Finasteride Does Not Increase the Risk of High-grade Prostate Cancer: A Bias-adjusted Modeling Approach

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Abstract

The Prostate Cancer Prevention Trial found that seven years of administration of finasteride reduced the risk of prostate cancer by 25% but with an apparent increased risk of high grade disease. Subsequent analyses found that finasteride affects cancer detection and improves accuracy of tumor grading at biopsy. We herein estimate the impact of finasteride on the risk of overall and high grade prostate cancer, accounting for these biases. Study endpoints (biopsy-proven cancer or a 7-year end-of-study biopsy) were available in 10,182 of 15,990 subjects assessable for 7-year status and grading information from 500 subjects diagnosed with cancer who underwent radical prostatectomy. Prostate cancer was observed in 22.9% (4.8% with high grade) in the placebo group versus 16.6% (5.8% with high grade) in the finasteride group. In this bias-adjusted analysis, the estimated rates are 21.1% (4.2%) and 14.7% (4.8%), respectively, a 30% risk reduction in prostate cancer (RR =0.70 (95% confidence interval (CI) =0.64-0.76, $p<0.0001$) and a non-significant 14% increase in high grade cancer (RR=1.14 (95% CI = (0.96-1.35), p=0.12) with finasteride. Incorporating the prostatectomy data, estimated rates of high grade cancers are 8.2% (placebo) versus 6.0% (finasteride), a 27% risk reduction (RR = 0.73 (95% CI=0.56-0.96, p=0.02)) with finasteride. While the observed risk of high grade disease is greater with finasteride, this appears to be through facilitated diagnosis, primarily due to increased biopsy sensitivity. Men undergoing regular prostate cancer screening or who express an interest in cancer prevention should be informed of this prevention opportunity.

Background

With one man in seven in the U.S. expected to develop prostate cancer in his lifetime due primarily to aggressive screening for the disease and with an uncertain impact of screening on morbidity and mortality as well as a human and economic cost of treatment, prevention of this common disease is an attractive public health strategy.[1,2,3] The Prostate Cancer Prevention Trial was initiated in 1993, testing the hypothesis that finasteride, a selective inhibitor of type 2 five-alpha reductase, could reduce the risk of prostate cancer detection. Fifteen months prior to planned study completion, the independent Data and Safety Monitoring Committee recommended closure due to overwhelming evidence that the primary endpoint had been reached: a 25% reduction in risk of prostate cancer with finasteride.[4] Concurrent with this observation was an apparent higher risk of high-grade disease with finasteride. While the number of high grade tumors was considerably smaller than the overall number of tumors detected, the increased risk of aggressive disease as well as an editorial accompanying the initial publication counseling against its use for prevention, led to little use of this agent for cancer prevention.[5] In the U.S., early detection and treatment remain the primary foci for control of this disease.

Since the initial publication of the primary outcome of this study, analyses of these contrasting conclusions have continued as well as a widespread debate on the utility of finasteride for prostate cancer prevention. Analyses have uncovered a series of effects of finasteride on the detection of prostate cancer including improved performance characteristics of for-cause biopsies by (a)

improved sensitivity of PSA for cancer and high grade cancer detection in subjects receiving finasteride, (b) improved sensitivity of digital rectal examination for cancer detection in subjects receiving finasteride, and (c) the suspected improvement in detection and more accurate grading of high grade prostate cancer with prostate biopsy in those subjects receiving finasteride.[6,7,8] While these three detection biases would be expected to lead to 'over detection' of tumors in study subjects receiving finasteride, there was a counteracting bias for greater cancer detection in men in the placebo group who more commonly underwent biopsy.

To better understand the cumulative effect of these biases on detection of prostate cancer in the PCPT, we conducted a set of analyses to explore the impact of finasteride on both prostate cancer and high grade disease had all study participants submitted to an endpoint biopsy. These analyses account for the selection biases attributable to improved detection of cancer by for-cause biopsies with finasteride. We then conducted an analysis to estimate the true prevalence of high grade prostate cancer among men with biopsy-detectable prostate cancer, using information from the subset of patients who underwent radical prostatectomy. Radical prostatectomy is a procedure that allows a more definitive evaluation of actual tumor grade whereas biopsy has been shown to be less reliable and varies in accuracy by finasteride versus placebo. Finally, we examine the impact of imperfect sensitivity of biopsy (to detect prostate cancer) on the prevalence within each treatment arm and the overall risk reduction associated with finasteride.

