopsies could not be an acceptable overall end point. Therefore, an end-of-study prostate biopsy was recommended to all cancer-free participants who reached the 7-year mark regardless of their PSA or DRE. The end-of-study biopsy was a major technique incorporated into the design of the PCPT in an attempt to account for any biases that may have resulted in an unequal biopsy rate between the two groups.

Finasteride Prevents Clinically Significant Cancer

Approximately half of the prostate cancer cases identified in the PCPT were identified by the end-of-study biopsy [1]. Because these men had normal DREs and PSA ≤ 4.0 ng/mL, skeptics argued that finasteride primarily reduced the risk of clinically insignificant tumors. A recent exhaustive study of the PCPT pathology biopsy cores analyzed the characteristics of biopsies between the placebo and finasteride groups stratified by PSA level in an effort to determine the rate of clinically insignificant disease identified in the PCPT [3•]. Lucia et al. [3•] reviewed every single biopsy core from 1626 subjects with cancer (671 treated with finasteride and 955 with placebo) to perform the analysis. Clinical insignificance was defined using the Epstein criteria, including stage T1c, PSA density less than 0.15 ng/mL/g, Gleason score ≤ 6 (with no Gleason 4 or 5), less than three cores positive on biopsy (no core > 50% involvement), or less than 3 mm of one core positive for cancer [4]. The results of this analysis demonstrated that only 25% of all cancers and 38% of cancers with Gleason scores of ≤ 6 detected in the PCPT were clinically insignificant. Further analysis of markers for disease significance, such as number of cores positive, percent of core involvement, linear involvement, and bilaterality, were all decreased in the finasteride arm of the PCPT. As a result of this analysis, it is now clear that finasteride can reduce the risk of clinically significant prostate cancer and it appears that overall, tumors in the finasteride group were smaller than those in the placebo arm of the study.

This analysis further reinforced the dilemma of PSA screening for prostate cancer. Previous studies of PCPT data demonstrated that PSA cannot be used as a dichotomous marker; men with very low levels of PSA have a risk for prostate cancer, including high-grade tumors. Although using a PSA cutoff of 2.5 or 4.0 ng/mL may increase the detection of significant cancer, it has been shown that chances of cure fall dramatically with rising PSA. Figure 2 shows the relationship between PSA, significant cancer, and potential for cure. A take-home message is that some men who undergo PSA screening have the primary goal of achieving the best chance of cure if they are diagnosed with cancer. As a result, consideration has to be given to using lower PSA values to prompt a biopsy. As an alternative, a risk calculator has been developed from the PCPT data using integrated clinical factors, including patient age, family history, PSA, DRE, and prior biopsy history to determine an individual's overall risk for prostate cancer and risk for high-grade tumors [5].

Finasteride Does Not Cause High-Grade Cancer

Another significant concern prompted by the original PCPT data was the apparent increased incidence of high-grade

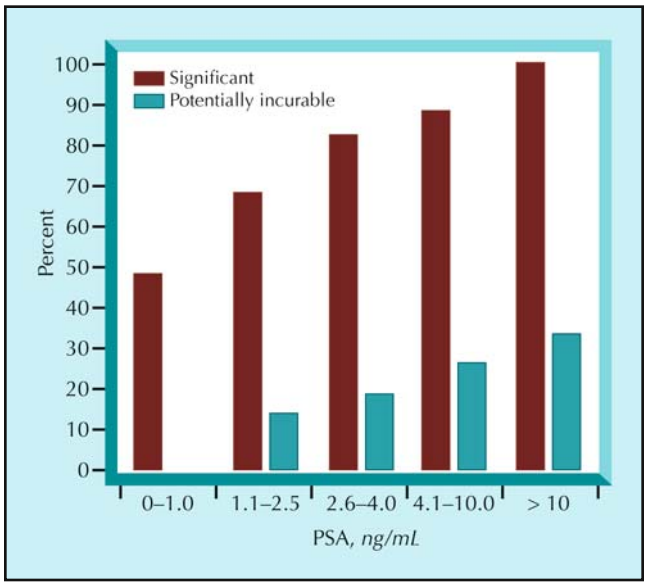

Figure 2. Relationship between PSA, significance using Epstein criteria, and curability. A potentially incurable cancer is defined as pT3 or N1 disease. PSA—prostate-specific antigen.

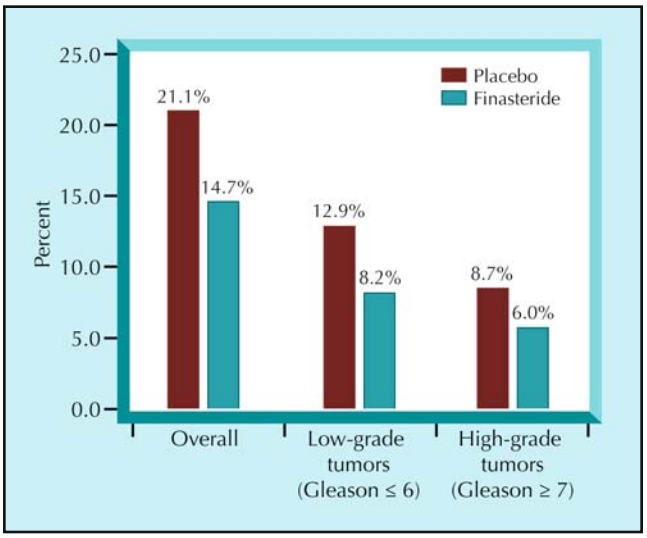

Figure 3. Cancer status by treatment arm by prostatectomy with estimated actual rates of low- and high-grade tumors.

tumors in the finasteride arm (6.4% vs 5.1% in the placebo arm) [1]. This is likely the most significant finding that led to a general lack of acceptance for finasteride as a chemoprevention agent for prostate cancer. Subsequent analyses of the PCPT revealed that finasteride enhanced the detection of high-grade tumors rather than causing them. Finasteride has now been shown to increase the sensitivity of both PSA and DRE for cancer detection (and high-grade cancer in the case of PSA) in addition to improving the diagnostic and grading accuracy of high-grade tumors on prostate biopsy [6,7]. However, these studies lacked the authority to declare that finasteride does not cause high-grade tumors.

