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ARTICLE

Finasteride and High-Grade Prostate Cancer in the Prostate Cancer Prevention Trial

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Background The Prostate Cancer Prevention Trial (PCPT) reported a decreased incidence of prostate cancer overall but an increase in the incidence of high-grade prostate cancer with finasteride compared with placebo. We assessed whether the increased high-grade prostate cancer associated with finasteride in the PCPT was due to finasteride's potential effects on tumor morphology or prostate size.

Methods Prostate biopsies with Gleason score 8–10 (n = 90, finasteride; n = 52, placebo) were examined histologically for hormonal effects, and those with Gleason score 7–10 (n = 282, finasteride; n = 244, placebo) were examined for pathologic surrogates of disease extent. Prostate volumes were measured at biopsy. Samples from radical prostatectomies (n = 222, finasteride; n = 306, placebo) were examined for tumor grade and extent, and, where possible, grades at biopsy and prostatectomy were compared between the groups. Logistic regression was used to analyze differences between treatment groups with respect to pathologic criteria. All statistical tests were two-sided.

Results Degenerative hormonal changes in high-grade biopsies were equivalent between the finasteride and placebo groups, but prostate volumes were lower in the finasteride group (median = 25.1 versus 34.4 cm^3, $P<.001$). Pathologic surrogates for tumor extent were lower with finasteride than with placebo, including mean percentage of positive cores (34% versus 38%, $P = .016$), mean tumor linear extent (greatest [4.4 versus 4.8 mm, $P = .19$] and aggregate [7.6 versus 9.2 mm, $P = .13$]), bilaterality (22.8% versus 30.6%, $P = .046$), and perineural invasion (14.2% versus 20.3%, $P = .07$). Among patients who had prostatectomy, the finasteride-associated increase in high-grade disease (Gleason score ≥ 7) at biopsy (42.7% finasteride versus 25.4% placebo, $P<.001$) was diminished at prostatectomy (46.4% finasteride versus 38.6% placebo, $P = .10$). Biopsy identified a greater proportion of patients with high-grade disease present at prostatectomy in the finasteride group than in the placebo group (69.7% versus 50.5%, $P = .01$). The rate of upgrading (from low-grade cancer at biopsy to high-grade cancer at prostatectomy) and pathologic stage at prostatectomy were similar in both groups.

Conclusions Effects of finasteride on prostate volume and selective inhibition of low-grade cancer, rather than effects on tumor morphology, may have contributed to the increase in high-grade cancers with finasteride in the PCPT. Although induction of high-grade cancer cannot be excluded, the results suggest that high-grade cancer was detected earlier and was less extensive in the finasteride group than in the placebo group.

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The Prostate Cancer Prevention Trial (PCPT) compared the ability of the 5α-reductase inhibitor finasteride (5 mg/day) versus placebo to reduce the risk of prostate cancer. Prostate cancers were detected during the study by "for-cause" biopsy following an abnormal digital rectal examination (DRE) and/or elevated serum prostate-specific antigen (PSA) level or in end-of-study biopsies that were performed regardless of DRE/PSA status.

The PCPT found a 24.8% reduction in the 7-year period prevalence of prostate cancer, i.e., the cumulative number of

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CONTEXT AND CAVEATS

Prior knowledge

Results from the Prostate Cancer Prevention Trial (PCPT) indicated a higher incidence of high-grade prostate cancer among men who were treated with finasteride than men who were treated with placebo.

Study design

Disease extent in prostate biopsies with high-grade tumors (Gleason score 7–10), prostate gland volume, and tumor grade and extent in radical prostatectomy samples were compared among men who were treated with finasteride and men treated with placebo in the PCPT.

Contributions

Men who were treated with finasteride had reduced tumor extent in prostate biopsies and lower prostate gland volumes than men who were treated with placebo. The increase in high-grade disease observed at initial diagnostic needle biopsy in the finasteride group compared with the placebo group was less apparent at prostatectomy. In the finasteride group, needle biopsy identified a larger proportion of the men found to have high-grade disease at prostatectomy. Stage at prostactectomy and the proportion of men with prostate cancer that was upgraded from low grade to high grade at prostatectomy were similar in the two groups.

Implications

The increase in high-grade prostate cancer incidence with finasteride observed in the PCPT may have been due in part to effects of finasteride on prostate gland volume and reduced low-grade cancer rather than to effects on tumor morphology or biology.

Limitations

Not all men who had biopsies had prostatectomy, and unknown differences among the men who did and did not might have affected the findings in the two groups. This was a multicenter study, and different centers used different methods to prepare prostatectomy samples for analysis, which may have led to variations in the detection of high-grade disease. In addition, long-term outcomes, such as death from prostate cancer or overall survival, were not followed in this study.

prostate cancers identified during the 7-year period of the trial, including those in the end-of-study biopsies, in the finasteride group (1). However, the proportion and number of high-grade tumors (defined as Gleason score 7–10) were higher in the finasteride group than in the placebo group: 280 of 757 (37.0%) of the graded tumors (and 6.4% of evaluated men) in the finasteride group versus 237 of 1068 (22.2%) of the graded tumors (and 5.1% of evaluated men) in the placebo group. This finding raised concerns over the safety of finasteride for prostate cancer prevention (2,3). It has been proposed that finasteride increases the risk of high-grade cancer through changes in intraprostatic androgen and/or estrogen signaling (4–7). The increased risk of high-grade disease with finasteride in the PCPT, however, was noted in the first year, and the relative risk (RR) did not increase over time, raising the suspicion that the increase may have been due to causes other than induced aggressive disease (8,9).

