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## The Influence of Finasteride on the Development of Prostate Cancer

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### ABSTRACT

#### BACKGROUND

Androgens are involved in the development of prostate cancer. Finasteride, an inhibitor of 5 $\alpha$ -reductase, inhibits the conversion of testosterone to dihydrotestosterone, the primary androgen in the prostate, and may reduce the risk of prostate cancer.

#### METHODS

In the Prostate Cancer Prevention Trial, we randomly assigned 18,882 men 55 years of age or older with a normal digital rectal examination and a prostate-specific antigen (PSA) level of 3.0 ng per milliliter or lower to treatment with finasteride (5 mg per day) or placebo for seven years. Prostate biopsy was recommended if the annual PSA level, adjusted for the effect of finasteride, exceeded 4.0 ng per milliliter or if the digital rectal examination was abnormal. It was anticipated that 60 percent of participants would have prostate cancer diagnosed during the study or would undergo biopsy at the end of the study. The primary end point was the prevalence of prostate cancer during the seven years of the study.

#### RESULTS

Prostate cancer was detected in 803 of the 4368 men in the finasteride group who had data for the final analysis (18.4 percent) and 1147 of the 4692 men in the placebo group who had such data (24.4 percent), for a 24.8 percent reduction in prevalence over the seven-year period (95 percent confidence interval, 18.6 to 30.6 percent;  $P < 0.001$ ). Tumors of Gleason grade 7, 8, 9, or 10 were more common in the finasteride group (280 of 757 tumors [37.0 percent], or 6.4 percent of the 4368 men included in the final analysis) than in the placebo group (237 of 1068 tumors [22.2 percent],  $P < 0.001$  for the comparison between groups; or 5.1 percent of the 4692 men included in the final analysis,  $P = 0.005$  for the comparison between groups). Sexual side effects were more common in finasteride-treated men, whereas urinary symptoms were more common in men receiving placebo.

#### CONCLUSIONS

Finasteride prevents or delays the appearance of prostate cancer, but this possible benefit and a reduced risk of urinary problems must be weighed against sexual side effects and the increased risk of high-grade prostate cancer.

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**T**O DATE, THE MANAGEMENT OF PROSTATE cancer, the most common nondermatologic neoplasm in men in the United States, has focused on early diagnosis and treatment. Given that the development of prostate cancer is a long-term process involving multiple steps, however, prevention may be a more effective approach.

There is abundant evidence that androgens influence the development of prostate cancer.<sup>1-3</sup> The development of finasteride, an inhibitor of steroid 5 $\alpha$ -reductase, the enzyme that converts testosterone to the more potent androgen dihydrotestosterone, created an opportunity to test the possibility that lowering the androgen levels in the prostate would reduce the risk of prostate cancer. We undertook a study to determine whether finasteride can reduce the prevalence of prostate cancer among initially healthy men during a seven-year study period.

## METHODS

### STUDY DESIGN

Men 55 years of age or older with a normal digital rectal examination, no clinically significant coexisting conditions, and an American Urological Association symptom score<sup>4</sup> of less than 20 were recruited. The study was approved by institutional review boards at all sites. After the men had given written informed consent, blood was drawn to determine the level of prostate-specific antigen (PSA), and the men were issued a three-month supply of placebo tablets for the run-in phase of the trial. If, after this three-month period, the PSA level was 3.0 ng per milliliter or lower, adherence was within 20 percent of the expected rate of placebo use, and there were no clinically significant toxic effects, the men were randomly assigned to finasteride (5 mg per day) or placebo. The planned duration of treatment was seven years. A dynamic allocation scheme was used for randomization to ensure that the treatment groups were balanced within each of the 221 study sites.

The men underwent annual digital rectal examinations and measurements of PSA. Biannually, they were seen for reissuing of medication, counts of pills, and recording of clinically significant medical conditions and side effects. Every three months, the men were contacted by telephone for the collection of data on interim medical events.

Because of the effect of finasteride on the PSA level, the measure of which is the primary method of detection of prostate cancer, an end-of-study biopsy was planned. At the end of seven years, all men who had not been given a diagnosis of prostate can-

cer were offered an end-of-study prostate biopsy. This biopsy was to be performed within 7 years  $\pm$ 90 days after the date of randomization.