Materials and Methods

The Prostate Cancer Prevention Trial randomized 18,882 eligible men to receive either placebo or finasteride for seven years and to be followed for 7-year period prevalence of prostate cancer. Prostate biopsy was performed either due to an abnormal digital rectal examination (DRE) or an 'elevated' PSA. An elevated PSA was defined as either a value above 4.0 ng/mL in the placebo group or an adjusted value in the finasteride group that annually resulted in a similar number of biopsy recommendations.[9,10] All cancer-free men were recommended to undergo an end-of-study prostate biopsy after 7 years of study participation, regardless of PSA or DRE findings. The trial was closed early due to overwhelming evidence that finasteride significantly reduced the risk of prostate cancer. At the time of the initial publication of results, a 25% reduction in the 7-year period prevalence of prostate cancer attributable to finasteride was observed. These results were based on a dataset frozen in March 2003. Subsequent analyses use data through the day of the trial unblinding (June 23, 2003) yielding additional cases that result in an observed risk reduction of 28%. It is this larger dataset we use for the present analyses.

For the present analyses, a man was defined to have an endpoint if he had an interim diagnosis of prostate cancer or if he underwent an end-of-study biopsy within 90 days of his 7-year anniversary of his randomization or by June 23, 2003 (which ever came first). Due to early closure of the study, 15,990 (85%) of the 18,882 men were assessable for the endpoint. Endpoints were observed in 8024 men on the placebo arm and 7966 men on the finasteride arm for a total

of 10,182 (64%) of the 15,990 men. A 60% compliance rate for endpoint ascertainment was specified in the protocol design assumptions. For the purposes of this paper, we will consider the study's sample size to be the 15,990 men who reached their seven year anniversary when the study was reported and unblinded. High grade prostate cancer was defined as a Gleason score of 7 or higher.

A. Predicting prostate cancer prevalence if all subjects had an endpoint

It is likely that men who did not have an endpoint evaluated have a different underlying probability of prostate cancer than those who did have an endpoint evaluated. In order to estimate the cancer prevalence if all subjects had an endpoint, a reasonable and often employed assumption is that that there are measured study covariates which both explain the differences between men with and without endpoints and are related to the risk of prostate cancer. [11] Under this assumption, for two men with similar covariate values, such as age, family history of prostate cancer, and treatment arm assignment, one with an endpoint evaluated and one without, the outcome data from the man with the evaluated endpoint informs the cancer status for the man without the endpoint evaluation.

An approach which employs this assumption and can be used to estimate the prevalence of prostate cancer and high grade disease is Inverse probability of censoring weighted (IPCW) estimation. [12] Use of this analysis approach is a two-step process; the first step is to estimate the probability of having an endpoint evaluated conditional on covariates and the second step is to estimate

the probability of cancer given the probabilities estimated in the first step. The probability of cancer is estimated by the weighted average of cancers within each treatment arm among men with observed endpoint, using the inverse of the probabilities from the first step as weights.

To estimate the probability of having an endpoint evaluated in the first step, logistic regression was used. To model the predicted probabilities, we chose study covariates related to both (a) having the study endpoint and (b) having a diagnosis of prostate cancer. The baseline covariates that were included in these analyses were treatment arm, age, ethnicity/race, prostate-specific antigen value, and family history of prostate cancer. Covariates measured after randomization that were included in this analysis were interim biopsy prompts based on PSA levels or digital rectal examination and ever having a negative biopsy result during follow-up and before end of study. The weights were then calculated as the inverse of the fitted (predicted) probabilities for men with an endpoint evaluated. The same weights and approach were used to estimate the prevalence of biopsy-detectable high grade cancers in each treatment arm.

B. Predicting high grade prostate cancer by integrating prostatectomy data

The previous analysis attempts to account for selection bias between the treatment arms regarding which participants have a study endpoint evaluated. In particular, it addresses the bias that fewer biopsies were conducted in the finasteride group, a bias in favor of finasteride, and the bias associated with

improved performance of PSA and DRE for indication of for-cause biopsies, a bias in favor of placebo.

The next analysis performed was to account for the effect of finasteride on the improved accuracy of prostate biopsy on Gleason grading in men on finasteride due to reduced prostate gland volume. Prostatectomies were known to be performed and data were available on 500 of 2017 subjects with cancer. This analysis proceeded as the first analysis; first, a logistic regression model was used to estimate the probability of prostatectomy conditional on covariates for the subset of men diagnosed with prostate cancer. Next, the prevalence of high grade cancer among men with a cancer diagnosis was estimated by the weighted proportion of men with high grade disease determined by prostatectomy, using a weight that is the inverse of the probability of having had both a biopsy and prostatectomy. The overall prevalence of high grade cancer within each treatment arm was then estimated by the product of a) the estimates from this analysis (the probability of high grade disease among men with cancer) and b) the estimates of prostate cancer prevalence from the first analysis.