Finasteride alters the levels of intraprostatic androgens, which may have morphologic effects on prostatic carcinomas and cause lower grade tumors to appear higher grade (10–13). Finasteride reduced prostate volume by an average of 24% in the PCPT ($P<.001$) and has recently been found to increase the sensitivity of both DRE and PSA for cancer detection, which jointly could have improved the detection of high-grade tumors in the treatment arm (14–17).

This study addresses these potential volume and pathologic biases by using a detailed pathologic analysis of biopsies with high-grade cancer and prostatectomies from the PCPT. Specifically, we report on the results from a panel of pathology experts who blindly examined high-grade biopsies to evaluate whether there was evidence of a hormonal artifact in the finasteride group compared with placebo. We compared pathologic stage and margin status in prostatectomies and measures of disease extent in high-grade biopsies between treatment groups to see whether there was evidence that high-grade cancers from the finasteride group had indications of greater disease extent. In the subset of men for whom we had both biopsy and prostatectomy specimens, we compared Gleason grading patterns to determine whether needle biopsy of the smaller volume prostates in the finasteride group led to improved detection of high-grade cancer foci compared with the placebo group, using grade at prostatectomy as the gold standard for the presence of high-grade disease.

Subjects and Methods

Cancer Diagnosis in the Prostate Cancer Prevention Trial

A total of 18 882 men were randomly assigned to either finasteride (5 mg/day orally, n = 9423) or placebo (n = 9459). All patients provided written informed consent, and the study was approved by each study site's Internal Review Board. Participants had annual DRE and PSA measurements, and prostate biopsy was recommended if either test was abnormal. Because finasteride lowers serum PSA, annual PSA values in the finasteride group were adjusted upward, by a factor of 2.0 initially that then increased to 2.3 after year 4, to keep pace with biopsies in the placebo group (1). To minimize bias from this PSA adjustment, the protocol specified an end-of-study biopsy at the end of 7 years, with a minimum of six cores, for all subjects without a prior diagnosis of prostate cancer. Prostate volume at biopsy was measured by transrectal ultrasound. Treatment for prostate cancer diagnosed in the PCPT was not specified, and information about treatment received was not collected systematically.

A histologic diagnosis of prostate cancer on needle biopsy was established by the pathologist (G. J. Miller, MD, PhD, until May 2001, M. S. Lucia thereafter) at the PCPT Core Pathology Laboratory (CPL) and by the pathologist at the participant's study site. Disagreements between these two pathologists were resolved by a consensus diagnosis involving an arbiter pathologist. Tumor grading was provided by the CPL pathologist (M. S. Lucia), who was blinded to the participant's study group. The CPL pathologist reviewed 94.3% of all PCPT cancer biopsies. The final biopsy Gleason score included the biopsy core with the highest grade tumor (18,19).

Evaluation of High-Grade Cancers for Evidence of Hormonal Artifact

An independent panel of genitourinary pathologists (J. I. Epstein, V. E. Reuter, and F. Civantos) conducted blinded reviews to evaluate a possible grading bias in the PCPT due to the hormonal effects of finasteride. Because the major difference in high-grade cancers between the two study groups was noted among patients with tumors with Gleason score 8–10 (1), the panel first reviewed general degenerative changes in all available biopsy cores from men with Gleason score 8–10 prostate cancer. The panel then, by consensus, developed a set of pathologic criteria for potentially discriminating the degenerative changes caused by finasteride from the histologic appearance of tumors in placebo-treated subjects. A training set of 29 cancers with Gleason score 8–10 from the placebo (n = 10) and finasteride (n = 19) groups were examined in an unblinded fashion to identify individual features that suggested a degenerative effect of finasteride on the cancer that could potentially interfere with proper grading. The sample size was chosen because it was felt that it would provide a diverse enough sample to characterize any patterns of change without unblinding too many samples. Based on this preliminary review and histologic changes known to occur with hormone ablation (10,11), nine potentially discriminating criteria were selected: nuclear size (large = larger than normal epithelial nucleus, small = equal or smaller than normal epithelial nucleus), nuclear smudge (loss of chromatinic detail), nucleolar prominence, cytoplasmic vacuolization, stromal fibrosis, intratumoral inflammation, empty clefts, apoptosis, and mitotic figures. The panel then conducted a blinded review of biopsy cores from the remaining tumors with Gleason score 8–10 (n = 90, finasteride; n = 52, placebo) and quantified the number (per ×400 field) of apoptotic bodies and mitoses and the extent (percent area) of tumor (0 = 0%, 1 = ≤5%, 2 = 6%–25%, 3 = 26%–50%, 4 = 51%–75%, 5 = >75%) that showed the other degenerative features.

Pathologic Features at Prostatectomy and Grading Comparison Between Biopsy and Prostatectomy

Pathologic materials were requested for all patients who were known to have undergone radical prostatectomy, regardless of grade, and every prostatectomy specimen received by the CPL (n = 528; 222 finasteride, 306 placebo) was analyzed by one pathologist (M. S. Lucia), who was blinded to treatment assignment. All prostatectomy specimens were processed in accordance with published guidelines (20). Tumor Gleason score (18) in the prostatectomy specimens was based on the predominant and secondary tumor pattern. Tumors from men treated with hormonal ablation therapy before prostatectomy (n = 28) were not graded because of the known effects of the therapy on grading (10,11,13). Tumors were staged using 1997 American Joint Committee on Cancer guidelines (21) and were considered margin positive if tumor was present at the inked surface of the specimen. Biopsy and prostatectomy specimens were available for comparison from 206 men in the finasteride group and 283 men in the placebo group.

Biopsy Analysis of Disease Extent Parameters

Complete biopsy materials were available for 282 of the 288 men in the finasteride group with Gleason score 7 or greater and 244 of the 252 men in the placebo group with Gleason score 7 or greater. The CPL pathologist recorded features associated with tumor extent, including total number of biopsy cores, number and percentage of cores positive for cancer, greatest linear extent of cancer (mm) for each core (measured by an optical reticule), aggregate linear extent (mm) of cancer within all cores, bilateral involvement (if known), and perineural invasion (19,22–25).

