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Does the level of prostate cancer risk affect cancer prevention with finasteride?

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Abstract

Objectives—Finasteride reduced the risk of prostate cancer by 24.8% in the Prostate Cancer Prevention Trial; whether this represents treatment or prevention and who is most likely to benefit are unknown. We sought to clarify these issues by this investigation.

Methods—We fit a logistic regression model to men in the placebo group of the PCPT using risk factors for prostate cancer at entry to predict prostate cancer during the subsequent 7 years of study. Men in the two treatment groups were categorized into quintiles of risk of prostate cancer based on the predictive logistic model. A second model was fit evaluating finasteride's effect on prostate cancer for each subgroup defined by quartiles of baseline PSA. The magnitude of the prevention effect of finasteride on prostate cancer was then evaluated across risk and PSA strata.

Results—Finasteride significantly reduced prostate cancer risk for all risk quintiles. For quintiles 1 through 5, odds ratios were 0.72, 0.52, 0.64, 0.66, and 0.71, respectively (all $p \leq 0.05$). For quartiles of risk of entry PSA (< 0.7 ng/mL, 0.7–1.1 ng/mL, 1.1–1.7 ng/mL, and 1.8–3.0 ng/mL), odds ratios increased (smaller treatment effect) as PSA increased: 0.60, 0.62, 0.66, and 0.69 respectively, but remained significant for all strata (each $p < 0.001$).

Conclusions—Finasteride significantly reduced prostate cancer risk, regardless of the level of this risk, estimated either by multivariable risk or by PSA stratum; this suggests that finasteride exerts both treatment and preventive effects. All men undergoing PSA screening should be informed of the potential for finasteride to reduce their risk of prostate cancer.

Keywords

Prostate neoplasms; prostate specific antigen; risk; finasteride; prevention

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The Prostate Cancer Prevention Trial (PCPT), completed in 2003, reported a 24.8% reduction in the risk of prostate cancer for men at low risk of prostate cancer who were randomized to receive finasteride daily for seven years.¹ Since that time, the trial's results have received considerable scrutiny. Initially, concern over the higher number of high grade prostate cancers detected in the men who received finasteride led to little interest in using this medication for this purpose. Since the time of the trial's initial report, analyses have demonstrated that at least three biases were operational in increasing the detection of high grade cancers including (1) improved performance of PSA [greater sensitivity] for detection of cancer and high grade cancer with finasteride², (2) improved performance of digital rectal examination in men receiving finasteride³, and (3) better sampling and grading of biopsies performed in men receiving finasteride due to the drug's reduction of gland volume.⁴

A number of consensus statements have been developed or are under development in several countries regarding the use of finasteride. An issue that frequently arises is how to select a man who should receive finasteride. Some have suggested offering the medication to high-risk men. The wide range of cancer risk among the 18,882 PCPT participants, allows a rigorous assessment of this important clinical question.

In addition, a fundamental question regarding the mechanism of finasteride chemoprevention (treatment versus prevention) has arisen as a result of the high end-of-study positive biopsy rate (15%) among men who had PSA values below 4.0 ng/mL⁵ throughout the seven-year study and among men whose PSA values were less than or equal to 3.0 ng/ml after seven years on-study (14%). These data suggest that, among men meeting the PCPT eligibility requirement of PSA less than or equal to 3.0 ng/ml, at least 14% had undiagnosed cancer at the time of enrollment.⁵ With this recognition, the student of this disease could ask the question: was the primary effect of finasteride to *prevent* or *treat* prostate cancer? We herein also explore this issue.

Materials and Methods

The Prostate Cancer Prevention Trial randomized 18,882 men to either finasteride 5 mg per day or to placebo. Eligible men had a PSA of 3.0 ng/mL or less, a normal digital rectal examination (DRE), were over age 55, and had no previous diagnosis of prostate cancer. Annually, PSA and DRE were performed. In the placebo group, if PSA exceeded 4.0 ng/mL or if DRE was abnormal, a biopsy was recommended. Similar recommendations were given for men in the finasteride group with an adjustment in PSA made centrally so as to result in a similar number of biopsy recommendations. After 7 years of therapy, all men who had not previously been diagnosed with prostate cancer, were recommended to undergo a prostate biopsy.