C. Impact of differential biopsy sensitivity on disease prevalence

The first two analyses addressed biases related to imperfect ascertainment of biopsy endpoints on all study participants and differentially inaccurate grading of disease severity by biopsy between the treatment arms. The first analysis accounted for biases related to missing endpoints to estimate the overall prevalence of biopsy-detectable prostate cancer and high grade cancer. The second analysis accounted for biases related to more accurate

grading of high grade disease with finasteride to estimate the prevalence of true high grade cancer (as determined by prostatectomy) among participants with *biopsy-detectable* prostate cancer.

These analyses employ the assumption that biopsy perfectly detects cancer; although there is substantial evidence that 1) biopsy operating characteristics are less than perfect and 2) the operating characteristics are improved under finasteride. The final analysis addressed the impact that a plausible range of biopsy sensitivity values would have on the true underlying risk of prostate cancer and high grade cancer in each arm. For this analysis we assumed that biopsy has perfect specificity (the probability of a negative biopsy given no cancer equals 1.0) and perfect positive predictive value (probability of cancer given a positive biopsy equal 1.0).[13] The probability of true cancer within each treatment arm is then estimated by the proportion of observed cancers divided by the sensitivity (the probability of a positive biopsy given cancer). Biopsy sensitivity to detect cancer was also incorporated into estimates of high grade cancer prevalence in the same way. This employed an additional assumption that the true presence of high grade cancer did not depend on whether cancer status was observed or not. This is a somewhat strong assumption if in fact the hypothesis that high grade tumors are more prominent is true, thereby making cancer more easily detectable on biopsy. If the sensitivity was equal across treatments, then the risk ratio would be unaffected by imperfect sensitivity. Alternatively, if the sensitivities are not equal across treatments then the true risk ratio is equal to the observed ratio multiplied by the sensitivity of

biopsy under placebo divided by the sensitivity under finasteride. Therefore, if biopsy sensitivity under finasteride is larger than under placebo, the risk reduction is underestimated and if the sensitivity is smaller under finasteride then the risk reduction is overestimated.

All of the analyses presented include weights that are a function of measured covariates. Since the weights are estimated, their inclusion affects the variability of overall prevalence and risk estimates. To account for estimation of the weights, 10,000 bootstrap samples of the observed data were constructed. The analysis procedures were repeated on each data set and the variance of the prevalence estimates was estimated by the variance over all samples. All analyses were done in Splus (Insightful Co., Seattle, WA).

Results

Table 1 presents a comparison of the characteristics of men with and without a study endpoint. Characteristics determined to be associated with a reduced odds of having an endpoint were randomization to finasteride (OR=0.89) and older age (OR=0.98). Additionally, white race versus other race/ethnicities, family history of prostate cancer, interim biopsy prompts based on PSA or DRE and a negative interim biopsy were all associated with an increased odds of having an endpoint. While PSA at randomization was marginally associated with an increased odds of observed endpoint (OR = 1.14, $p < 0.0001$) the association was no longer significant after adjusting for other covariates ($p=0.6$).

Table 1 Comparison of men with and without endpoint evaluated

	Endpoint evaluated			
	No	Yes		
N (%) /mean±std	N=5,809	N=10,181	OR *(95% CI)	p-value*
Treatment arm				
Finasteride	3,008 (52%)	4,958 (49%)	0.89 (0.84-0.95)	0.0007
Placebo	2,801 (48%)	5,223 (51%)	1.0 (ref.)	
Age at randomization	63.4±5.9	62.9±5.4	0.98 (0.97-0.99)	<.0001
Race				
White	5,297 (91%)	9,483 (93%)	1.37(1.21-1.55)	<.0001
Other	512 (9%)	699 (7%)	1.0 (ref.)	
Family history of PCA				
Yes	782 (13%)	1,698 (17%)	1.23 (1.12-1.35)	<.0001
No	5,026 (87%)	8,484 (83%)	1.0 (ref.)	
PSA at randomization	1.2±0.7	1.3±0.7	0.99 (0.94-1.04)	0.60
Prior negative study biopsy				
Yes	463 (8%)	1,349 (13%)	1.60 (1.43-1.80)	<.0001
No	5,345 (92%)	8,833 (87%)	1.0 (ref.)	<.0001
Biopsy prompt for Elevated PSA				
Yes	69 (1%)	803 (8%)	6.80 (5.32-8.84)	<.0001
No	5,739 (99%)	9,381 (92%)	1.0 (ref.)	
Biopsy prompt for Suspicious DRE				
Yes	82 (1%)	830 (8%)	5.66 (4.52-7.18)	<.0001
No	5,726 (99%)	9,352 (92%)	1.0 (ref.)	

