Effect of Finasteride on the Sensitivity of PSA for Detecting Prostate Cancer

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Background: **In the Prostate Cancer Prevention Trial (PCPT), men receiving finasteride had a 24.8% lower risk of prostate cancer than men receiving placebo but a higher risk of high-grade cancer. We examined the impact of finasteride on the sensitivity and area under the receiver operating characteristic curve (AUC) of prostate-specific antigen (PSA) for detecting prostate cancer.** ***Methods:*** **We studied men in the placebo and finasteride groups of the PCPT who had a prostate biopsy and concurrent PSA tests during the 7-year study. We compared the placebo and finasteride groups for sensitivity and AUC of PSA for the detection of all prostate cancer, of Gleason grade 7 or higher prostate cancer, and of Gleason grade 8 or higher prostate cancer. All statistical tests were two-sided.** ***Results:*** **Of 5112 men in the placebo group, prostate cancer was detected in 1111. Gleason tumor grade was available for 1100 men, of whom 240 had grade 7 or higher and 55 had grade 8 or higher. Of 4579 men in the finasteride group, 695 had prostate cancer. Gleason grade was available for 686 men, of whom 264 had grade 7 or higher and 81 had grade 8 or higher. The AUC of PSA for all outcomes was greater for the finasteride group than the placebo group. For detecting prostate cancer versus no cancer, the AUCs were 0.757 and 0.681, respectively ($P<.001$); for detecting Gleason grade ≥7 versus ≤6 or no cancer, the AUCs were 0.838 and 0.781, respectively ($P = .003$); and for detecting Gleason grade ≥8 versus ≤7 or no cancer, the AUCs were 0.886 and 0.824, respectively ($P = .071$). The sensitivity of PSA was higher for men in the finasteride group than in the placebo group at all PSA cutoffs matched by specificity.** ***Conclusions:*** **PSA had statistically significantly better sensitivity and AUC for detecting prostate cancer in the finasteride arm of the PCPT than in the placebo arm. This bias would be expected to contribute to greater detection of all grades of prostate cancer with finasteride. [J Natl Cancer Inst 2006;98:1128–33]**

The Prostate Cancer Prevention Trial (PCPT) was designed to determine whether the 5α-reductase inhibitor finasteride would reduce the prevalence of prostate cancer after 7 years of treatment. In this trial, 18 882 men were randomly assigned to receive either finasteride (5 mg/day) or placebo and were followed up with annual digital rectal examination (DRE) and prostate-specific

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antigen (PSA) measurements; a prostate biopsy was recommended (referred to hereafter as "for-cause biopsy") if the result of either test was abnormal *(1)*. After 7 years on study, men who had not been diagnosed with prostate cancer were requested to undergo an end-of-study biopsy, which was defined as a biopsy after 7 years of study participation for a man with a PSA level of less than or equal to 4.0 ng/mL and a normal DRE result.

The PCPT was closed more than a year earlier than planned at the recommendation of the independent data and safety monitoring committee, when it found that the primary objective of the trial had been achieved. That is, the prevalence of prostate cancer over the 7-year period was reduced by 24.8% in the finasteride group compared with the placebo group. However, both the proportion and absolute numbers of high-grade tumors (i.e., those with a Gleason score of 7–10) were higher in the finasteride group (37%, i.e., 280 of 757 tumors) than in the placebo group (22.2%, i.e., 237 of 1068 tumors) *(1)*. Despite the possible benefit of finasteride in preventing or delaying prostate cancer, this increase in high-grade tumors dampened public interest for using finasteride.

Several observations from the PCPT study data have suggested that the increase in high-grade disease may have been due to detection bias rather than to a change in the biology of the disease *(1)*. First, more subjects in the finasteride group who underwent a for-cause biopsy had high-grade tumors (n = 188) than subjects in the placebo group (n = 148), whereas the number of subjects with high-grade disease among those receiving end-of-study biopsies was similar in the two groups (n = 92 for the finasteride group and n = 89 for placebo group). Although men in the finasteride group who underwent an end-of-study biopsy had a higher proportion of high-grade tumors (25.3% [92 of 364] of graded tumors) than men in the placebo group (15.8% [89 of 564] of graded tumors), this difference primarily reflected the substantial reduction in total numbers of tumors in the finasteride group. Second, the increased hazard ratio for high-grade tumor detection with finasteride appeared early in the study and did not increase with time *(1)* (Supplementary Fig. 1, available at http://jncicancerspectrum.oxfordjournals.org/jnci/content/vol98/issue16). These observations raised the possibility that the increased detection of high-grade disease by PSA- and DRE-prompted biopsies in the finasteride group could have been due in part to the higher sensitivity of the PSA test for detecting high-grade disease in the finasteride group. We analyzed the detection of prostate cancer in PCPT participants to determine whether finasteride treatment may have affected the performance characteristics of PSA as a diagnostic test.