Statistical Methods

Comparisons between the finasteride and placebo groups used the following tests: the chi-square and Fisher exact tests (as appropriate) for comparing the pathologic features of prostatic carcinomas and patient characteristics at prostatectomy and the Mann–Whitney test and chi-square tests for comparing the biopsy characteristics of Gleason score 7–10 tumors. For the hormonal artifact analysis, results were analyzed to determine whether the criteria could identify a "finasteride-treated" tumor within this group of tumors. Logistic regression models were formed to evaluate the discriminative capability of the criteria with the concordance index, and the estimates were corrected using bootstrapping methods to reduce the optimistic bias in the concordance index. The logistic regression models considered each criterion as either a binary variable split at the median value for that criterion or as a continous variable using restricted cubic splines.

The extended Mantel–Haenszel correlation statistic was used to evaluate the pattern of up- and downgrading of Gleason scores from biopsy to prostatectomy. A general chi-square test was used to test for differences in sensitivity of the needle biopsy between treatment groups. In the dichotomous analysis, high-grade tumors were defined as those with Gleason score 7 or greater and low-grade tumors were defined as those with Gleason score 6 or less.

All statistical tests were two-sided. *P* values less than .05 were considered statistically significant. Statistical analyses were done using SAS, version 9.0 (SAS Institute, Inc, Cary, NC) and S-Plus 2000 (Insightful Corp, Seatlle, WA).

Results

A total of 1901 participants (n = 778 finasteride; n = 1123 placebo) were diagnosed with prostate cancer on biopsy in the PCPT as of June 23, 2003, when the treatment results were made public (Table 1). This includes 76 tumors (n = 21 finasteride; n = 55 placebo) that were graded after the dataset was frozen for the original report (1) and reflects diagnoses of prostate cancer within 7 years (+90 days) of the date that the participant was randomly assigned to treatment. In the finasteride group, 288 cancers (37.4% of graded tumors) were Gleason score 7 or greater, whereas there were 252 such cancers (22.7% of graded tumors) in the placebo group. Table 1 also indicates the numbers of participants (by biopsy Gleason score) who had prostatectomy samples submitted to the CPL. Among men with highest grade (Gleason 8–10) disease at biopsy, those in the finasteride group were more likely to undergo prostatectomy (38 [41.8%] finasteride versus 16 [27.1%] placebo), although this difference did not achieve statistical significance (*P* = .07).

Biopsies of tumors with Gleason score 8–10 (n = 90, finasteride; n = 52, placebo) were examined for degenerative changes by the pathology review panel. Specimens from eight other patients

Table 1. Gleason scores of Prostate Cancer Prevention Trial biopsies through June 23, 2003

	Finasteride			Placebo		
Gleason score	No. of cancers	Percentage of cancers graded	No. having prostatectomy (%)	No. of cancers	Percentage of cancers graded	No. having prostatectomy (%)
2–5	82	10.7	22 (26.8)	160	14.4	50 (31.3)
6	399	51.9	96 (24.1)	699	62.9	161 (23.0)
7	197	25.6	50 (25.4)	193	17.4	56 (29.0)
8–10	91	11.8	38 (41.8)	59	5.3	16 (27.1)
NG*	9	–	3 (33.3)	12	–	3 (25.0)
Total	778	100	209 (26.9)†	1123	100	286 (25.5)†

* NG = not graded due to inadequate material from study sites.

† These numbers reflect prostatectomy patients for whom pathologic material and biopsy grades were available.

(one finasteride and seven placebo) could not be obtained from their study sites. Degenerative changes that were considered sufficiently severe to have potentially impacted accurate grading were found in 30 of 90 (33.3%) patients in the finasteride group and in 17 of 52 (32.7%) patients in the placebo group, which prompted examination of the nine specific morphologic features that were potentially capable of discriminating between finasteride-treated and untreated (placebo) tumors (Table 2). In logistic regression models, none of the nine criteria could discriminate between treatment groups when considered as either a binary or a continuous variable. The ability of the overall model to discriminate between treatment groups when each criterion was included as a covariate had a bootstrap-corrected concordance index of 0.51, i.e., no better than that expected by chance. Thus, degenerative changes were present in equivalent percentages of tumors of both the finasteride and placebo arms, and no distinctive histopathologic features distinguished the tumors of either group.

The CPL examined 528 prostatectomy specimens of PCPT participants (n = 222 finasteride; n = 306 placebo) to determine tumor characteristics at prostatectomy for the two groups. As a group, participants with a known prostatectomy were younger, were more likely to be white, were more likely to have been diagnosed on a for-cause biopsy, and had higher PSA values than those without prostatectomy (Table 3). Despite the greater proportion of participants with biopsy Gleason scores of 7 or greater in the finasteride group relative to placebo, in the prostatectomy samples no statistically significant differences in pathologic stage, nodal involvement, or margin status between the two groups were observed, either overall (Table 4) or in prostatectomies following a for-cause diagnosis versus an end-of-study diagnosis (data not shown).

Although prostatectomy specimens were processed in accordance with published guidelines at all sites that submitted prostatectomies (20), study sites varied in the quantity of prostatic tissue sampled, ranging from complete to representative sampling of quadrants. For this reason, accurate tumor volumes across study sites could not be obtained.