### PROSTATE BIOPSY

Measurements of PSA were performed in a central laboratory (with the use of the Tandem E assay [Hybritech] until 2000 and the Access assay [Beckman Coulter] thereafter). After the measurement of PSA at enrollment, all PSA measurements for men in the finasteride group were adjusted before being reported, because finasteride causes a decrease in the PSA level.<sup>5</sup> A centralized adjustment, overseen by an independent data and safety monitoring committee, ensured that the men in the finasteride group had a rate of recommendation for prostate biopsy approximately equal to that among men in the placebo group. Initially, the adjustment consisted of a doubling of the PSA values for finasteride-treated men, but on the basis of the goal of an equal percentage of biopsies in each group, the factor was changed to 2.3 at the beginning of the man's fourth year in the study. PSA levels were initially reported as elevated or not elevated, but in October 1995, as clinical practice changed, adjusted values began to be reported for men with elevated PSA levels. The PSA values reported to the men were thus the adjusted values for men in the finasteride group and the unadjusted values for men in the placebo group. If the digital rectal examination was abnormal or if the reported PSA level was higher than 4.0 ng per milliliter at the annual examination, prostate biopsy was recommended.

Biopsy was performed with the use of transrectal ultrasonographic guidance, and a minimum of six specimens was obtained. If the biopsy was positive, the subject was removed from the study; if it was negative, he remained in the study. If prostatic intraepithelial neoplasia was found, a second biopsy was recommended.

All prostate biopsies were reviewed by a central pathology laboratory and by pathologists at the study site, all of whom were unaware of the treatment-group assignment. Prostate tissue from any other procedures performed (e.g., transurethral resection of the prostate) was sent to the central pathology laboratory for evaluation. Discordant interpretations were arbitrated by a referee pathologist, and concordance was achieved in all cases.

### STATISTICAL ANALYSIS

The primary objective of the study was to determine whether the administration of finasteride for seven

years could reduce the prevalence of prostate cancer during that period. We assumed that the prevalence of prostate cancer during the seven years of the study would be 6 percent in the placebo group and that a 25 percent reduction in the prevalence in the finasteride group at seven years would be of clinical significance. We calculated that with a two-sided alpha of 0.05, a power of 0.92, and a three-year accrual period, we needed a sample size of 18,000. We also assumed that 60 percent of the men either would have an interim diagnosis of prostate cancer or would undergo an end-of-study biopsy. It was estimated that 20 percent of the participants would die during the study, that 5 percent would decline to undergo a prostate biopsy, and that 15 percent would be lost to follow-up.

Another assumption was that the rate of nonadherence to the study treatment would be 14 percent and that 5 percent of the men in the placebo group would end up taking finasteride (the drop-in rate). Serum dihydrotestosterone was measured in a randomly selected 5 percent sample of men as a marker of adherence to study medication in the finasteride group and as a measure of the drop-in rate in the placebo group.<sup>6,7</sup>

The primary intention-to-treat analysis included men who received a diagnosis of prostate cancer during the study or who underwent an end-of-study biopsy. Medical events, side effects, and the rates of temporary discontinuation of treatment are reported for all eligible men. All reported P values are two-sided.

An independent data and safety monitoring committee met every six months and reviewed data on safety, adherence, and diagnoses of prostate cancer, as well as other data related to the monitoring of the study assumptions. This committee reported to the chair of the steering committee and made recommendations regarding revisions to the protocol or adjustments for possible differences in prostate-cancer-detection rates due to the effect of finasteride on the PSA level and prostate size. Because of the known PSA-related bias and other potential detection biases that were anticipated, no formal interim stopping rules were specified.

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## RESULTS

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### STUDY PARTICIPANTS AND TERMINATION OF THE STUDY

Over a period of three years, 24,482 men were enrolled in the study, and of these men, 18,882 underwent randomization between January 1994 and

May 1997 — 12,016 of them during the first year of the trial. Most of the men who did not undergo randomization (3997) had a PSA level of more than 3.0 ng per milliliter. On February 21, 2003, 15 months before the anticipated completion of the study, the data and safety monitoring committee met and, on the basis of sensitivity analyses, recommended early termination of the study, since the study objective had been met and the conclusions were extremely unlikely to change with additional diagnoses of prostate cancer and end-of-study biopsy results. Because of the rapid initial accrual of participants, at the time of the analysis of the data and safety monitoring committee, 81.3 percent of the men had completed the seven years of the study. The current analysis is based on the 86.3 percent of the men who have now completed the seven years of the study.