Redman et al. [8•] recently performed a series of three analyses to address this issue. In the first analysis, the expected prostate cancer rates were determined in the placebo and finasteride arms as if all participants underwent a biopsy. This analysis was possible because of the large study size and bolstered with additional data gathered during the 3 months between the original PCPT publication date and the final unblinding date in July 2003. This investigation showed the expected actual prostate cancer rate in the placebo group was 21.1% (of 8024 subjects), compared with an expected actual rate of cancer in the finasteride group of 14.7% (of 7966 subjects). This showed an RR of 0.72 (95% CI, 0.67–0.79; $P < 0.0001$) in the finasteride group. Importantly, the difference between rates of high-grade (Gleason ≥ 7) tumors between the placebo and finasteride groups (4.2% vs 4.8%) was not statistically significant, with an RR of 1.14 (95% CI, 0.96–1.35; $P = 0.12$). The first analysis determined cancer rates based on biopsy data and corrected for the bias of fewer end-of-study biopsies in the finasteride arm and the improved performance of PSA and DRE with finasteride as indications of for-cause biopsies.

As previously stated, finasteride improves the diagnostic accuracy of prostate biopsy likely due to the typical 25% reduction in prostate size with finasteride. A second analysis was performed to account for this improved accuracy by incorporating pathologic data from radical prostatectomy specimens and determining the "true" rate of high-grade tumors. The outcome of this analysis demonstrated an estimated overall relative risk reduction (RRR) of 30% with finasteride (Fig. 3). For tumors with Gleason scores of ≤ 6, the estimated RRR is 34% (RR, 0.66; 95% CI, 0.55–0.80; $P \leq 0.0001$); for tumors with Gleason scores of ≥ 7, the RRR is 27% (RR, 0.73; 95% CI, 0.56–0.96; $P = 0.02$). The final analysis performed in this study showed that as the sensitivity of prostate biopsy improves with finasteride, even greater reductions in high-grade tumors can be expected. Overall, this study has shown that finasteride can reduce the risk of all prostate cancer regardless of grade.

Finasteride Causes Minimal Sexual Dysfunction

A chemoprevention strategy must overcome significant obstacles to be accepted for widespread use as it must be proven to be effective, have few side effects, and be inexpensive. Finasteride has been shown to reduce the risk of clinically significant prostate cancer, including high-grade tumors. Finasteride also has well-known efficacy in treating urinary symptoms in benign prostatic processes, making it all the more attractive as a potential chemopreventive agent. However, various studies have shown significant declines in sexual function associated with finasteride over relatively short study periods. Because of the PCPT's large study population and long follow-up period (7 years), sexual dysfunction was made a prespecified secondary end point. The results of this analysis were published in July 2007 and demonstrated that finasteride had only a modest effect on sexual function over the

study period [9•]. The Sexual Activity Scale was used in the PCPT and covers four domains of sexual activity, including ability to attain an erection (five response levels), degree of participant satisfaction with sexual activity (four response levels), change in sexual performance (seven response levels), and frequency of sexual activity (seven response levels). Each response was converted to a 0 to 100 scale, with the overall score being the mean of the four responses. Scores could therefore range from 0 to 100, with higher scores reflecting worsened sexual function. As men progressed through the study period during the PCPT, the overall average increase in their score was 8.22. Men in the finasteride arm had an average score 3.21 points higher than their counterparts in the placebo arm, and the effect of finasteride on sexual function tended to diminish with time. Overall, it is felt that the effect of finasteride on sexual function is not clinically significant and should not detract from the use of finasteride.

Conclusions

Although there are ongoing, large scale randomized clinical trials for the chemoprevention of prostate cancer, such as the REDUCE [10] and SELECT [11] trials, the PCPT remains the only large randomized trial demonstrating an effective chemoprevention strategy. Various modeling analyses have calculated an overall population survival benefit of approximately 1.7 months with the use of finasteride, which compares favorably with population survival gains in other well-established prevention programs, such as childhood immunizations [12,13]. However, cost analysis models have shown that widespread use of finasteride may not be cost-effective at current prices [14]. Nevertheless, the benefit to the 25% (30% in the most recent analysis) of men who would not be affected by prostate cancer should not be forgotten. There are still a number of questions that need to be answered, such as the optimal age to start finasteride, optimal duration of therapy, and identification of those men who will benefit most from therapy. However, finasteride is a drug shown to be safe with minimal side effects and has now been proven to reduce the overall risk of prostate cancer, including high-grade tumors. In a country with about 200,000 cases per year, a 30% reduction could have significant public health consequences. Therefore, it is our recommendation that men aged 55 or older should be informed of the opportunity to reduce their risk of prostate cancer with finasteride.

Disclosures

No potential conflicts of interest relevant to this article were reported.

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- • Of importance
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