Tumor grade at biopsy and prostatectomy were compared for the 206 finasteride and 283 placebo-arm tumors in which cancer grades on both specimens were available (Table 5). Because participants were off study treatment by the time of prostatectomy, degenerative changes were not quantified as was done for the Gleason 8–10 biopsies (Table 2). Among patients who had both biopsy and prostatectomy (excluding those participants who received hormone therapy before prostatectomy), the difference in the percentage of high-grade (Gleason 7–10) cancers between the finasteride and placebo groups at biopsy (88 of 206 [42.7%] versus 72 of 283 [25.4%], respectively, RR = 1.68, 95% confidence interval [CI] = 1.30 to 2.17; $P<.001$) diminished at prostatectomy (89 of

Table 2. Logistic regression models to distinguish finasteride (n = 71) versus placebo (n = 42) Gleason 8–10 tumors on biopsy using degenerative criteria in the Prostate Cancer Prevention Trial

Criterion*	Finasteride mean (median) [range]	Placebo mean (median) [range]	*P*†	*P*‡
Large smudged nuclei	1.3 (1.0) [0–5]	1.4 (1.0) [0–5]	.93	.93
Small smudged nuclei	2.6 (2.0) [0–5]	2.5 (2.0) [0–5]	.46	.43
Nucleolar prominence	1.6 (1.0) [0–5]	1.6 (1.0) [0–5]	.56	.51
Apoptotic bodies	0.6 (0.3) [0–4.8]	0.7 (0.2) [0–5.6]	.54	.70
Mitotic figures	0.3 (0.1) [0–3.8]	0.4 (0.1) [0–4.1]	.45	.56
Vacuoles	1.3 (1.0) [0–5]	1.7 (1.0) [0–5]	.52	.31
Stromal fibrosis	0.8 (0.0) [0–5]	0.9 (0.5) [0–5]	.44	.26
Intratumoral inflammation	0.5 (0.0) [0–5]	0.5 (0.0) [0–5]	.27	.17
Empty clefts	0.03 (0.0) [0–1]	0.0 (0.0) [0–0]	.17	.81

* Each criterion scored on a scale of 1–5 (0 = 0%, 1 = <5%, 2 = 6%–25%, 3 = 26%–50%, 4 = 51%–75%, 5 = >75%) for each tumor, except for apoptotic bodies and mitotic figures, which are expressed as number per high-power field (10 fields counted).

† *P* values (two-sided) for univariate analyses were calculated using using a Wald test.

‡ *P* values (two-sided) for multivariable analyses were calculated using a Wald test.

Table 3. Characteristics of subjects in the Prostate Cancer Prevention Trial with cancer who did and did not undergo prostatectomy*

Characteristic	No Prostatectomy		Prostatectomy			
	Finasteride (n = 600) N (%)	Placebo (n = 887) N (%)	Finasteride (n = 222) N (%)	Placebo (n = 306) N (%)	*P*‡	*P*†
Age at diagnosis, y					.45§	<.001§
55–65	127 (21.2)	190 (21.4)	103 (46.4)	147 (48.0)		
66–70	161 (26.8)	245 (27.6)	81 (36.5)	108 (35.3)		
71–75	177 (29.5)	272 (30.7)	33 (14.9)	46 (15.0)		
>75	135 (22.5)	180 (20.3)	5 (2.2)	5 (1.6)		
Mean (SD)	70.9 (5.8)	70.7 (5.6)	66.3 (4.2)	66.1 (4.2)		
Race					.12‖	.06‖
White	555 (92.5)	818 (92.2)	202 (91.0)	291 (95.1)		
African American	32 (5.3)	48 (5.4)	11 (5.0)	6 (2.0)		
Other	13 (2.2)	21 (2.4)	9 (4.1)	9 (2.9)		
Biopsy prompt					.14‖	<.001‖
Cause	293 (48.8)	391 (44.1)	149 (67.1)	186 (60.8)		
EOS	307 (51.2)	496 (55.9)	73 (32.9)	120 (39.2)		
PSA, ng/mL¶					.001§	<.001§
<1.0	107 (17.8)	119 (13.4)	24 (10.8)	25 (8.2)		
1.0–2.5	193 (32.2)	315 (35.5)	48 (21.6)	111 (36.3)		
2.6–4.0	84 (14.0)	149 (16.8)	37 (16.7)	46 (15.0)		
4.1–10.0	155 (25.8)	195 (22.0)	72 (32.4)	86 (28.1)		
>10.0	17 (2.8)	11 (1.2)	17 (7.7)	2 (0.7)		
Missing	44 (7.3)	98 (11.0)	24 (10.8)	36 (11.8)		
Median	2.3	2.3	3.5	2.5		

* Prostatectomy patients include only the men for whom we collected samples. SD = standard deviation; EOS = end of study; PSA = prostate-specific antigen.

† No prostatectomy versus prostatectomy (not adjusted for treatment).

‡ Among those with a prostatectomy, finasteride versus placebo.

§ *P* values (two-sided) were calculated by using a Mann–Whitney nonparametric test.

‖ *P* values (two-sided) were calculated by using the chi-square test.

¶ Last-adjusted PSA test before date of prostate cancer diagnosis.

192 [46.4%] versus 105 of 272 [38.6%], RR = 1.20, 95% CI = 0.97 to 1.49; *P* = .10). Over the full spectrum of biopsy Gleason scores, tumors were more commonly downgraded at prostatectomy in the finasteride than in the placebo group (38/192 [19.8%] finasteride, 34/272 [12.5%] placebo) and were more commonly upgraded in the placebo than in the finasteride group (47/192 [24.5%] finasteride, 83/272 [30.5%] placebo). The difference in upgrading/downgrading distribution between the two treatments was statistically significant (*P* = .03). However, these patterns diminished when dichotomous changes from 6 or less to 7 or greater Gleason scores were compared: change from low (≤6) to high (≥7) grade was 27/113 (23.9%) with finasteride versus 52/202 (25.7%) with placebo, and change from high to low grade was 17/79 (21.5%) with finasteride versus 17/70 (24.3%) with placebo (Table 5, test of change in upgrading/downgrading distribution between groups, *P* = .09).