### RATES OF PROSTATE CANCER AND END-OF-STUDY BIOPSY

The rate of diagnosis of prostate cancer or end-of-study biopsy was 59.6 percent in the finasteride group and 63.0 percent in the placebo group ( $P < 0.001$ ). Men with such a diagnosis made more than 7 years plus 90 days after randomization or with an end-of-study biopsy performed after that time were excluded from the primary analysis (Table 1). Men were considered to have refused a biopsy if the biopsy was not performed because of a co-existing condition or because the personal physician recommended against the procedure, as well as if the men themselves refused the biopsy. The rate of refusal of biopsy was higher than had originally been estimated, but because the death rate and the rate of loss to follow-up were lower than had been anticipated, the overall ascertainment goal was achieved.

Of the 9060 men who were included in the final analysis, prostate cancer was detected in 803 of the 4368 in the finasteride group (18.4 percent) and 1147 of the 4692 in the placebo group (24.4 percent), a relative risk reduction of 24.8 percent (95 percent confidence interval, 18.6 to 30.6 percent;  $P < 0.001$ ). The number of cases of prostate cancer detected either during the course of the study in a biopsy performed for cause (an elevated PSA level or an abnormal digital rectal examination) or in a biopsy performed at the end of the study was higher in the placebo group than in the finasteride group. Of the cases of prostate cancer that were diagnosed in a biopsy performed for cause, 96.0 percent were found on biopsy and 4.0 percent were found after

**Table 1. Status of Men at the Time of the Analysis.**

Variable	Finasteride Group	Placebo Group
	no. (%)	
Randomized	9423	9459
Ineligible because of previous prostate cancer	0	2
Did not complete study because of early termination of study	1286	1299
Unaffected by early termination of study	8137	8158
Died	573 (7.0)	550 (6.7)
Declined end-of-study biopsy	2065 (25.4)	1862 (22.8)
Lost to follow-up	652 (8.0)	604 (7.4)
Prostate-cancer status known*	4847 (59.6)	5142 (63.0)
Included in analyses†	4368	4692
Diagnosis of prostate cancer	803	1147
Biopsy performed for cause or other procedure‡	1639	1934
Positive for cancer	435	571
End-of-study biopsy§	3652	3820
Positive for cancer	368	576
Excluded from analyses¶	479	450
Positive for cancer	75	99

\*  $P < 0.001$  for the difference between groups.

† Because 926 men in the finasteride group and 1067 men in the placebo group had a negative result on a biopsy performed for cause and underwent an end-of-study biopsy, the sum of the subtotals does not equal the total number in the analysis.  $P < 0.001$  for the comparison between groups in the rate of prostate cancer.

‡ Data are the numbers of men in whom a biopsy was performed for cause either during the study or at the end of the study and men who underwent another procedure such as transurethral resection of the prostate during the course of the trial.  $P = 0.05$  for the comparison between groups in the rate of prostate cancer.

§ End-of-study biopsies performed for cause are excluded.  $P < 0.001$  for the comparison between groups in the rate of prostate cancer.

¶ Data are the numbers of men who were excluded because the review of their data is in process (64 men) or because their end-of-study biopsy was performed more than 7 years and 90 days after randomization (865 men).  $P = 0.01$  for the comparison between groups in the rate of prostate cancer.

other procedures such as transurethral resection of the prostate. Figure 1 shows the incidence of prostate cancer in the two treatment groups among all surviving men who underwent randomization, excluding cases diagnosed on end-of-study biopsy. Finasteride was associated with a reduced prevalence of prostate cancer in all subgroups we examined (Table 2).

#### RATES OF RECOMMENDED BIOPSY

Biopsies were recommended during the trial if there was an elevated PSA level, an abnormal digi-

