

## EDITORIAL



## The Prevention of Prostate Cancer — The Dilemma Continues

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Prostate cancer is the most common non-skin cancer in the United States, the second leading cause of death from cancer among U.S. men, and the seventh leading cause of death in the United States. The number of new cases of prostate cancer, now estimated at more than 220,000 per year, is expected to increase to more than 380,000 by 2025 because of the aging male population. The incidence of prostate cancer and the rate of death due to the disease increase exponentially with age. The other major risk factors for prostate cancer include a family history of prostate cancer, black race, and a high-fat diet. There is no proven method of prevention.

Finasteride inhibits the conversion of testosterone to dihydrotestosterone by the enzyme 5 $\alpha$ -reductase, reducing the level of dihydrotestosterone, the most active androgen in the prostate, by 90 percent. Approved by the Food and Drug Administration as an oral medication for the treatment of symptoms of benign prostatic hyperplasia, finasteride shrinks the prostate by 20 to 30 percent and improves urinary flow rates and symptom scores. In long-term, placebo-controlled trials, finasteride has significantly reduced the risk of acute urinary retention and the need for surgical intervention for benign prostatic hyperplasia from about 10 percent to 5 percent.<sup>1</sup>

Because of its beneficial effect on benign prostatic hyperplasia, finasteride was tested, in short-term, placebo-controlled trials, as a treatment for prostate cancer, but it had little effect, reducing serum levels of prostate-specific antigen (PSA) slightly but effecting no commensurate change in the measurable tumor burden.<sup>2</sup> Nevertheless, in the early 1990s, it seemed reasonable to postulate that finasteride might prevent prostate cancer by reducing androgenic stimulation. The Prostate Cancer Prevention Trial (PCPT) was initiated to test this hypothesis

and is the first major trial of chemoprevention for prostate cancer. In this issue of the *Journal*, Thompson et al.<sup>3</sup> report the results of this seven-year trial involving more than 18,000 men. At entry, eligible men were considered to have a low risk of prostate cancer (as indicated by a normal digital rectal examination and a serum PSA level of no more than 3.0 ng per milliliter). The men were randomly assigned to 5 mg of finasteride per day or placebo and were monitored annually with a digital rectal examination and measurement of serum PSA. “Systematic” needle-biopsy samples were obtained either “for cause” (if the digital rectal examination or PSA level became abnormal) or at the end of the study, when all men who were still alive and had not received a diagnosis of prostate cancer were given a recommendation to have a biopsy. The end point of the study was the rate of detection of biopsy-confirmed prostate cancer. The study was designed to detect a relative reduction of 25 percent or more in the cancer-detection rate in the treatment group from the expected 6 percent rate in the placebo group.

Contrary to the expectations of many experts, there was a substantial effect of finasteride on the rate of detection of cancer. The cumulative incidence was reduced from 24.4 percent in the placebo group to 18.4 in the finasteride group. Toxic effects were limited. Adverse effects on sexual function were somewhat offset by beneficial effects on urinary function, including a significant reduction in the risks of acute urinary retention and the need for a surgical intervention — transurethral resection of the prostate — for relief of benign prostatic hyperplasia.

Should finasteride now be recommended to men in order to lower their risk of prostate cancer? Several disturbing findings in the report argue that it should not. In the placebo group, cancer was detect-

ed four times as often as was expected — in 24.4 percent rather than 6 percent of the men. Furthermore, the relative rate of high-grade cancers and the absolute number of such cancers were greater in the finasteride group than in the placebo group. How can we explain these findings?

The high rate of detection of cancer in both groups in this study raises serious concern about the clinical significance of the cancers that were detected and of the reduction achieved with finasteride treatment. In previous screening trials, detection rates were much lower — about 3 to 8 percent.<sup>4,5</sup> The detection rate in both groups of the PCPT approaches the 30 to 40 percent prevalence of histologically proved cancer found at autopsy in men older than 50 years of age who die from other causes and exceeds the estimated 16.7 percent lifetime risk of a diagnosis of prostate cancer among men older than 50 years of age. The risk of death from prostate cancer is lower still, at 3.6 percent.<sup>6,7</sup>

Most of the cancers detected in the PCPT were low-grade or intermediate-grade cancers and were found to be clinically localized. Were these clinically important cancers? What risk did they pose to the men harboring them? Albertsen et al. have estimated that the risk of death due to prostate cancer within 15 years after diagnosis in men who receive no curative therapy ranges from 4 to 30 percent, depending on the age at diagnosis and the grade of the cancer.<sup>8</sup> In the PCPT, cancers were detected by serial screening or planned biopsy at the end of the study. These cancers were detected much earlier in their natural history than those in the study by Albertsen et al. and thus probably confer a substantially lower risk of death. To understand the malignant potential of the large number of cancers detected in this trial, it will be important to document the type of treatment these men receive, their long-term survival, and which cancers progress. After all, improved survival is the goal of cancer prevention, and the intermediate end point used in this trial — the histologic detection of cancer — is not a proven surrogate.