*From a multivariable logistic regression model with endpoint evaluated (yes/no) as the outcome, adjusting for other factors in Table 1.

A. Predicting prostate cancer prevalence if all subjects had an endpoint

Prostate cancer prevalence results from the analyses accounting for non-random missing biopsy results are presented in Table 2. The observed rates of prostate cancer for the 5223 men in the placebo group and 4959 men in the finasteride group with an endpoint were 22.9% and 16.6%, respectively. Had all subjects had a biopsy endpoint, our analysis suggests that the true rate of cancer in the 8024 men in the placebo group would have been 21.1% and in the 7966

men in the finasteride group would have been 14.7%. As expected, these percentages are slightly smaller than what was observed, suggesting that the men without the endpoint evaluated were slightly less likely to have prostate cancer. Similarly, while the observed rates of high grade cancer in the placebo and finasteride groups were 4.8% and 5.8%, respectively, our analysis estimates that the true rates of high grade cancer are 4.2% and 4.8%, respectively. Of interest, the relative risk of prostate cancer is changed minimally from the raw data (0.72 vs. 0.70). The risk of high grade disease associated with finasteride after accounting for the missing data decreased from an observed and significant 21% increased risk to a non-significant 14% increased risk (p=0.12).

Table 2 Observed and **estimated** numbers and proportions of **prostate** cancer detected on biopsy

	Placebo arm N=8024	Finasteride arm N=7966	RR (95% CI)
Prostate Cancer			
Estimate of overall prevalence	1693 (21.1%)	1171 (14.7%)	0.70 (0.64-0.76)
Observed	1194 (22.9%)	823 (16.6%)	0.72 (0.67-0.79)
High grade cancer			
Estimate of overall prevalence	337 (4.2%)	382 (4.8%)	1.14 (0.96-1.35)
Observed	252 (4.8%)	288 (5.8%)	1.21 (1.02-1.42)

B. Predicting high grade prostate cancer by integrating prostatectomy data

The target of this analysis was to estimate the high grade prostate cancer status if all biopsy-detected cancers had undergone prostatectomy. Study participants who underwent radical prostatectomy were not a random sample of the participants with cancer detected on biopsy. While treatment group, family history, white race, a prior negative study biopsy, and high grade cancer on

biopsy did not significantly impact on whether a prostatectomy was performed and the results were available, younger age, PSA at randomization, biopsy prompt by PSA or DRE were positively and significantly associated with having a prostatectomy (Table 3). The majority of biopsies associated with a prompt by PSA or DRE (so-called for-cause biopsies) were interim biopsies. It follows, for interim biopsies, there was a longer time observed post-diagnosis to both have a prostatectomy and to observe/obtain the prostatectomy results.

Table 3 Comparison of men with and without prostatectomy verification of biopsy result

	No prostatectomy N=1517	**Prostatectomy** N=500	**OR (95% CI)***	**p-value***
Treatment arm				
Finasteride	617 (41%)	206 (41%)	0.97 (0.78-1.21)	0.80
Placebo	900 (59%)	294 (59%)	1.0 (ref.)	
Age at randomization	64.6±5.6	61.1±4.2	0.86 (0.84-0.88)	<.0001
Race			1.0 (ref.)	
White	1,403 (92%)	466 (93%)	1.41 (0.94-2.16)	0.11
Other	114 (8%)	34 (7%)	1.0 (ref.)	
Family history of PCA				
Yes	317 (21%)	117 (23%)	1.02 (0.78-1.31)	0.90
No	1,200 (79%)	383 (77%)	1.0 (ref.)	
PSA at randomization	1.6±0.8	1.7±0.7	1.25 (1.07-1.82)	0.006
Prior negative biopsy			1.0 (ref.)	
Yes	206 (14%)	67 (13%)	1.05 (0.76-1.44)	0.78
No	1,311 (86%)	433 (87%)	1.0 (ref.)	
Biopsy prompt for PSA				
Yes	350 (23%)	154 (31%)	1.4 (1.07-1.82)	0.01
No	1,167 (77%)	346 (69%)	1.0 (ref.)	
Biopsy prompt for DRE				
Yes	281 (19%)	123 (25%)	1.69 (1.30-2.18)	<.0001
No	1,236 (81%)	377 (75%	1.0 (ref.)	
High Grade on biopsy				
Yes	391 (26%)	149 (30%)	1.26 (0.98-1.61)	0.07
No	1,126 (74%)	351 (70%)	1.0 (ref.)	

*From a multivariable logistic regression model with prostatectomy (yes/no) as the outcome, adjusting for other factors in Table 3.