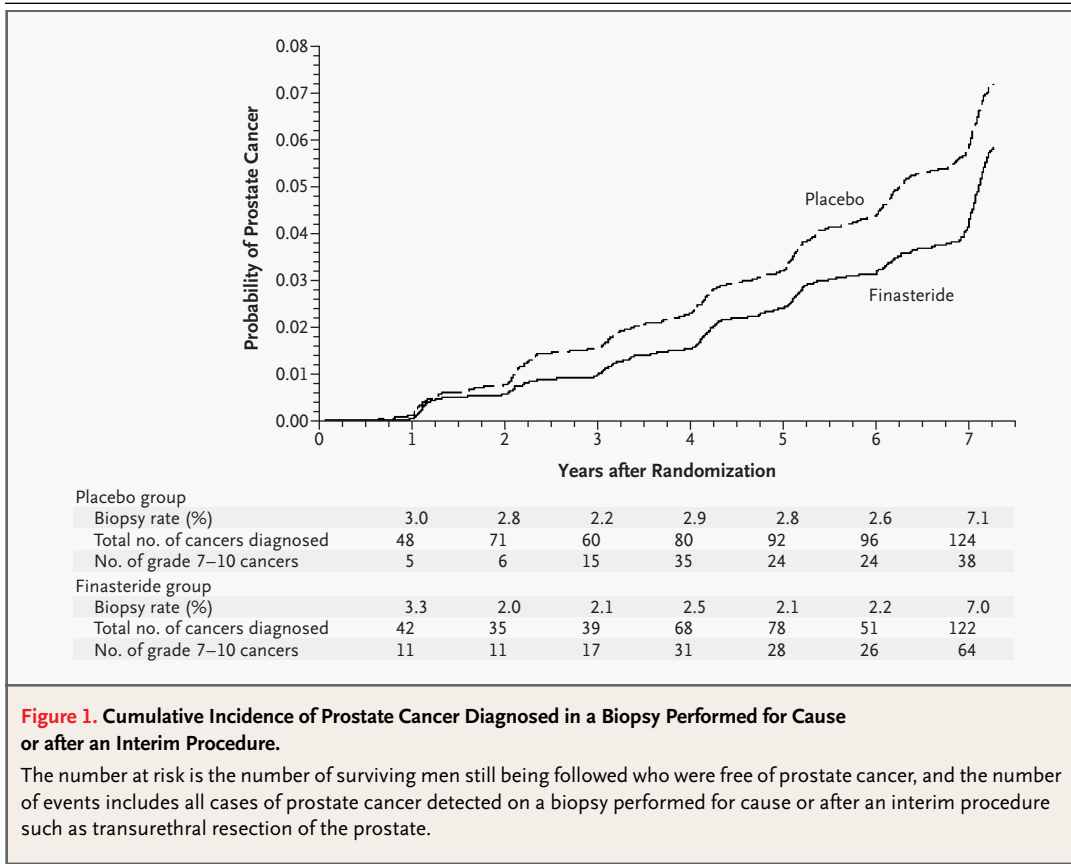
tal rectal examination, or both. Such recommendations for biopsy during the trial were given to 2122 of the 9423 men who were randomly assigned to the finasteride group (22.5 percent) and 2348 of the 9457 eligible men who were randomly assigned to the placebo group (24.8 percent,  $P < 0.001$ ) (Table 3).

Although the rates of the prompts of biopsy among men in whom a biopsy was recommended and among men in whom a biopsy was performed differed according to treatment group, there was no significant difference between the proportions of recommended biopsies that were performed in the two groups either according to the number of recommendations for biopsy ( $P = 0.10$ ) or according to the number of men who had such a recommendation during the course of the trial ( $P = 0.29$ ). In the placebo group but not in the finasteride group, the degree of elevation of the PSA level was related to whether or not a recommended prostate biopsy was performed. The annual rate at which biopsies were performed for cause is shown in Figure 1. Of the 246 cancers found on biopsies performed for cause at seven years, 57 were in men in whom biopsies had previously been recommended but had not been performed. If a PSA-adjustment factor of 2.0 had been used for the finasteride group throughout the study, 222 men in the finasteride group who received a recommendation to undergo a biopsy during the course of the study because of an elevated PSA level would not have had such a recommendation. A total of 69 of these men underwent biopsy at the time of the recommendation, and 17 cases of prostate cancer were detected.

#### RATES OF NONADHERENCE

The rate of nonadherence, estimated as the percentage of days of treatment missed in men who had a diagnosis of prostate cancer or an end-of-study biopsy, was 14.7 percent in the finasteride group and 10.8 percent in the placebo group. The rate of nonadherence in the finasteride group, as indicated by a dihydrotestosterone level of more than 16 ng per milliliter, was 14.5 percent, and the drop-in rate in the placebo group, as indicated by a dihydrotestosterone level of 16 ng per milliliter or lower, was 6.5 percent.