If one assumes that the Gleason score at prostatectomy is the true disease grade, i.e., the "gold standard," then the sensitivity of biopsy to detect high-grade disease can be compared for each treatment group. Among patients who underwent biopsy and prostatectomy, the Gleason score at biopsy identified high-grade (Gleason score ≥7) disease that was present at prostatectomy more often in the finasteride group (62 of 89 [69.7%]) than in the placebo group (53 of 105 [50.5%]) (*P* = .01). However, among men who had a Gleason score of 6 or less at biopsy, the rate of upgrading to Gleason score 7 or greater was similar between the treatment groups (27 of 113 [23.9%] for finasteride, 52 of 202 [25.7%] for placebo; *P* = .72).

We hypothesized that if finasteride does induce high-grade disease, pathologic surrogates may indicate greater disease extent for those cancers in the treatment group than in the placebo group. Because prostatectomy data were available for only a subset of the tumors detected in the PCPT, pathologic features of tumor extent were compiled from all available biopsies of men diagnosed with Gleason score 7–10 tumors (Table 6). Complete biopsy materials were available for 282 of 288 and 244 of 252 Gleason score 7–10 tumors in the finasteride and the placebo groups, respectively. Pathologic surrogates of disease extent were lower on average in the finasteride than in the placebo group. These included percentage of cores positive for cancer (34% finasteride versus 38% placebo, difference = 4.7%, 95% CI = 1.3% to 8.1%; *P* = .016), linear extent of tumor (greatest [4.4 mm finasteride versus 4.8 mm placebo, difference = 0.4 mm, 95% CI = −0.21 to 0.93 mm; *P* = .19], aggregate [7.6 mm finasteride, 9.2 mm placebo, difference = 1.6 mm, 95% CI = −0.04 to 3.2 mm; *P* = .13]), bilateral involvement (22.8% finasteride, 30.6% placebo, difference = 7.8%, 95% CI = 0.1% to 15.4%; *P* = .046), and perineural invasion (14.2% finasteride, 20.3% placebo, difference = 6.1%, 95% CI = −0.5 to 12.7%; *P* = .07). Median prostate gland volume in men with a biopsy Gleason score 7–10 tumor was 25.1 cm^3 (finasteride) versus 34.4 cm^3 (placebo) (*P*<.001). The finasteride-associated reduction in prostate gland volume was first detected at year 1

Table 4. Pathologic features of prostatic carcinomas at prostatectomy in the Prostate Cancer Prevention Trial*

Feature	Finasteride (n = 222)			Placebo (n = 306)			*P*†	
	Total N (%)	GS 2–6 N (%)	GS 7–10 N (%)	Total N (%)	GS 2–6 N (%)	GS 7–10 N (%)	Comparison of totals	Comparison of GS 7–10
Gleason score at prostatectomy							.05‡	
2–6	110 (49.6)			183 (59.8)				
7	75 (33.8)			97 (31.7)				
8–10	21 (9.5)			14 (4.6)				
Not graded§	16 (7.2)			12 (3.9)				
T stage‖							.76¶	.76¶
T2	179 (80.6)	105 (95.4)	63 (65.6)	245 (80.1)	167 (91.3)	68 (61.3)		
T3	40 (18.0)	4 (3.6)	33 (34.4)	51 (16.7)	11 (6.0)	39 (35.1)		
Tx	3 (1.4)	1 (0.9)	0 (0)	10 (3.3)	5 (2.7)	4 (3.6)		
N stage							.33#	.62#
N0	154 (69.4)	68 (61.8)	76 (79.2)	191 (62.4)	111 (60.7)	72 (64.9)		
N1	3 (1.4)	0 (0)	3 (3.1)	1 (0.3)	0 (0)	1 (0.9)		
Nx	62 (27.9)	41 (37.3)	17 (17.7)	107 (35.0)	68 (37.2)	35 (31.5)		
Missing	3 (1.4)	1 (0.9)	0 (0)	7 (2.3)	4 (2.2)	3 (2.7)		
Surgical margins							.49**	.70**
Negative	166 (74.8)	91 (82.7)	66 (68.8)	233 (76.1)	146 (79.8)	77 (69.4)		
Positive	52 (23.4)	18 (16.4)	29 (30.2)	63 (20.6)	32 (17.5)	30 (27.0)		
Missing	4 (1.8)	1 (0.9)	1 (1.0)	10 (3.3)	5 (2.7)	4 (3.6)		
Seminal vesicle invasion							.46**	1.00**
Negative	209 (94.1)	109 (99.1)	88 (91.7)	286 (93.5)	176 (96.2)	100 (90.1)		
Positive	9 (4.1)	0 (0)	7 (7.3)	8 (2.6)	0 (0)	7 (6.3)		
Missing	4 (1.8)	1 (0.9)	1 (1.0)	12 (3.9)	7 (3.8)	4 (3.6)		

* These numbers reflect every prostatectomy sample received by the Core Pathology Laboratory; biopsy high-grade tumors graded in prostatectomies numbered 79 in the finasteride group and 70 in the placebo group (detailed in Table 5).

† *P* values were calculated by using two-sided chi-square test, except for N stage and seminal vesicle invasion, which used a two-sided Fisher exact test.

‡ Grade 2–6 versus grade 7–10.

§ Not graded because of anti-androgen therapy between biopsy and prostatectomy.

‖ T = tumor, N = node. (21).

¶ T2 versus T3.

N0 versus N1.

** Negative versus positive.

(18.7%), when the increased risk of high-grade disease was first noted (data not shown).