High grade cancer prevalence estimates from the analysis which incorporated the prostatectomy data are 8.2% in the placebo arm and 6.0% in the finasteride arm (see Figure 1). This results in an estimated number of high grade cancers on the finasteride arm to be 478 and 658 on the placebo arm.

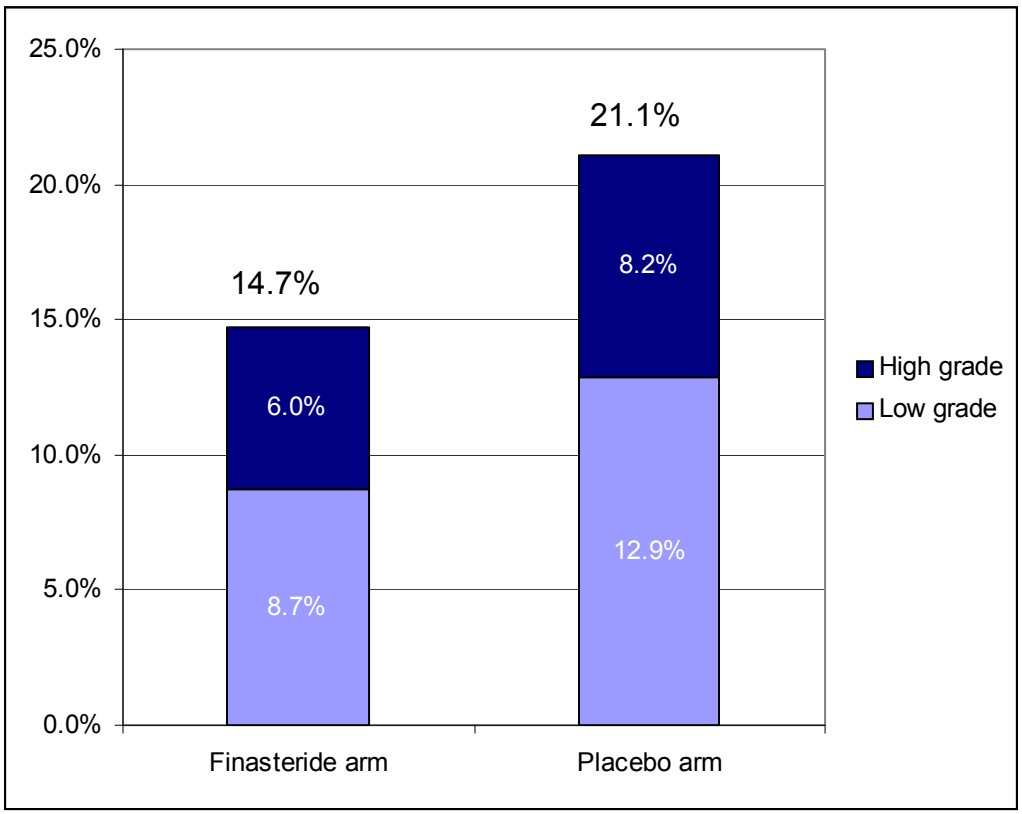

Figure 1 Low and high grade cancer status by treatment arm by prostatectomy Estimated actual fractions of total subjects with low and high-grade cancer

The estimated risk reduction with finasteride for Gleason ≤ 6 is 34% (RR (95% CI) = 0.66 (0.55-0.80), p=<0.0001) and for Gleason ≥ 7 is 27% (RR (95% CI) 0.73 (95% CI=0.56-0.96, p=02).

C. Impact of differential biopsy sensitivity on disease prevalence

Lastly, we explored what ranges of biopsy sensitivity pairs would need to be operational to change the original conclusions of the study with respect to high grade disease. From the prostatectomy data, there is evidence that finasteride improves the biopsy sensitivity and therefore there is likely greater sensitivity of biopsy to detect both cancer and high grade cancer on the finasteride arm. The most likely cause of improved sensitivity of biopsy under finasteride is its impact on prostate volume.

In order to understand how different sensitivities of prostate biopsy for detection of prostate cancer and high grade cancer in men receiving finasteride or placebo might affect observed rates of disease, we constructed Table 4 using data from this last analysis. We used a range of values of biopsy sensitivity from 50% to 90%. Prevalence estimates are presented for both high grade disease detected by biopsy and as determined by prostatectomy. The prevalence estimates in the first two columns represent the probability of true high grade cancer accounting for biopsy sensitivity to detect high grade cancer. The second set of prevalence estimates in the last two columns represent the true high grade cancer prevalence accounting for biopsy sensitivity to detect prostate cancer, using the prostatectomy data to determine the severity of cancer. It is likely that within a treatment arm, the sensitivity of biopsy to detect high grade cancer versus any cancer is not the same. This Table allows an understanding of how different pairs of sensitivities of biopsy may affect observed rates of cancer detection. For example, if the sensitivity for high grade prostate cancer in the