Subjects and Methods

Design of the Prostate Cancer Prevention Trial

The PCPT randomly assigned 18 882 men to finasteride (5 mg/day) or placebo *(1)*. Participants were tested annually for their PSA levels, which were measured in a central laboratory (Esoterix, Inc, Calabasas Hills, CA), and underwent annual DRE. Men in the placebo group were recommended to undergo prostate biopsy if their PSA level exceeded 4.0 ng/mL or if they had an abnormal DRE. Because finasteride causes a decrease in PSA level *(2)*, PSA measurements for men in the finasteride group were adjusted centrally to equalize the recommended annual biopsy rates in the two groups. It was the adjusted values that were reported and used as the basis for biopsy recommendations. The independent data safety and monitoring committee oversaw the adjustment process. The PSA level of men on finasteride was initially multiplied by a factor of 2.0, but it was necessary to increase this multiplier to 2.3 at the beginning of each man's fourth year on finasteride to maintain a biopsy recommendation rate in the finasteride arm similar to that in the placebo arm. All subjects provided written informed consent, and the study was approved by the institutional review boards of the participating institutions. Prostate biopsy specimens were reviewed by a central pathology laboratory as well as by pathologists at the study site. Pathologists were blinded to treatment assignment. Discordant interpretations were arbitrated by a referee pathologist *(1)*.

Statistical Analysis

This analysis included all participants in the placebo and finasteride groups who underwent prostate biopsy at any of the seven annual visits, were on treatment at the time of the PSA measurement, and had a PSA measurement and DRE within 1 year before the biopsy. For participants with multiple biopsies, the most recent biopsy was used. The receiver operating characteristics (ROC) of PSA for detection of prostate cancer by biopsy in the placebo and finasteride groups were summarized in terms of the sensitivity and specificity of a series of cutoff values of PSA; ROC curves were calculated for prostate cancer versus no prostate cancer, for Gleason grade 7 or higher prostate cancer versus Gleason grade less than 7 or no prostate cancer, and for Gleason grade 8 or higher prostate cancer versus Gleason grade less than 8 or no prostate cancer. Sensitivity was defined as the proportion of men with prostate cancer whose PSA value exceeded each cutoff value and specificity as the proportion of men without prostate cancer whose PSA value was equal to or less than each cutoff value. Sensitivity and specificity in the placebo group were calculated at standard PSA level cutoffs of 1.0, 1.5, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, and 10.0 ng/mL.

As mentioned above, finasteride reduces PSA by an unknown, possibly nonlinear factor that exceeds 50% *(2)*, so comparisons of sensitivity between the finasteride and placebo groups were made for PSA cutoffs that achieved the same specificity in each group. PSA cutoffs for the finasteride group were defined as those that yielded the same specificity as the corresponding PSA cutoffs for the placebo group (see Table 2). Confidence intervals (95%) for sensitivities and specificities were calculated using the binomial formula. The ROC curve was plotted as 1 minus the specificity (i.e., the false-positive rate) versus sensitivity for all cutoff values in the range of PSA values observed. A test of the null hypothesis, that the area under the ROC curve (AUC) is 50%, was performed using the Wilcoxon rank sum test, and a test of differences between the areas underneath the curve for the finasteride versus placebo groups was computed using the *U* statistic of DeLong et al. *(3)*. All statistical tests reported are two sided. Analyses were conducted using SAS (version 9.0) and STATA software.

An adjustment for verification bias was not made in this analysis because in our earlier analysis of the placebo arm, AUCs with and without verification bias adjustment were practically identical, a condition met due to the required end-of-study biopsy for the PCPT *(4)*.