Discussion

Three possibilities, not mutually exclusive, may explain the increased prevalence of high-grade prostate cancer among men in the finasteride group of the PCPT (1). The first is that finasteride induces growth of high-grade cancer despite the decrease in low-grade cancer. This study provides no data to support or refute the possibility that finasteride may have induced high-grade cancer in some men. The second possible explanation is that finasteride, through its effects on PSA, DRE, and prostate volume, increased detection of existing high-grade cancer. As previously reported,

Table 5. Comparison of grades at needle biopsy and prostatectomy in the finasteride and placebo groups in the Prostate Cancer Prevention Trial

Gleason score on biopsy*	Gleason score at radical prostatectomy†									
	Finasteride (N = 206)					Placebo (N = 283)				
	2–5	6	7	8–10	NG‡	2–5	6	7	8–10	NG‡
2–5	0	14	6	1	1	10	28	8	1	3
6	7	65	20	0	4	12	100	43	0	6
7	2	12	28	6	2	1	13	38	3	1
8–10	0	3	14	14	7	0	3	5	7	1

* Three men on finasteride and three men on placebo who had a prostatectomy had a biopsy that was not graded.

† Extended Mantel–Haenszel correlation statistic (increase, unchanged, decrease) between groups, $P = .03$.

‡ NG = not graded (because of anti-androgen therapy between biopsy and prostatectomy).

Table 6. Biopsy characteristics of tumors with Gleason score 7–10 in the Prostate Cancer Prevention Trial*

Characteristic	Finasteride (N = 282)		Placebo (N = 244)		*P*
	Mean (SD)	Median (10%–90%)	Mean (SD)	Median (10%–90%)	
No. of total biopsy cores taken	6.6 (1.8)	6 (5–9)	6.6 (2.0)	6 (5–10)	.22†
No. of positive cores	2.2 (1.3)	2 (1–4)	2.5 (1.6)	2 (1–4)	.06†
Percentage of positive cores	33.6 (18)	33.3 (17–50)	38.3 (21)	33.3 (17–67)	.016†
Greatest linear extent, mm	4.4 (3.0)	3.8 (1.0–8.9)	4.8 (3.3)	4.0 (1.3–9.4)	.19†
Aggregate linear extent, mm	7.6 (8.1)	5.0 (1.3–17.0)	9.2 (9.9)	5.8 (1.5–20.0)	.13†
Percent bilateral	22.8		30.6		.046‡
Percent perineural invasion	14.2		20.3		.07‡

* Data from biopsies conducted through June 23, 2003. SD = standard deviation.

† *P* values (two-sided) calculated using a Mann–Whitney nonparametric test.

‡ *P* values (two-sided) calculated using a chi-square test.

finasteride does increase the sensitivity of PSA and DRE for detecting cancer, particularly high-grade disease (16,17), and the results of this study suggest that finasteride decreases prostate volume. Furthermore, selective inhibition of low-grade cancer in men with cancers that contain both low- and high-grade components could have increased the relative proportion of high- to low-grade cancer, thereby favoring detection of the high-grade component by needle biopsy. The third potential explanation is that finasteride interferes with the histologic grading of cancer, causing lower-grade tumors to appear high grade.

Histopathologic changes with androgen ablation therapy are known to affect tumor grading (10,11,13) but are less established with finasteride (10,12). Three genitourinary pathologists reviewed biopsies of the majority of tumors diagnosed as Gleason 8–10 for features indicative of a hormonal degenerative effect (Table 2). This group of tumors was chosen because the majority of the excess high-grade tumors in the finasteride group were Gleason grade 8–10. We postulated that if grade differences between the two treatment groups were due to morphologic changes induced by finasteride, those changes should be evident in the tumors at the time of diagnosis. The panel of pathologists instead found similar histologic features in the two groups and concluded that a grading bias due to the effect of finasteride on tumor morphology was of insufficient magnitude to have caused the difference in high-grade tumors between the study arms.

Pathologic examination of the PCPT prostatectomy specimens revealed that the difference in proportion of high-grade tumors between the finasteride and placebo groups was diminished compared with the difference seen at biopsy (ratio of 1.68 at biopsy versus 1.20 at prostatectomy for graded tumors), despite the greater likelihood of radical prostatectomy for high-grade disease in subjects receiving finasteride. Pathologic stage and node and margin status were not different between treatment groups. Comparison of tumor grade on prostatectomy and biopsy showed that, when high-grade disease was present at prostatectomy, it was more likely to have been detected at biopsy in the finasteride group (62 of 89 [69.7%]) than in the placebo group (53 of 105 [50.5%]) (P = .01), indicating that finasteride increased the sensitivity of prostate biopsy for high-grade disease.

Differences in detection of high-grade cancer by biopsy between the two treatment groups are reflective of the random nature of prostate biopsies and the resulting potential for sampling error. The detection and grading of cancer on biopsy is subject to two factors: the ratio of tumor volume to prostate volume (26,27) (which affect overall detection) and the relative proportions of Gleason patterns that exist within the tumor (which affect grading). The greater the relative volume of any high-grade component, the more likely it will be sampled (28–33). Gland volume in the finasteride group (25.1 cm^3) was 27% smaller than in the placebo group (34.4 cm^3, P<.001). Reduced prostate gland volume with finasteride may have increased the tumor-to-prostate volume ratio and improved detection of both cancer overall and any high-grade component of cancer. This hypothesis is supported by findings of other investigators, who reported a relationship between smaller gland size and improved sensitivity of prostate biopsy for high-grade disease (33).