finasteride arm is 80% and 70% for the placebo arm the resulting actual risk of high grade disease on biopsy would be 6% and 6%, equal to no difference in high grade prostate cancer prevalence on biopsy. Alternatively, if the sensitivity for prostate cancer ; cancer in the finasteride arm is 80% and 70% for the placebo arm taking into account the change in grade anticipated with prostatectomy, the risk of high grade disease being truly present would be 7.5% and 11.7% respectively, equal to a 36% reduction in risk of high grade cancer prevalence with finasteride. The observed risk ratios estimate the risk reduction in biopsy-detectable high grade prostate cancers whereas the sensitivity-adjusted risk ratios are estimates of the risk reduction in true high grade prostate cancer prevalence.

Table 4 High grade cancer prevalence estimates under sensitivity of biopsy to detect cancer

Biopsy sensitivity	High grade on biopsy		High grade on prostatectomy	
	Placebo	Finasteride	Placebo	Finasteride
50%	8.4%	9.6%	16.4%	12.0%
60%	7.0%	8.0%	13.7%	10.0%
70%	6.0%	6.9%	11.7%	8.6%
80%	5.2%	6.0%	10.2%	7.5%
90%	4.7%	5.3%	9.1%	6.7%

Using these data, Figures 2 and 3 present the risk ratios under all pairs of sensitivity of prostate biopsy (for finasteride and placebo) to detect high grade cancer. The purpose of Figure 2 is to Beginning with Figure 2, the reader's attention is directed first to the thicker 45° line which represents the risk ratios

when the sensitivity is the same under placebo and finasteride. If biopsy sensitivity for cancer detection in both finasteride and placebo-treated subjects is presumed equal, from Table 2, one can see that the relative risk for high grade disease on biopsy is approximately 1.14, representing the overall 14% higher risk of high grade prostate cancer that was estimated if everyone had a biopsy. The values above this line represent risk estimates where biopsy has a greater sensitivity for high grade cancer detection if the subject is receiving finasteride while the values below the line represent risk estimates where biopsy has a greater sensitivity for high grade cancer detection if the subject is receiving placebo. The upper shaded region with risk ratio estimates less than one represent values where the 95% confidence interval excludes one where we would conclude that finasteride is protective against high grade cancer; conversely, the lower shaded region with risk ratios above one represent values for which the conclusion would be that finasteride increases the risk of high grade cancer. The white area represents the region where the 95% confidence interval around the relative risk estimate includes one and we would conclude there is no significant difference in high grade cancer rates between the treatment arms.