A total of 36.8 percent of men in the finasteride group and 28.9 percent in the placebo group temporarily discontinued treatment at some time during the study for reasons other than death or an interim diagnosis of prostate cancer ( $P < 0.001$  for the comparison between groups). The yearly rate of



**Figure 1. Cumulative Incidence of Prostate Cancer Diagnosed in a Biopsy Performed for Cause or after an Interim Procedure.**

The number at risk is the number of surviving men still being followed who were free of prostate cancer, and the number of events includes all cases of prostate cancer detected on a biopsy performed for cause or after an interim procedure such as transurethral resection of the prostate.

temporary discontinuation of treatment was highest during the men’s first year in the study (10.0 percent in the finasteride group and 6.3 percent in the placebo group) and decreased steadily, so that by year 5, the rate was 3.6 percent in the finasteride group and 3.4 percent in the placebo group. Side effects of finasteride represented the primary reason for the difference in the proportion of men who temporarily discontinued treatment (1722 of 9423 men in the finasteride group [18.3 percent] vs. 931 of 9457 men in the placebo group [9.8 percent]).

**MEDICAL EVENTS AND SIDE EFFECTS**

Medical events and side effects (Table 4) were graded according to the toxicity criteria of the Southwest Oncology Group.<sup>8</sup> These events and side effects were reported by the men during directed interviews over the course of their treatment. Reduced volume of ejaculate, erectile dysfunction, loss of libido, and gynecomastia were more common in the finasteride group than in the placebo group (P<0.001 for all comparisons), whereas urinary urgency, urinary frequency, or both; prostatitis; urinary tract infec-

tion; and urinary retention were more common among men in the placebo group (P<0.001 for all comparisons). There was no significant difference in the number of deaths between the two groups: five men in each group died from prostate cancer.

**BIOPSY RESULTS**

Table 5 shows Gleason scores assigned by the central pathology laboratory for all biopsies. There was a higher proportion of tumors with Gleason scores of 7, 8, 9, or 10 in the finasteride group (280 of 757 graded tumors [37.0 percent], or 6.4 percent of the 4368 men included in the analysis) than in the placebo group (237 of 1068 graded tumors [22.2 percent], or 5.1 percent of the 4692 men included in the analysis; P<0.001 for the comparison between groups in terms of the percentage of graded tumors; relative risk of a high-grade tumor, 1.67 [95 percent confidence interval, 1.44 to 1.93]; P=0.005 for the comparison between groups in terms of the percentage of all men; relative risk, 1.27 [95 percent confidence interval, 1.07 to 1.50]). To understand the risk of high-grade disease from the perspectives

**Table 2. Prevalence of Prostate Cancer during the Seven Years of the Study, Overall and in Subgroups.\***

Variable	Finasteride Group			Placebo Group			Relative Risk of Prostate Cancer
	No. at Randomization	No. Included in Analysis	No. Positive for Prostate Cancer (%)	No. at Randomization	No. Included in Analysis	No. Positive for Prostate Cancer (%)	
All men	9423	4368	803 (18.4)	9457	4692	1147 (24.4)	0.75
Age							
<55 Yr	1	0	0	1	1	0	—
55–59 Yr	2954	1380	205 (14.9)	2954	1492	309 (20.7)	0.72
60–64 Yr	2970	1442	254 (17.6)	2825	1477	357 (24.2)	0.73
≥65 Yr	3498	1546	344 (22.3)	3677	1722	481 (27.9)	0.80
Race or ethnic group							
Non-Hispanic white	8667	4056	739 (18.2)	8713	4387	1067 (24.3)	0.75
Non-Hispanic black	356	152	41 (27.0)	353	146	50 (34.2)	0.79
Hispanic	262	117	19 (16.2)	237	114	23 (20.2)	0.80
Other	138	43	4 (9.3)	154	45	7 (15.6)	0.60
Prostate cancer in a first-degree relative							
Yes	1458	719	176 (24.5)	1455	794	241 (30.4)	0.81
No	7965	3649	627 (17.2)	8002	3898	906 (23.2)	0.74
PSA level at study entry							
0.0–1.0 ng/ml	4493	1975	212 (10.7)	4639	2196	357 (16.3)	0.66
1.1–2.0 ng/ml	3397	1616	344 (21.3)	3311	1647	457 (27.7)	0.77
2.1–3.0 ng/ml	1533	777	247 (31.8)	1506	848	332 (39.2)	0.81
3.1–4.0 ng/ml	0	0	0	1	1	1 (100.0)	