In this study, we examined all men who had a study endpoint defined as an interim prostate cancer or an end-of-study biopsy performed within ± 90 days of a patient's seven year anniversary on the study. Only men with an endpoint obtained before the unblinding of study results in June 2003 are included in the analysis.

To determine the risk at study entry of being diagnosed with prostate cancer during the subsequent seven years of the PCPT, we fit a logistic regression model to the men randomized to the placebo group who had a study endpoint. The dependent variable was prostate cancer (Yes vs. No) with four baseline risk factors in the model: (1) age at study entry, (2) PSA at study entry, (3) Race: African American vs. Other, and (4) family history of prostate cancer: Yes vs. No. This risk equation differs from the Prostate Cancer Prevention Trial risk calculator because it excludes prior negative biopsy and DRE status at time of biopsy, because we did not want to use risk factors that were evaluated post-randomization.⁶ The prostate cancer

logistic model that was built from the placebo group was then applied to men from both treatment groups using the values of their baseline risk factors to get a predicted probability of prostate cancer. Men on both treatment arms were categorized into quintiles based on the magnitude of their predicted probability of prostate cancer, with roughly equal numbers of men from each treatment group in each quintile category. A logistic regression model was then fit for each of the quintile subsets where prostate cancer was the dependent variable and treatment assignment (1=finasteride, 0=placebo) was the independent covariate. To evaluate the interaction of quintiles with finasteride, a logistic model was fit to all men with indicators for the quintiles of risk and treatment, and a residual score chi-square was used to calculate the four degree of freedom interaction term.

To evaluate whether the effect of finasteride varied by baseline PSA, by itself a significant predictor of prostate cancer, a logistic regression model of prostate cancer was fit for men in each quartile of PSA, and the finasteride odds ratio was estimated. The PSA $\times$ treatment interaction was tested with the three degree of freedom residual chi-square in the full model which included three indicators for quartiles and finasteride. All analyses used the Logistic procedure in SAS, version 9.0.

Results

The overall study patient characteristics have been previously reported.¹ The median age at study entry was 63 years, 4% were African American, 92% were white, and 2% identified themselves as another race. 15% of men reported having a first degree family member with prostate cancer. PSA values at enrollment were 0 – 1.0 ng/ml in 48%, 1.1 – 2.0 ng/ml in 36%, and 2.1 – 3.0 ng/mL in 16%.

Just over 2000 men were categorized in each of the quintiles for a total of 10,181 men (4958 finasteride, 5223 placebo). The lowest quintile of risk had a probability of prostate cancer less than 0.14, and the group with the highest probability, with four times the number of cases, had individual probabilities of cancer greater than 0.31. As can be seen in Table 1, finasteride's effect was lowest for the first and last quintiles (odds ratio for treatment 0.72, 0.71, respectively), whereas the middle quintiles had odds ratios of 0.52, 0.64, and 0.66. However, as can be seen in Figure 1, the 95% confidence interval for the finasteride odds ratio overlapped for each of the quintiles. The confidence interval is widest for the first quintile because of the lower event rate. In each of the five intervals, finasteride significantly reduced the risk of prostate cancer (each $p \leq 0.05$).

Because PSA was the strongest predictor in the PCPT risk calculator, we hypothesized that perhaps PSA at study entry is a more informative predictor of who had prostate cancer at study entry. In Table 2, the odds ratio for finasteride versus placebo for the outcome of prostate cancer is reported for each quartile of PSA (each $p < 0.001$). The odds ratio increases slightly with each PSA quartile (OR = 0.60, 0.62, 0.66 and 0.69). As with the risk quintiles, the 95% confidence interval for each PSA quartile overlaps with the others.