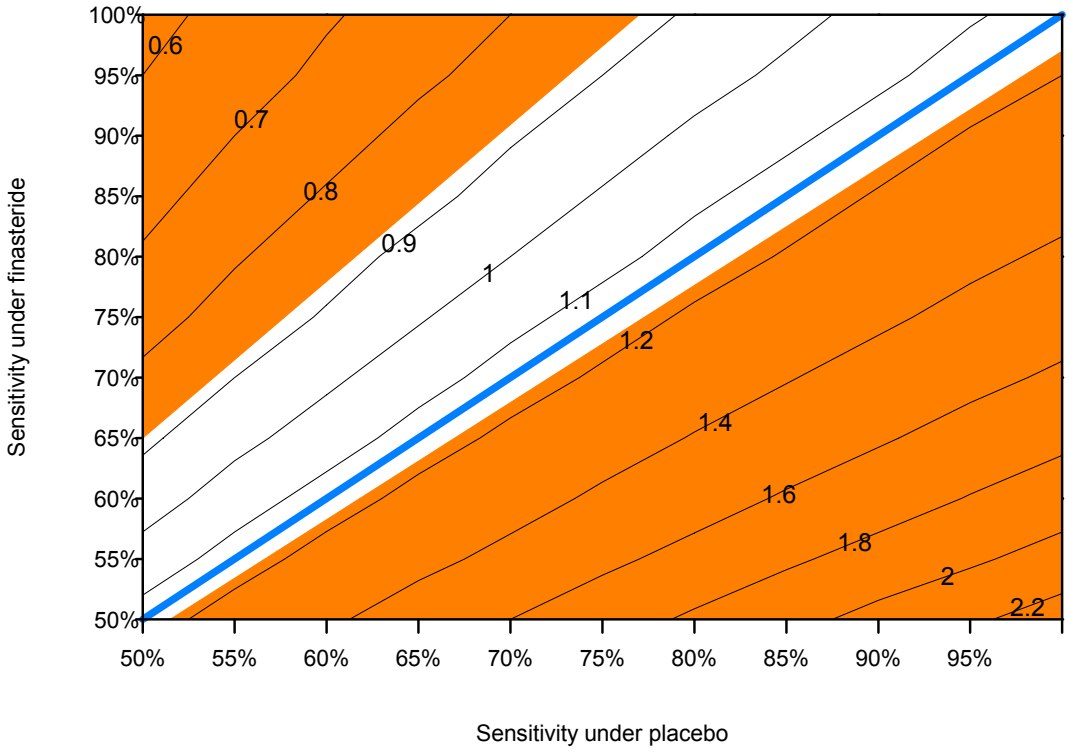

Figure 2 Risk ratios for high grade prostate cancer under imperfect sensitivity of biopsy to detect high grade cancer with placebo and finasteride

Figure 2 demonstrates that if biopsy sensitivity under finasteride is greater than under placebo, the risk of high grade disease on finasteride is either not different from or less than the risk of high grade disease on placebo. More specifically, this figure demonstrates that small differences in biopsy sensitivity between the treatment arms could explain the observed increased risk of high grade cancer with finasteride.

Figure 3 now presents the risk ratio estimates of high grade disease under various values of sensitivity of biopsy to detect cancer incorporating the

prostatectomy data to account for differential misclassification of grade. As in Figure 2, the white area represents the region where the 95% confidence interval around the relative risk estimate includes one and the upper shaded region represents the values of placebo biopsy sensitivity and finasteride biopsy sensitivity where finasteride reduces the risk of high grade cancer. There are no pairs of biopsy sensitivity values between 50-100% where the conclusion would be an increased risk of high grade prostate cancer with finasteride. Of note, a conclusion that there is an increased risk of high grade disease with finasteride only occurs if biopsy sensitivity were greater than 85% on the placebo arm and 25 -30% in the finasteride arm, values strongly contraindicated by the observed prostatectomy data. .

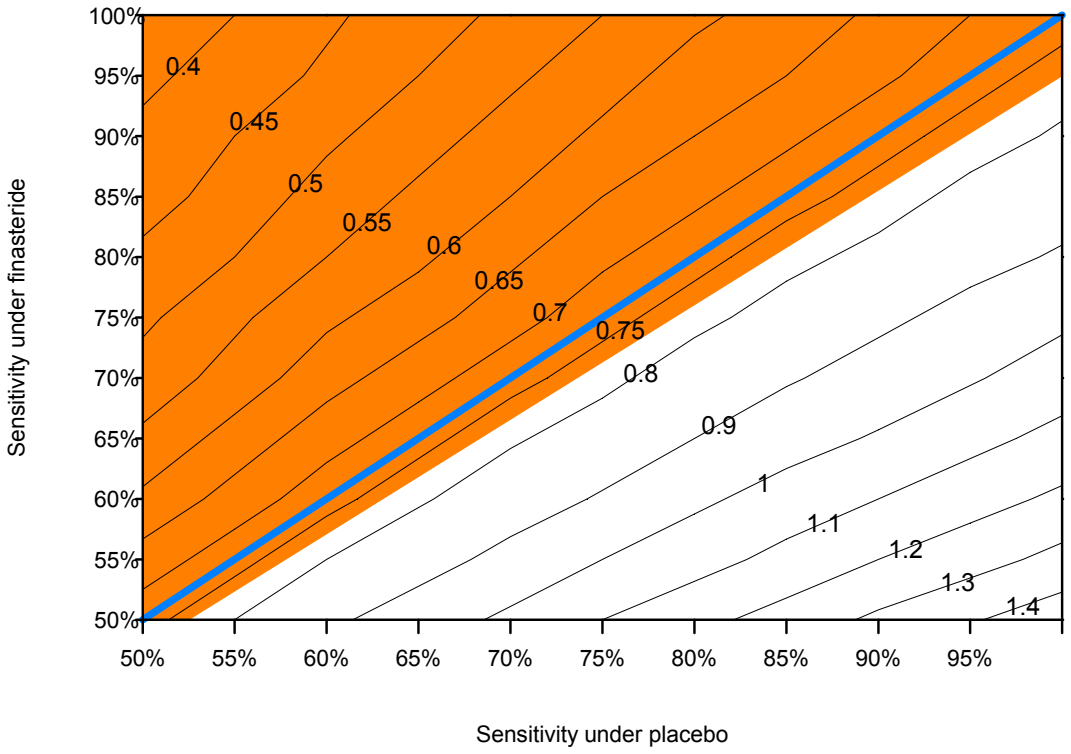

Figure 3 Risk ratios for sensitivity to biopsy incorporating the prostatectomy data