Table 1. Characteristics of participants in the Prostate Cancer Prevention Trial who were included and not included in the analysis*

Characteristic	Placebo group		Finasteride group	
	Included (n = 5112)	Not included (n = 4347)	Included (n = 4579)	Not included (n = 4844)
Age at baseline, y				
<60	1654 (32.4)	1303 (30.0)	1433 (31.3)	1522 (31.4)
60–64	1589 (31.1)	1235 (28.4)	1472 (32.1)	1498 (30.9)
65–69	1189 (23.3)	1032 (23.7)	1043 (22.8)	1067 (22.0)
≥70	680 (13.3)	777 (17.9)	631 (13.8)	757 (15.6)
	P<.001		*P* = .07	
Family history of prostate cancer				
No	4256 (83.3)	3748 (86.2)	3843 (83.9)	4122 (85.1)
Yes	856 (16.7)	599 (13.8)	736 (16.1)	722 (14.9)
	P<.001		*P* = .12	
Race				
White	4893 (95.7)	4035 (92.8)	4355 (95.1)	4533 (93.6)
African American	158 (3.1)	202 (4.6)	168 (3.7)	204 (4.2)
Other	61 (1.2)	106 (2.4)	56 (1.2)	103 (2.1)
Missing	0 (0.0)	4 (0.1)	0 (0.0)	4 (0.1)
	P<.001		*P* = .001	
No. of PSA measures†				
0	0 (0.0)	500 (11.5)	0 (0.0)	614 (12.7)
1–3	210 (4.1)	1111 (25.6)	144 (3.1)	1327 (27.3)
4–6	849 (16.6)	1697 (39.0)	738 (16.1)	1704 (35.2)
≥7	4053 (79.3)	1039 (23.9)	3697 (80.7)	1199 (24.8)
	P<.001		*P*<.001	
No. of DRE measures‡				
0	0 (0.0)	486 (11.2)	0 (0.0)	599 (12.4)
1–3	201 (3.9)	1118 (25.7)	141 (3.1)	1320 (27.3)
4–6	760 (14.9)	1693 (38.9)	606 (13.2)	1753 (36.2)
≥7	4151 (81.2)	1050 (24.2)	3832 (83.7)	1172 (24.2)
	P<.001		*P*<.001	
Reason for biopsy				
End of study	3967 (77.6)		3584 (78.3)	
For cause	1145 (22.4)		995 (21.7)	
No. of previous biopsies				
0	4393 (85.9)		3962 (86.5)	
≥1	719 (14.1)		617 (13.5)	
≥2	127 (2.5)		107 (2.3)	
Age at biopsy, y				
<60	35 (0.7)		36 (0.8)	
60–64	1061 (20.8)		902 (19.7)	
65–69	1595 (31.2)		1416 (30.9)	
≥70	2421 (47.4)		2225 (48.6)	

*PSA = prostate-specific antigen; DRE = digital rectal exam. *P* values are for comparisons between included and not-included participants and are from chi-square test.

†*P* = .03 from chi-square test for placebo-included men versus finasteride-included men.

‡*P* = .003 for placebo-included men versus finasteride-included men.

Results

Of the 18 882 patients in the PCPT, 9423 were randomly assigned to finasteride and 9459 to placebo. A total of 5676 men in the finasteride group had at least one biopsy during the study period, either for cause or as required at the end of study. Of these men, 357 were excluded from this analysis because no PSA or DRE result within 1 year of biopsy was available and 740 were excluded because they were off treatment when their PSA level was measured. A total of 5947 men in the placebo group had at least one biopsy during the study; 360 of these men were excluded from this analysis because of a missing PSA or DRE result and 475 were excluded because they were off treatment when their PSA level was measured. Therefore, 4579 men in the finasteride group (995 with a for-cause biopsy and 3584 with an end-of-study biopsy) and 5112 men in the placebo group (1145 with a for-cause biopsy and 3967 with an end-of-study biopsy) were included in the analysis.

Characteristics of the included and not-included men in each treatment group are shown in Table 1. Within the placebo group, the participants included in this analysis were statistically significantly younger at baseline and more likely to have a family history of prostate cancer than the participants who were not included. The statistical significance of these differences may reflect a greater tendency of these men to undergo the screening required by this study but is more likely driven by the large sample sizes because the differences were small in magnitude and not observed in the finasteride group. In both the finasteride and placebo groups, there were statistically significantly greater proportions of white participants in the included group than in the not-included group that, again, were statistically significant but small in magnitude. There were no statistically significant differences between the included men in the finasteride and placebo groups in age at baseline, family history of prostate cancer, or race. In both treatment groups, there was more screening—as reflected by a greater total number of annual DRE and PSA screens over the duration of