Discussion

This analysis was born out of this question: did finasteride *prevent* or *treat* prostate cancer and thereby reduce the risk of cancer detection in men who received this drug? When the PCPT was designed in the early 1990's, information suggested that men who enrolled would have an approximate 2% risk of prostate cancer if a biopsy were performed.⁷ As a result, it was thought that any reduction in prostate cancer risk would actually be through *prevention*. At the time of early study closure, it was apparent that there were far more prostate cancers detected than had been predicted and that many of these tumors were found at lower levels of PSA; levels below

4.0 ng/mL. Our subsequent analysis confirmed that the risk of prostate cancer among those men undergoing end of study prostate biopsy was 15%; of these men, 15% had high grade disease.⁵ Given that this group was restricted to those men who, over 7 years, never had a PSA above 4.0 ng/mL nor an abnormal DRE, the risk of prostate cancer among men at enrollment may have been even greater.

Recognizing that if prostate cancer is not uncommon among men who had PSA values less than 3.0 ng/mL, it has been questioned whether the reduction in risk seen with finasteride was due to *treatment* of these smaller tumors. If we assume that finasteride actually treated or eliminated some prostate cancers, one would expect the benefit of finasteride to be greatest among those men at greatest risk of harboring occult disease at study entry. Conversely, if finasteride exerted a predominantly preventive effect, the greatest benefit would be expected among those least likely to have prostate cancer at baseline. Figure 2 displays how these two curves would appear. The greatest effect (lowest odds ratio^a) of finasteride if it treated prostate cancer would be at the highest risk quintile at entry. Conversely, if the drug prevented cancer, the curve would be the opposite.

When we stratify men by risk of prostate cancer at the time they enrolled in the study, calculated using risk factors for the disease, the resulting reduction in risk of cancer with finasteride across the quintiles of risk are inconsistent with a pure treatment effect. Interestingly, the magnitude of risk reduction for the highest and lowest quintiles of risk was similar, while the second lowest risk quintile was associated with the lowest relative risk of prostate cancer with finasteride. However, the 95% confidence intervals were wide. Similarly, if we examine the magnitude of the effect of finasteride by PSA quartile, there is a relatively narrow range of odds ratios with over-lapping confidence intervals, again suggesting a decrease in finasteride efficacy with increasing risk, consistent with a cancer prevention effect.

Given what is known about finasteride, is it possible that the agent may ‘treat’ some prostate tumors? (We must recognize that our surrogate of treatment effect in this study is an inability to detect cancer with biopsy; an alternative explanation is that the tumors decreased in size sufficiently to prevent detection.) The evidence of a treatment effect is not clear as most studies have employed the agent in patients with metastatic disease, most of whom had high-grade disease. Presti, in a small randomized study, found significantly-greater reduction in the rate of change of PSA in men with metastatic disease who received finasteride compared with placebo.⁸ Another small single-arm study of 13 subjects with advanced disease found no significant change in PSA with finasteride.⁹ Others have successfully used the combination of finasteride and flutamide for the treatment of advanced disease.^{10,11,12} Perhaps the best study of the drug in patients with earlier stage disease was a randomized, placebo-controlled study of 120 men with detectable PSA after radical prostatectomy.¹³ The authors found a significant delay in PSA progression after treatment. Intriguingly, among those men with PSA levels below 1.0 ng/mL who received finasteride, no subsequent increase was seen in PSA over the course of the study. Several preclinical models have documented activity of five alpha reductase inhibitors against prostate neoplasms.^{14,15,16}

Although we had initiated this analysis with the purpose of evaluating the prevent/treat hypothesis, the results speak to the clinical use of finasteride for reducing a man’s risk of a prostate cancer diagnosis. The magnitude of risk reduction appears to be substantial across the ranges of risk, from the lowest (risk of prostate cancer < 14%) to the highest risk range (risk of prostate cancer > 31%). The implication of this analysis is that the man who is undergoing