\* Relative risks are for the finasteride group as compared with the placebo group. PSA denotes prostate-specific antigen.

of a man considering taking finasteride and of a man who is found to have prostate cancer, we report these data in two ways. The rate of high-grade disease among men in whom prostate cancer was diagnosed on a biopsy performed for cause was 188 of 393 men in the finasteride group (47.8 percent) and 148 of 504 men in the placebo group (29.4 percent;  $P < 0.001$ ; relative risk, 1.62 [95 percent confidence interval, 1.37 to 1.93]); the rate among all men who underwent biopsy for cause was 188 of 1639 men in the finasteride group (11.5 percent) and 148 of 1934 men in the placebo group (7.7 percent;  $P < 0.001$ ; relative risk, 1.50 [95 percent confidence interval, 1.22 to 1.84]).

Prostate volume was determined at the time of biopsy. The median volume among men in the finasteride group was 25.5 cm<sup>3</sup>, as compared with 33.6 cm<sup>3</sup> among men in the placebo group (a 24.1 percent relative difference). There was no significant difference between the two groups in the number of biopsy specimens obtained: sextant biopsy was performed in 81.5 percent of men in the finasteride group and 81.0 percent of men in the placebo group. Most prostate cancers detected during the trial were clinically localized. A total of 97.7 percent of cancers in men in the finasteride group were classified as T1 or T2, as were 98.4 percent of those in men in the placebo group. Of the tumors found

**Table 3. Reasons for Recommendations for Biopsy and Characteristics of Men Who Underwent the Recommended Biopsy and Men Who Did Not.\***

Variable	Finasteride Group		Placebo Group		P Value
	Biopsy Recommended	Biopsy Performed	Biopsy Recommended	Biopsy Performed	
All men with biopsy recommended — no. (%)	2122	1476 (69.6)	2348	1667 (71.0)	0.29
All recommendations for biopsy — no. (%)†	3309	1662 (50.2)	3544	1850 (52.2)	0.10
Prompt for biopsy recommendation — no. (%)					
Abnormal digital rectal examination	1736	879 (50.6)	1977	946 (47.9)	0.11
Elevated PSA level	1464	708 (48.4)	1454	821 (56.5)	<0.001
Abnormal digital rectal examination and elevated PSA level	109	75 (68.8)	113	83 (73.5)	0.43
PSA level at the time of biopsy recommendation — ng/ml					
Geometric mean‡	2.56	2.59	2.45	2.70	
Interquartile range	1.05–5.10	1.00–5.20	1.20–4.70	1.40–4.90	

\* P values are for the comparison between groups in the percentages of recommended biopsies that were performed. PSA denotes prostate-specific antigen.

† Participants may have had more than one biopsy recommendation.

‡ The PSA values were log-adjusted because of non-normal distribution. Within the finasteride group, P=0.53 for the comparison of log-adjusted PSA values between men in whom the biopsy was performed and men in whom it was not performed; within the placebo group, P<0.001 for the corresponding comparison.

on end-of-study biopsies that were not performed for cause, 21.1 percent were in men who had a concurrent PSA level between 2.6 and 3.9 ng per milliliter. Of the remaining tumors found on end-of-study biopsies that were not performed for cause in men with a concurrent PSA level of 2.5 ng per milliliter or less, 15.4 percent had a Gleason grade of 7, 8, 9, or 10.

#### DISCUSSION

The lifetime risk of prostate cancer in the United States is 16.7 percent, and 28,900 men are expected to die of this disease in 2003.<sup>9</sup> This high rate and the unpredictable biology of prostate cancer make prevention of the disease an appealing strategy. Finasteride is an attractive chemopreventive agent, because it inhibits the conversion of testosterone to the more potent androgen dihydrotestosterone within the prostate and has low toxicity. At the inception of our study, finasteride became available for the treatment of benign prostatic hyperplasia (as Proscar [Merck]), and since then, it has been approved for the treatment of male pattern baldness

(Propecia [Merck]). Although it is used by millions of men for these indications, little is known about its long-term effects on the prostate.

We faced a challenge in designing our study, because of the effect of finasteride on the PSA level, measurement of which is the primary method of screening for prostate cancer. For this reason, we planned to perform a prostate biopsy at the end of the study.<sup>6</sup> We recognized the possibility that there would be an increased number of positive biopsies among men who received finasteride, because a proportionately greater volume of gland would be sampled from smaller glands.<sup>10,11</sup> This effect could introduce a bias against any evidence of benefit from finasteride.