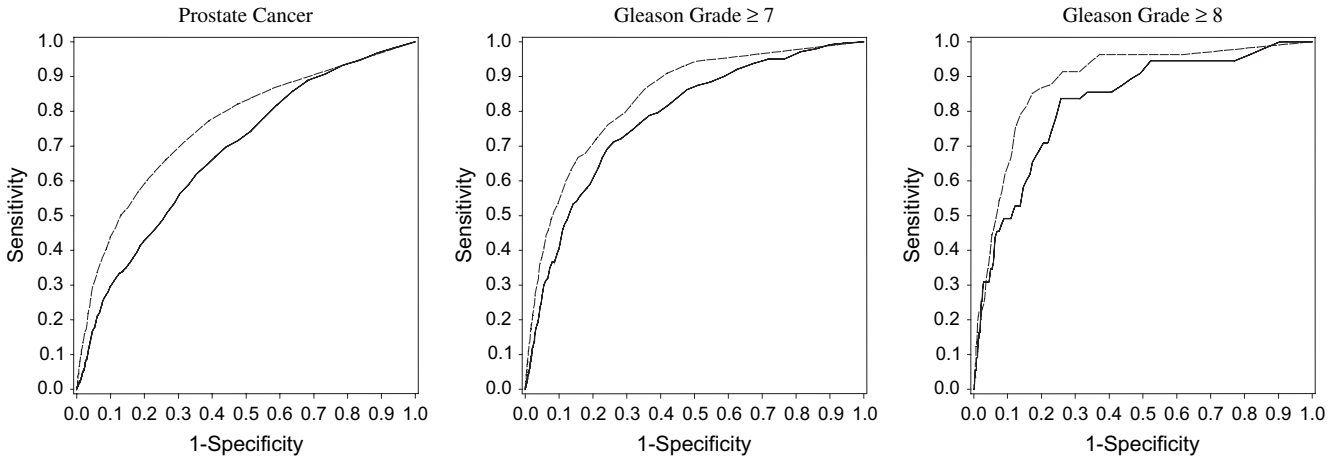

Fig. 1. Receiver operating characteristic (ROC) curves for prostate-specific antigen detection of all prostate cancer and high-grade prostate cancer. **Left**, ROC curves for all prostate cancer; **middle**, ROC curves for Gleason grade 7 or higher prostate cancer; **right**, ROC curves for Gleason grade 8 or higher prostate cancer. **Solid line** = placebo group; **dashed line** = finasteride group. *P* values for difference between placebo and finasteride groups [from test of DeLong et al. *(3)*] are <.001 for all prostate cancer, .003 for Gleason grade 7 or higher prostate cancer, and .071 for Gleason grade 8 or higher prostate cancer.

participation in the study—in the included men than in the not-included men, a difference that emphasizes that the subgroups used for analysis were not a random subgroup of the PCPT but rather an actively screened subgroup. For the participants included in the analysis, slightly more screens (PSA and DRE) were performed in the finasteride arm than in the placebo group ($P = .03$ and $P = .003$, respectively). Finally, the two treatment groups did not differ with respect to the proportions of the biopsies that were performed for the two reasons (i.e., for cause or end of study), the number of previous biopsies, and age at biopsy.

Of the 5112 men in the placebo group, 1111 (21.7%) were diagnosed with prostate cancer. Information on tumor grade was available for 1100 of these men, of whom 240 had a Gleason score of 7 or higher (21.8% of evaluable cancers) and 55 had a Gleason score of 8 or higher (5% of evaluable cancers). Of the 4579 men who received finasteride, 695 (15.2%) were diagnosed with prostate cancer. Information on tumor grade was available for 686 of these men, of whom 264 had a Gleason score of 7 or higher (38.5% of evaluable cancers) and 81 had a Gleason score of 8 or higher (11.8% of evaluable cancers).