^aAn odds ratio is the measure of the magnitude of effect. It is defined as the ratio of the odds of an event (in this case, cancer) in one group compared to the odds of the event in another group. In this case, the odds ratios refer to the risk of cancer among men treated with finasteride versus those who received placebo; the lower the value, the greater the cancer risk reduction with finasteride.

regular screening with PSA and DRE for the early detection of prostate cancer should be informed of the potential preventive role of finasteride, regardless of his level of risk. This is especially important given that the majority of men diagnosed with prostate cancer do not have any identifiable risk factors other than age. (For example, in the PCPT only 21% of men ultimately diagnosed with prostate cancer had a first degree relative with prostate cancer.) As a result, focusing only on men with specific risk factors would leave many men without an opportunity to reduce their risk of prostate cancer. Given that the number of men needed to treat with finasteride for seven years to prevent one cancer case is in the 12–14 range for all quintiles of risk except for the first in which the value is 42, and as this is in the range of other commonly-used preventive interventions such as aspirin to prevent cardiovascular disease, it would be reasonable to inform all men over the age of 55, and especially those men undergoing PSA screening, of this potential preventive intervention.¹⁷ We hope that these data will be helpful for informative discussions with men at risk of prostate cancer and for subsequent analyses regarding resource allocation for disease prevention.

Conclusion

When men who enrolled in the Prostate Cancer Prevention Trial were stratified by their risk of prostate cancer at the time of study enrollment, all strata of risk exhibited a statistically significant reduction in risk of subsequent prostate cancer with administration of finasteride. All men who are undergoing regular PSA and DRE screening should be informed of these results.

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Figure 1.
Estimated odds ratio of prostate cancer for finasteride vs. placebo group, stratified by quintile of prostate cancer risk

Figure 2.
Hypothetical figure for two effects of finasteride: prevention or treatment.

Table 1
Effect of Finasteride Treatment by Prostate Cancer Risk Group at Study Entry

Quintile of Predicted Prostate Cancer Risk	Number of subjects/cases	Predicted Probability of Prostate Cancer range	PSA (ng/ml) range	Odds ratio (finasteride/placebo) 95% confidence interval	p-value	Number Needed to Treat [#] to Prevent One Cancer Case
1	2040/159	<0.14	0.3–0.9	0.72 (0.51, 1.00)	0.05	42.2
2	2012/288	0.14–0.18	0.2–1.3	0.52 (0.40, 0.67)	<0.0001	12.8
3	2050/404	0.18–0.23	0.3–1.8	0.64 (0.51, 0.79)	<0.0001	14.1
4	2043/488	0.23–0.31	0.3–2.5	0.66 (0.54, 0.81)	<0.0001	13.3
5	2036/676	>0.31	0.6–3.0	0.71 (0.59, 0.86)	0.0003	13.4

[#] treat for duration of PCPT trial: 7 years

Test of interaction of quintiles of risk × finasteride: 4 degree of freedom chi-square, $p=0.38$

Table 2
Effect of Finasteride Treatment by Quartile of PSA at Study Entry

Quartile of PSA at Study Entry	PSA level	Number of Subjects/Cases	Odds ratio(finasteride vs. placebo) and 95% CI	p-value	Number Needed to Treat [#] to Prevent One Cancer Case
1	< 0.7	2402/229	0.60 (0.45, 0.80)	0.0004	23.5
2	0.7 – 1.1	2319/365	0.62 (0.49, 0.78)	<0.0001	16.2
3	1.1– 1.7	2881/623	0.66 (0.55, 0.79)	<0.0001	14.3
4	1.8–3.0	2579/798	0.69 (0.59, 0.88)	<0.0001	12.8

[#] treat for duration of PCPT trial: 7 years

Test of interaction of quartiles of PSA × finasteride: 3 degree of freedom chi-square, p=0.81