Finasteride may also have caused a relative increase in the high-grade component by one of two other possible mechanisms. One could be that finasteride potentiates the growth of high-grade cancer. However, pathologic measures of tumor extent on biopsy (Table 6) do not lend support to this conclusion. A second possibility, which is supported by the primary results of the PCPT (1) and studies involving another 5α-reductase inhibitor, dutasteride (35), is that finasteride reduces the volume contribution of low-grade tumor. Because many carcinomas are a mixture of low- and high-grade components, such a reduction would alter the ratio of the two components within a gland containing both components so that, when biopsy is performed, the high-grade component is more likely to be sampled.

If finasteride does alter the tumor-to-prostate volume ratio, particularly for high-grade disease, by decreasing prostate volume, it would result in the detection of smaller tumors that could be missed in the larger glands of the placebo group. Because accurate tumor volumes could not be obtained from the prostatectomies due to differences in sampling techniques between sites, we examined surrogate measures of tumor extent on needle biopsies. Review of all high-grade (Gleason score 7–10) biopsies showed that the number and percentage of cores with cancer, greatest linear and aggregate tumor extent, percent bilateral cancer, and percent perineural invasion were either decreased or similar in finasteride versus placebo high-grade tumors. These biopsy features are also influenced by the ratio of tumor-to-prostate volume (22–27,34). Because finasteride reduced gland volume, one would expect the values of these biopsy features to be greater in the finasteride group if those tumors were of the same size or larger

than tumors in the placebo group. Lower values for these features in finasteride high-grade tumors compared with those in the placebo group are consistent with detection of lower volume disease. Therefore, it is plausible that decreased prostate volume with finasteride led to improved detection of high-grade but lower-volume cancers. It also is possible that an upward shift in grade due to the selective effect of finasteride on reducing the volume contribution of low-grade tumor components contributed to the detection of low-volume, but not necessarily more advanced, high-grade tumors in the finasteride group.

Because a greater proportion of high-grade cancers at prostatectomy were correctly identified by needle biopsy in the finasteride group than in the placebo group, it would have been reasonable to expect a higher rate of upgrading from low- to high-grade disease in the placebo group at prostatectomy. However, the low-to-high upgrading rates were similar (25.7% placebo, 23.9% finasteride; $P = .72$), arguing against the detection-bias hypothesis. The up- and downgrading rates are dependent on the prevalence of high-grade disease in the two groups at prostatectomy, which again was higher in the finasteride group. Because PSA and DRE are more sensitive for the detection of high-grade prostate cancer in the finasteride group than in the placebo group (16,17), it follows that the finasteride group was enriched with more high-grade cancers due to the improved detection properties of these tests. Therefore, treatment comparisons of up- and downgrading may not be as valid as comparisons of biopsy sensitivity to high-grade disease, which does not depend on disease prevalence.

Our study has a number of limitations. First, because long-term outcomes were not followed, prostatectomy results were the only measure of disease outcome available. Second, not all men underwent radical prostatectomy. Differences may exist between the two study groups in the men who did or did not undergo prostatectomy. Third, prostatectomies were sectioned in different manners by different institutions. For those institutions with greater assiduity, there may have been a higher likelihood of better sampling of high-grade disease. This difference also prevented adequate analysis of tumor volumes at prostatectomy. Finally, we assumed that the definitions of degenerative changes by the expert panel are hallmarks of a hormonal effect that may have affected grading. Because these changes were also seen in subjects in the placebo group and because it is doubtful that men in the placebo group were taking androgen deprivation therapy without a diagnosis of prostate cancer, it is possible that these degenerative changes were not pathognomonic of a hormonal effect. Thus, it remains possible that histologic changes may develop after finasteride administration in some individuals that could affect tumor grading.

It is likely that no single mechanism is sufficient to explain the increase in high-grade cancer in the finasteride group of the PCPT. Although the evidence does not exclude the possibility that finasteride may have induced high-grade prostate cancer in some men, the analysis of prostatectomies from the PCPT does indicate that the relative increase in high-grade tumors in the finasteride group is less than originally believed. This evidence further suggests that increased detection due to reduced gland volume and selective inhibition of low-grade tumors may have contributed to the finasteride-associated increase in high-grade disease. The systematic blinded pathologic examinations in this study of the high-grade biopsies and all available prostatectomy specimens from a large number of men in the PCPT contribute important data to the debate on how to interpret the study's overall results.

References

(1) Thompson IM, Goodman PJ, Tangen CM, Lucia MS, Miller GJ, Ford LG, et al. The influence of finasteride on the development of prostate cancer. N Engl J Med 2003;349:215–24.

(2) Scardino PT. The prevention of prostate cancer—the dilemma continues. N Engl J Med 2003;349:297–9.

(3) Zuger A. A big study yields big questions. N Engl J Med 2003;349: 213–4.

(4) Koivisto PA, Schleutker J, Helin H, Ehren-van Eekelen C, Kallioniemi OP, Trapman J. Androgen receptor gene alterations and chromosomal gains and losses in prostate carcinomas appearing during finasteride treatment for benign prostatic hyperplasia. Clin Cancer Res 1999;5:3578–82.

(5) Hoffman MA, DeWolf WC, Morgentaler A. Is low serum free testosterone a marker for high grade prostate cancer? J Urol 2000;163:824–7.

(6) Weihua Z, Lather R, Warner M, Gustafsson J-Å. An endocrine pathway in the prostate, EPβ, AR, 5α-androstane-3β, 17β-diol, and CYP7B1, regulated prostate growth. Proc Natl Acad Sci USA 2002;99:589–94.

(7) Ho SM. Estrogens and anti-estrogens: key mediators of prostate carcinogenesis and new therapeutic candidates. J Cell Biochem 2004;91:491–503.

(8) Marberger M, Adolfsson J, Borkowski A, Fitzpatrick J, Kirk D, Prezioso D, et al. The clinical implications of the Prostate Cancer Prevention Trial. BJU Int 2003;92:667–71.