Comparisons between the finasteride and placebo groups of the ROC curves of PSA for detection of prostate cancer versus no prostate cancer, of Gleason grade 7 or higher versus Gleason grade 6 or less or no cancer, and of Gleason grade 8 or higher versus Gleason grade 7 or less or no cancer (Fig. 1) showed that, in every case, the AUCs of PSA were greater for the finasteride group than the placebo group. For detection of prostate cancer overall, the AUCs were 0.757 in the finasteride group and 0.681 in the placebo group ($P<.001$); for detection of Gleason grade 7 or higher disease, the AUCs were 0.838 and 0.781, respectively ($P = .003$); and for detection of Gleason grade 8 or higher disease, the AUCs were 0.886 and 0.824, respectively ($P = .071$). In the finasteride group, there were no statistically significant differences in the AUC of PSA for overall prostate cancer detection by DRE status (abnormal versus normal) or age at biopsy (<70 years versus ≥70 years) (both $P>.05$; data not shown). In the placebo group, there was also no difference in AUC by DRE status and a borderline statistically significant increase in AUC for younger (<70 years) versus older men (AUC = 0.697 versus 0.663, $P = .06$; data not shown).

We compared the specificities and sensitivities of a series of PSA cutoffs for detecting the three categories of disease—prostate cancer, Gleason grade 7 or higher prostate cancer, and Gleason grade 8 or higher prostate cancer—in the placebo and finasteride arms (Table 2). For the placebo group we used commonly used PSA cutoffs; for the finasteride group, we used PSA cutoffs that were matched to obtain the same specificities as each cutoff in the placebo arm. The PSA cutoff of 4.0 ng/mL in the placebo group and the matched cutoff in the finasteride group achieved specificities exceeding 90% for detecting each of the three categories of prostate cancer. However, the sensitivities of PSA were uniformly greater in the finasteride group than in the placebo group: 37.8% (95% confidence interval [CI] = 34.2 to 41.4), 53.0% (95% CI = 47.0 to 59.0), and 64.2% (95% CI = 53.8 to 74.6) for prostate cancer, Gleason grade 7 or higher disease, and Gleason grade 8 or higher disease, respectively, in the finasteride arm compared with 24.0% (95% CI = 21.5 to 26.5), 39.2% (95% CI = 33.0 to 45.4), and 49.1% (95% CI = 35.9 to 62.3), respectively, in the placebo arm. At a PSA cutoff in the placebo group of 2.5 ng/mL, a commonly recommended contemporary threshold for which the specificity for cancer detection in the placebo group of this study was 80%, finasteride increased PSA sensitivity relative to that in the placebo group by 14.0 (95% CI = 9.3 to 18.7), 5.3 (95% CI = −2.8 to 13.4), and 9.5 (95% CI = −3.6 to 22.6) percentage points for prostate cancer, Gleason grade 7 or higher disease, and Gleason grade 8 or higher disease, respectively.

Discussion

In this study, we found that finasteride introduces detection bias for both prostate cancer and for high-grade (i.e., Gleason grade 7–10) prostate cancer by increasing the sensitivity of PSA for these endpoints. This effect of finasteride is critically important to understand the primary and secondary findings of the PCPT. The impact of the primary finding, that finasteride caused a 24.8% reduction in prostate cancer prevalence in the PCPT, was tempered by the secondary observation of a small

Table 2. Sensitivities of PSA (with 95% CI) for detection of prostate cancer, Gleason grade 7 or higher disease, and Gleason grade 8 or higher disease in the placebo and finasteride arms of the PCPT for standard PSA cutoffs and finasteride cutoffs chosen to match PSA specificities in the placebo group*