The second surprising finding of the trial was the increase in the rate of high-grade cancers in the finasteride group. Overall, some 5.1 percent of men in the placebo group and 6.4 percent of those in the finasteride group had a cancer with a Gleason score of 7, 8, 9, or 10 — an increase of 1.3 percentage points (relative risk, 1.27; 95 percent confidence interval, 1.07 to 1.50). The Gleason scoring system is the accepted standard for the grading of prostate

cancer, and in this trial, the score was assigned through central review by pathologists who were unaware of the men's treatment-group assignments. Cancers with a Gleason score of 7 to 10 contain poorly differentiated components that are known to behave aggressively.<sup>6</sup> The risk of death due to prostate cancer within 15 years after diagnosis among men with such cancers that are managed conservatively ranges from 42 percent to 87 percent, depending on age and Gleason grade at diagnosis, according to one study.<sup>8</sup>

The increased number of high-grade cancers is not likely to be an artifact of the effects of finasteride on the histology of the prostate.<sup>9</sup> The proportion of high-grade cancers in the placebo group, 22.2 percent, was similar to those found in other clinical series. However, a previous analysis of cancers found on biopsy in a smaller randomized, placebo-controlled trial of finasteride found no difference in the proportion of high-grade cancers.<sup>10</sup> The higher incidence and greater proportion of high-grade cancers in the finasteride-treated patients in the current study may have resulted from increased sampling by needle biopsy (more specimens per gram of prostate). Or, more likely, by reducing intraprostatic androgen levels, finasteride may have created an environment in which high-grade cancers that were less dependent on androgens for their growth had a competitive advantage.<sup>11</sup> The reduction in the serum PSA level induced by finasteride and the diminished level of PSA produced per gram of poorly differentiated cancer may also have resulted in some delay in the triggering of a biopsy in men in the finasteride group, thus allowing high-grade components to proliferate.

What should we advise the public and our patients? On balance, finasteride does not seem to be an attractive agent for the chemoprevention of prostate cancer. Although it reduced the cumulative incidence of cancer in the PCPT trial, the reduction was relative to the incidence in a control group in which biopsy was recommended for all men, regardless of risk factors — an approach that is destined to lead to the overdetection of histologically identified cancers of little clinical significance. We do not know the malignant potential of such cancers and have no evidence that any benefit would be worth the risk associated with treatment. Furthermore, the study results suggest that finasteride may accelerate the growth of high-grade cancers, which may pose a threat to life and health if they are not treated successfully. Finally, the effects of finasteride

on sexual function lessen the attractiveness of the drug as a preventive agent.

Should men taking finasteride for relief of urinary symptoms be counseled to stop taking the drug? Probably not. Finasteride is as effective as alpha-adrenergic–blocking agents in relieving the symptoms of benign prostatic hyperplasia and has the added benefit of reducing the risk of acute urinary retention and the need for transurethral resection of the prostate.<sup>1</sup> As long as such men are monitored carefully for the development of cancer by periodic digital rectal examinations and measurement of serum PSA levels corrected for the effect of finasteride, there is little risk that any cancer would develop that could not be cured with modern therapy.<sup>6</sup>

Future studies should explore whether finasteride would be more effective if it were given earlier in the course of prostate cancer. Serum PSA levels begin to increase two decades before the clinical detection of cancer,<sup>12</sup> suggesting that early cancers begin to develop when the PSA level is below 0.5 ng per milliliter. In the PCPT, 52 percent of the men had a PSA level of more than 1.0 ng per milliliter.

It would help us to estimate the risks and benefits associated with finasteride for a given man if the characteristics (both at study entry and at the time of diagnosis) of men who were given a diagnosis of any cancer, those who were given a diagnosis of high-grade cancer, and those who had side effects from the drug were more fully described in future reports.

Finally, there is an urgent need for better ways to characterize the risks posed by a prostate cancer once it has been detected. Information on the stage, the grade, and the PSA level has served us well,<sup>13</sup> but we need better methods of characterizing more precisely the threat posed by a given cancer. Much hope rests on molecular and genetic analysis of cancers found in needle-biopsy specimens so that the malignant potential of this common type of cancer can be accurately defined and, ultimately, so that

treatment can be tailored to the risk the cancer confers on each individual man.

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This article was published at [www.nejm.org](http://www.nejm.org) on June 24, 2003.

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