Every attempt was made to ensure that an equal proportion of men in each group was evaluated for prostate cancer; this was the logic behind the initial doubling of PSA values for men in the finasteride group and the later increase by a factor of 2.3 at the beginning of each participant's fourth year in the study.<sup>5</sup> An additional difference in the rate of evaluation for prostate cancer between the two groups was a different number of abnormal digital rectal

**Table 4. Medical Events and Side Effects.\***

Variable	Finasteride Group (N=9423)	Placebo Group (N=9457)
	no. (%)	
Effects on sexual functioning or endocrine effects		
Reduced volume of ejaculate	5690 (60.4)	4473 (47.3)
Erectile dysfunction	6349 (67.4)	5816 (61.5)
Loss of libido	6163 (65.4)	5635 (59.6)
Gynecomastia	426 (4.5)	261 (2.8)
Breast cancer	1 (<0.1)	1 (<0.1)
Genitourinary effects		
Benign prostatic hyperplasia	488 (5.2)	823 (8.7)
Increased urinary urgency or frequency	1214 (12.9)	1474 (15.6)
Urinary incontinence	183 (1.9)	208 (2.2)
Urinary retention	398 (4.2)	597 (6.3)
Transurethral resection of the prostate performed	96 (1.0)	180 (1.9)
Prostatitis	418 (4.4)	576 (6.1)
Urinary tract infection	90 (1.0)	126 (1.3)

\*  $P < 0.001$ , without adjustment for multiple comparisons, for all comparisons between groups except those for breast cancer and urinary incontinence.

examinations (1845 in the finasteride group vs. 2090 in the placebo group) (Table 3) and transurethral resections of the prostate. In addition, more men in the finasteride group than in the placebo group were categorized as having refused the end-of-study biopsy (25.4 percent vs. 22.8 percent,  $P < 0.001$ ), most likely because of the higher rate of temporary discontinuation of treatment in a group of men less committed to the study requirements. Although the difference between the groups in the overall rate of ascertainment of prostate-cancer status of 3.4 percentage points (59.6 in the finasteride group vs. 63.0 percent in the placebo group) was statistically significant, we believe that this difference by itself is unlikely to have contributed substantially to the difference in the rate of detection of prostate cancer.

Seven years of finasteride treatment resulted in a 24.8 percent reduction in the prevalence of prostate cancer during that period. There was a reduction in relative risk among men who underwent a prostate biopsy before seven years and among men

who underwent biopsy at the end of the study. The risk reductions were similar in subgroups defined according to age, race or ethnic group, family history of prostate cancer, and stratum of PSA level at randomization.

Decreases in sexual potency, libido, and ejaculate volume were frequently reported over the course of the trial, as would be expected in men in this age group who were followed for seven years with repeated queries regarding these symptoms.<sup>12</sup> These side effects were more common in the finasteride group. Urinary symptoms or events related to benign prostatic hyperplasia were less common among men receiving finasteride — a finding that is consistent with a previous report.<sup>13</sup>

High-grade disease was noted in 6.4 percent of the men in the finasteride group, as compared with 5.1 percent of those in the placebo group. A difference in the rate of high-grade disease was seen within the first year of the study. One possible explanation for this difference is a grading bias: histologic changes that mimic those of high-grade disease are caused by androgen-deprivation therapy.<sup>14-18</sup> There are, however, differences of opinion as to whether this effect occurs with finasteride. It is possible that finasteride induces high-grade tumors by reducing the level of intracellular dihydrotestosterone within the prostate. There is evidence that the prostate tumors that develop in men with low testosterone levels have higher Gleason grades and worse outcomes than the prostate cancers that develop in men with normal testosterone levels.<sup>19-21</sup> It is also possible that finasteride selects for high-grade tumors by selectively inhibiting low-grade tumors. Long-term follow-up in these men and further laboratory research will be required to determine the reason for the association between finasteride and high-grade prostate cancer.

The tumors that were detected on biopsies performed for cause were clinically similar to those that are detected in clinical practice by screening of the PSA level and digital rectal examination. The clinical significance of cancers found in the end-of-study biopsies (those not performed for cause) is unknown. Of the men with such diagnoses, 21.1 percent had PSA levels between 2.6 and 3.9 ng per milliliter. Clinically significant tumors are as common among men with PSA levels in this range as they are among men with PSA levels between 4.0 and 10.0 ng per milliliter.<sup>22</sup> Of the remaining tumors found in men with PSA levels of 2.5 ng per milliliter or less, 15.4 percent had high-grade cancer.