PSA cutoff, placebo group, ng/mL	PSA cutoff, finasteride group, ng/mL	Specificity†	Sensitivity (95% CI)	
			Placebo group	Finasteride group
Prostate cancer versus no prostate cancer				
1.0	0.4	40.8	81.8 (79.5 to 84.1)	86.8 (84.3 to 89.3)
1.5	0.6	59.0	67.0 (64.2 to 69.8)	77.3 (74.2 to 80.4)
2.0	0.9	71.2	53.5 (50.6 to 56.4)	66.0 (62.5 to 69.5)
2.5	1.1	80.0	42.8 (39.9 to 45.7)	56.8 (53.1 to 60.5)
3.0	1.2	85.4	35.0 (32.2 to 37.8)	52.2 (48.5 to 55.9)
4.0	1.6	92.7	24.0 (21.5 to 26.5)	37.8 (34.2 to 41.4)
6.0	2.8	98.1	5.1 (3.8 to 6.4)	13.8 (11.2 to 16.4)
8.0	3.7	99.2	2.0 (1.2 to 2.8)	6.6 (4.8 to 8.4)
10.0	5.6	99.6	0.8 (0.3 to 1.3)	2.9 (1.7 to 4.1)
Gleason ≥7 cancer versus Gleason ≤6 or no prostate cancer				
1.0	0.4	37.3	92.1 (88.7 to 95.5)	95.5 (93.0 to 98.0)
1.5	0.6	55.2	83.8 (79.1 to 88.5)	90.9 (87.4 to 94.4)
2.0	0.9	67.9	75.0 (69.5 to 80.5)	79.5 (74.6 to 84.4)
2.5	1.1	77.2	66.7 (60.7 to 72.7)	72.0 (66.6 to 77.4)
3.0	1.2	82.9	56.7 (50.4 to 63.0)	67.8 (62.2 to 73.4)
4.0	1.6	90.5	39.2 (33.0 to 45.4)	53.0 (47.0 to 59.0)
6.0	3.0	97.9	11.7 (7.6 to 15.8)	19.3 (14.5 to 24.1)
8.0	4.1	99.1	4.2 (1.7 to 6.7)	9.5 (6.0 to 13.0)
10.0	6.5	99.6	1.7 (0.1 to 3.3)	4.2 (1.8 to 6.6)
Gleason ≥8 cancer versus Gleason ≤7 or no prostate cancer				
1.0	0.4	36.3	94.5 (88.5 to 100.5)	96.3 (92.2 to 100.4)
1.5	0.6	53.8	89.1 (80.9 to 97.3)	96.3 (92.2 to 100.4)
2.0	0.9	66.4	85.5 (76.2 to 94.8)	91.4 (85.3 to 97.5)
2.5	1.1	75.7	78.2 (67.3 to 89.1)	87.7 (80.5 to 94.9)
3.0	1.2	81.5	67.3 (54.9 to 79.7)	86.4 (78.9 to 93.9)
4.0	1.7	89.5	49.1 (35.9 to 62.3)	64.2 (53.8 to 74.6)
6.0	3.2	97.7	25.5 (14.0 to 37.0)	22.2 (13.1 to 31.3)
8.0	4.3	99.0	9.1 (1.5 to 16.7)	13.6 (6.1 to 21.1)
10.0	7.3	99.6	3.6 (0.0 to 8.5)	3.7 (0.0 to 7.8)

*PSA = prostate-specific antigen; CI = confidence interval; PCPT = Prostate Cancer Prevention Trial.

†Confidence intervals for specificities were on average within 0.9% (and at most 1.5%) of the estimates reported in the table for both finasteride and placebo.

but statistically significant increase in the rate of high-grade cancer *(1,5)*. This apparent increase was seen as limiting the potential public health benefit of the drug. However, the finding that the increased hazard ratio for high-grade tumor detection with finasteride appeared early and did not increase with time *(1)* was inconsistent with the theory that finasteride induced high-grade disease *(6)*. Moreover, the difference in the absolute numbers of high-grade tumors present in for-cause biopsies (i.e., those performed because of an elevated PSA level or an abnormal DRE result) was not present in the end-of-study biopsies (i.e., not-for-cause biopsies). These observations suggested a potential bias of PSA for detecting prostate cancer in association with for-cause biopsies in men taking finasteride. Such a bias has been suggested by previous, albeit limited, data, including findings from the Proscar Long-term Efficacy and Safety Study and the PCPT *(2,7,8)*.

Previous examinations of the usefulness of PSA screening for prostate cancer detection in men who did or did not take a 5α-reductase inhibitor have been limited by the lack of a large sample of subjects with low PSA levels who had a biopsy. The present study benefited from the fact that participants in the PCPT had an end-of-study biopsy at 7 years regardless of PSA level. This end-of-study biopsy was an essential component of the PCPT because of the unknown long-term effect of finasteride on PSA levels and the need to assess the primary PCPT endpoint of prostate cancer.