(9) Roehrborn CG. Prevention of prostate cancer with finasteride. N Engl J Med 2003;349:1569–72.

(10) Civantos F, Soloway MS, Pinto JE. Histopathological effects of androgen deprivation in prostatic cancer. Semin Urol Oncol 1996;14(Suppl 2): 22–31.

(11) Reuter VE. Pathological changes in benign and malignant prostatic tissue following androgen deprivation therapy. Urology 1997;49(Suppl):16–22.

(12) Yang XJ, Lecksell K, Short K, Gottesman J, Peterson L, Bonnow J, et al. Does long-term finasteride therapy affect the histologic features of benign prostatic tissue and prostate cancer on needle biopsy? PLESS Study Group. Proscar Long-Term Efficacy and Safety Study. Urology 1999; 53:696–700.

(13) Bostwick DG, Qian J, Civantos F, Roehrborn CG, Montironi R. Does finasteride alter the pathology of the prostate and cancer grading? Clin Prostate Cancer 2004;2:228–35.

(14) Stoner E. Three-year safety and efficacy data on the use of finasteride in the treatment of benign prostatic hyperplasia. Urology 1994;43:284–92.

(15) Lowe FC, McConnell JD, Hudson PB, Romas NA, Boake R, Lieber M, et al. Long-term 6-year experience with finasteride in patients with benign prostatic hyperplasia. Urology 2003;61:791–6.

(16) Thompson IM, Chi C, Pauler Ankerst D, Goodman PJ, Tangen CM, Lippman SM, et al. Effect of finasteride on the sensitivity of PSA for detecting prostate cancer. J Natl Cancer Inst 2006;98:1128–33.

(17) Thompson IM, Tangen CM, Goodman PJ, Lucia MS, Parnes HL, Lippman SM, et al. Finasteride improves the sensitivity of digital rectal examination for prostate cancer detection. J Urol 2007;177:1749–52.

(18) Gleason DF. Histologic grading of prostate cancer: a perspective. Hum Pathol 1992;23:273–9.

(19) Srigley JR, Amin MB, Bostwick DG, Grignon DJ, Hammond ME. Updated protocol for the examination of specimens from patients with carcinomas of the prostate gland. A basis for checklists. Arch Pathol Lab Med 2000;124:1034–9.

(20) Westra WH, Hruban RH, Phelps TH, Isacson C, editors. Surgical pathology dissection: an illustrated guide. 2nd ed. New York (NY): Springer-Verlag New York, Inc; 2003.

(21) American Joint Committee on Cancer. AJCC staging manual. 5th ed. Philadelphia (PA): Lippincott-Raven; 1997.

(22) Ravery V, Boccon-Gibod LA, Dauge-Geffroy MC, Billebaud T, Delmas V, Meulemans A, et al. Systematic biopsies accurately predict extracapsular

extension of prostate cancer and persistent/recurrent detectable PSA after radical prostatectomy. Urology 1994;44:371–6.
(23) Peller PA, Young DC, Marmaduke DP, Marsh WL, Badalament RA. Sextant prostate biopsies: a histopathologic correlation with radical prostatectomy specimens. Cancer 1995;75:530–8.
(24) Epstein JI. The diagnosis and reporting of adenocarcinoma of the prostate in core needle biopsy specimens. Cancer 1996;78:350–6.
(25) Bostwick DG. Evaluating prostate needle biopsy: therapeutic and prognostic importance. CA Cancer J Clin 1997;47:297–319.
(26) Crawford ED, Hirano D, Werahera PN, Lucia MS, DeAntoni EP, Brawn PN, et al. Computer modeling of prostate biopsy: tumor size and location—not clinical significance—determine cancer detection. J Urol 1998;159:1260–4.
(27) Mariappan P, Chong WL, Sundram M, Mohamed SR. Increasing prostate biopsy cores based on volume vs the sextant biopsy: a prospective randomized controlled clinical study on cancer detection rates and morbidity. BJU Int 2004;94:307–10.
(28) Makhlouf AA, Krupski TL, Kunkle D, Theodorescu D. The effect of sampling more cores on the predictive accuracy of pathological grade and tumour distribution in the prostate biopsy. BJU Int 2004;93:271–4.
(29) King CR, Long JP. Prostate biopsy grading errors: a sampling problem? Int J Cancer 2000;90:326–30.
(30) Bostwick DG. Grading prostate cancer. Am J Clin Pathol 1994;102(Suppl 1): S38–56.
(31) Djavan B, Kadesky K, Klopukh B, Marberger M, Roehrborn CG. Gleason scores from prostate biopsies obtained with 18-guage biopsy needles poorly predict Gleason scores of radical prostatectomy specimens. Eur Urol 1998;33:261–70.
(32) Sved PD, Gomez P, Manoharan M, Kim SS, Soloway MS. Limitations of biopsy Gleason grade: implications for counseling patients with biopsy Gleason score 6 prostate cancer. J Urol 2004;172:98–102.
(33) Kulkarni GS, Al-Azab R, Lockwood G, Toi A, Evans A, Trachtenberg J, et al. Evidence for a biopsy derived grade artifact among larger prostate glands. J Urol 2006;175:505–9.
(34) Lewis JS Jr, Vollmer RT, Humphrey PA. Carcinoma extent in prostate needle biopsy tissue in the prediction of whole gland tumor volume in a screening population. Am J Clin Pathol 2002;118:442–50.
(35) Iczkowski KA, Qiu J, Qian J, Somerville MC, Rittmaster RS, Andriole GL, et al. The dual 5-alpha-reductase inhibitor dutasteride induces atrophic changes and decreases relative cancer volume in human prostate. Urology 2005;65:76–82.

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