**Table 5. Gleason Scores for Prostate Cancers Detected.**

Gleason Score	All Cancers		Cancers Diagnosed in Biopsies Performed for Cause*		Cancers Diagnosed in End-of-Study Biopsies†	
	Finasteride Group (N=757)	Placebo Group (N=1068)	Finasteride Group (N=393)	Placebo Group (N=504)	Finasteride Group (N=364)	Placebo Group (N=564)
	<i>number (percentage of centrally graded tumors)</i>					
2	4 (0.5)	9 (0.8)	3 (0.8)	8 (1.6)	1 (0.3)	1 (0.2)
3	1 (0.1)	8 (0.7)	0	7 (1.4)	1 (0.3)	1 (0.2)
4	15 (2.0)	38 (3.6)	7 (1.8)	24 (4.8)	8 (2.2)	14 (2.5)
5	69 (9.1)	118 (11.0)	38 (9.7)	58 (11.5)	31 (8.5)	60 (10.6)
6	388 (51.3)	658 (61.6)	157 (39.9)	259 (51.4)	231 (63.5)	399 (70.7)
7	190 (25.1)	184 (17.2)	118 (30.0)	103 (20.4)	72 (19.8)	81 (14.4)
8	45 (5.9)	25 (2.3)	32 (8.1)	20 (4.0)	13 (3.6)	5 (0.9)
9	36 (4.8)	24 (2.2)	29 (7.4)	21 (4.2)	7 (1.9)	3 (0.5)
10	9 (1.2)	4 (0.4)	9 (2.3)	4 (0.8)	0	0
7, 8, 9, or 10	280 (37.0)	237 (22.2)	188 (47.8)	148 (29.4)	92 (25.3)	89 (15.8)
Not graded‡	46	79	42	67	4	12
All cancers	803	1147	435	571	368	576
All men evaluated	4368	4692	1639	1934	3652	3820

\* Data include cancers diagnosed in biopsies performed for cause either during the study or at the end of the study and those diagnosed after interim procedures.

† Data exclude cancers diagnosed in biopsies performed for cause at the end of the study.

‡ Data are for cancers that were not graded either because they were too small to be graded (in 20 cases), because they were not reviewed centrally (in 103 cases), or for other reasons (in 2 cases).

The overall cancer detection rate of 24.4 percent in the placebo group is a matter of concern, because the eligibility criteria for enrollment in the study selected for low-risk men with an expected lifetime incidence of prostate cancer of 16.7 percent and a rate of death from prostate cancer of 3 to 4 percent. The rate of 24.4 percent suggests the possibility of overdiagnosis of disease.

The study raises two interrelated questions: did finasteride prevent or treat prostate cancer,<sup>23</sup> and did finasteride prevent or delay<sup>24,25</sup> the appearance of prostate cancer? These issues are important for the field of cancer prevention. The early difference in the incidence of prostate cancer between the two groups suggests that finasteride may have treated subclinical, microscopical cancer early in the

study, and the fact that the difference continued to increase suggests that it prevented or delayed the onset of cancer. In either case, the effect is beneficial.<sup>23-25</sup>

Physicians can use these results to counsel men regarding the use of finasteride. It is important to stress that finasteride reduced the risk of prostate cancer in a clinical trial marked by frequent monitoring for disease and was associated with an increased risk of diagnosis of high-grade prostate cancer. For a man considering using this medication, the greater absolute reduction in the risk of prostate cancer must be weighed against the smaller absolute increase in the risk of high-grade disease.

There is also the matter of side effects: the incidence of adverse effects on sexual function was high-

er with finasteride, but the finasteride group had a lower incidence of urinary symptoms and complications than the placebo group. Using published information on the outcomes of prostate-cancer treatment, men can weigh these trade-offs in the context of their own priorities regarding the avoidance of prostate cancer as well as their urinary and sexual function to reach a personal decision regarding finasteride use.<sup>26-28</sup> As more is learned from the molecular biology of prostate cancer about the risk of aggressive disease, data from this and other stud-

ies will help to refine the appropriate use of interventions such as finasteride.

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This article is dedicated to the memory of Gary Miller, M.D., Ph.D.

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