The finding that the AUC of PSA for detection of prostate cancer overall as well as for detection of high-grade disease was statistically significantly higher in men treated with finasteride than in men treated with placebo is important for two reasons. First, it has been difficult to identify any single factor that leads to a statistically significant improvement in the AUC of PSA, a biomarker that has widespread use in the United States and that is better at detecting higher grade prostate cancer than lower grade prostate cancer *(4)*. Even the addition of markers that provide independent prognostic information for prostate cancer risk to that provided by PSA is unlikely to lead to a statistically significant increase in the AUC because large odds ratios are required to statistically significantly improve an AUC *(9)*. Given these two observations, it is noteworthy that finasteride statistically significantly increased the AUC of PSA for detecting prostate cancer ($P<.001$) and Gleason grade 7–10 disease ($P = .003$) and led to a borderline statistically significant increase for detecting Gleason grade 8–10 disease ($P = .071$). In other words, finasteride led to statistically significant improvements in the AUC of PSA for prostate cancer detection, an accomplishment that is difficult to attain, even for highly correlated risk factors, and one that has not yet been achieved by other biomarkers. Second, the present analysis suggests that finasteride may enhance the performance of PSA for detecting overall and high-grade prostate cancer in the general population. Indeed, this effect of finasteride on the sensitivity of PSA may have been at least in part responsible for the increased detection of high-grade disease in the PCPT.

The medical community has long been aware that higher PSA values in healthy men are more often associated with benign prostate conditions (e.g., prostatitis and benign prostatic hyperplasia) than with prostate cancer *(10)*. Because finasteride reduces the symptoms of benign prostatic hyperplasia and initiation of finasteride therapy causes a substantial decrease in PSA level that is greatest in men without cancer on biopsy *(2)*, finasteride treatment could be used to enhance detection of prostate cancer in the general population. Finasteride treatment of men with elevated PSA levels would cause the greatest fall in PSA level in men with benign conditions such as benign prostatic hyperplasia, whereas men with persistently elevated PSA levels would have a higher probability of cancer. Men with higher PSA levels in the group receiving finasteride would therefore be more likely to have cancer than men not taking finasteride who also had higher PSA levels. From our previous analyses, higher PSA levels are also more likely to reflect the presence of high-grade cancer *(4)*. These two phenomena (higher sensitivity for cancer detection with finasteride and higher risk of high-grade disease with higher PSA levels) would be expected to artificially increase high-grade cancer detection in men treated with finasteride.

Our study has several potential limitations. Regarding generalizability, the men in this study were generally healthy, had a median age of 62 at registration, and were predominantly white. Thus, our conclusions may not apply to other populations. In addition, not all men who were recommended for a biopsy had one, and more men on the placebo arm accepted the biopsy recommendation *(1)*. These factors are not an issue as long as the sample of included participants (i.e., those who underwent biopsy) do not differ in any systematic fashion from the not-included participants (i.e., those who did not undergo a biopsy) of each study group in terms of all factors—demographics, distribution of PSA values, DRE results, and prostate cancer rates—as well as in the relationship among these factors. Table 1 showed that, within the placebo group, participants undergoing biopsy were more likely to be younger and to have a family history of prostate cancer than those who did not undergo biopsy and that no such difference was found within the finasteride group. If the operating characteristics of PSA are truly worse in this category of men than in others, it would artificially translate into better operating characteristics for PSA in men in the finasteride group. However, our analyses of the effect of age within included participants showed increased AUC for younger men, which would bias a higher AUC in favor of the placebo group and not in favor of finasteride. For both the finasteride and placebo groups, included participants had substantially more PSA and DRE screens than not-included participants, and there were more PSA and DRE screens in the finasteride than placebo subjects. Although this set of circumstances could contribute to better ROCs of PSA in the finasteride group, it is unclear how this potential bias balances with the increased number of biopsies performed in the placebo group. The high rates of end-of-study biopsies performed regardless of PSA and DRE results, which were equal across both arms, imply that increased PSA, DRE, or biopsy screens in each group are unlikely to have biased the results observed.

The central finding of this analysis, i.e., that finasteride increased the sensitivity of PSA testing for detecting overall and high-grade prostate cancer, has three major implications. First, the increased risk of high-grade disease with finasteride in the PCPT was due, at least in part, to improved detection (i.e., increased sensitivity of PSA) rather than solely to true induction of high-grade disease by finasteride. Second, finasteride may improve the performance of PSA screening in the general population. Clinically, if finasteride does not reduce PSA by at least 50%, a man is more likely to have prostate cancer than if such a reduction is seen. Treatment with finasteride may be particularly helpful for determining the need for a repeat biopsy in men with a previously negative PSA measure-prompted biopsy. Finally, because PSA testing had better performance for identifying men with prostate cancer in the finasteride group, the 24.8% decrease in the 7-year period prevalence of prostate cancer reported among men on the finasteride arm of the PCPT is likely to be an underestimate of the actual reduction in prostate cancer risk with finasteride *(1)*.

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Notes

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