Discussion

Although finasteride reduced the risk of prostate cancer by at least 25% in the PCPT, the observed higher risk of high-grade tumors led to a general dismissal of finasteride for preventing prostate. Since the original PCPT report in 2003, investigators have uncovered the following biases in cancer detection caused by finasteride: A 'shift' in the receiver operating characteristic curve of PSA, enhancing detection of overall and high-grade prostate cancer, an increased sensitivity of DRE for cancer detection, and an increased sensitivity of biopsy for high-grade cancer detection, all of which were statistically

significant.[6,7,8] These three biases of finasteride were accompanied by a greater likelihood of biopsy in the PCPT placebo group

The present analyses systematically controlled for these and other factors in calculating the true rate of cancer in the two study groups. Multiple factors, including baseline characteristics and characteristics of participants at their annual visits, significantly influenced whether a man underwent a biopsy, as the PCPT primary endpoint required. Older subjects and men on finasteride had a lower likelihood of biopsy, and race (white), family history of prostate cancer, and an interim prostate biopsy recommendation increased biopsy likelihood.

Our first of two major analyses incorporated all of these covariates and showed that the biopsy cancer detection rates in the entire PCPT population (15,990 men) would have been similar, albeit slightly lower, than were observed in the 10,182 men who actually had an endpoint determined. (Table 2) Overall prostate cancer rates were estimated to be 14.7% (finasteride) and 21.1% (placebo) in the entire population and 16.6% (finasteride) and 22.9% (placebo) in those where the endpoint was actually evaluated. Estimates of high-grade prostate cancer rates were 4.8% (finasteride) and 4.2% (placebo) in the entire population and 5.8% (finasteride) and 4.8% (placebo) in those where the endpoint was actually evaluated. The modeled data substantiate the hypothesis that the biasing factor of an increased frequency of biopsy in the placebo group had a negligible impact on the outcome comparisons between the placebo and finasteride groups but accounting for PSA and DRE biases did result in a high grade cancer risk ratio estimate closer to 1.0 as we would expect. This

conclusion is important to our second analysis, which comprehensively assessed the influence of other factors that can bias biopsy results and thus the cancer comparisons between the two study groups.

Our second analysis controlled for the increased sensitivity of biopsy in finasteride-treated men for detecting high-grade prostate cancer among men with a cancer diagnosis. We extended the prostate-cancer grade changes from biopsy to radical prostatectomy in the subset of men who had a prostatectomy to the entire PCPT population. The estimated "true" rates of high-grade disease in this analysis were 8.2% (placebo) and 6.0% (finasteride), a 27% relative risk reduction suggesting that it was highly unlikely that finasteride actually increased the risk of high-grade cancer in the PCPT (Fig. 1).

Limitations of these analyses include imprecision of the 27% reduction in high-grade cancer risk because of the relatively small numbers of high-grade cancers in the PCPT, assumptions that all study participants could possibly have had a prostatectomy upon cancer diagnosis, and assumptions that the weights were modeled correctly and included all the relevant information. However, it should be noted that confounding factors would need to be related to both having an endpoint and prostate cancer to have an impact. A major limitation of all estimates is inherent with the prostate biopsy itself, which is only a sampling of the prostate. The majority of PCPT men had 6-core biopsies, which would be expected to have missed many cancers that would have been detected with the current 10-12-core biopsy regimens. The advantage of the 6-core biopsy,

however, was in detecting cancers that were more likely to be clinically significant (versus detection with 10-12 core biopsies).

A complex set of factors bear upon the recommendation and decision to take finasteride or virtually any other cancer preventive agent. Important factors in the finasteride recommendation/decision include the general burden of prostate cancer, clinical significance of the prevented cancers, and drug benefit-risk ratio. Consideration of each of these factors tends to throw a favorable light on finasteride prevention of prostate cancer. First, prostate cancer has a substantial medical, emotional and financial burden especially with its frequency of detection in the atmosphere of a strong emphasis on screening in the U.S. Second, the prevented cancers in the PCPT have been evaluated for, and found to have, a substantial proportion of clinically significant tumors (**[Lucia, CaPR 2008]**). Even men with less-consequential, low-grade prostate cancers, however, frequently seek and receive treatments , which have the consequences of high expense, risks of sexual, urinary, and bowel side effects, and an emotional toll on patients and families from lifetime follow-up surveillance for prostate cancer recurrence.[14]

Last and most relevant to the debate about finasteride prevention, is the consideration of the agent's benefit-risk ratio. Men must weigh the established benefits of an observed 25% reduction in prostate cancer (or a 30% actual risk reduction as found in this analysis) as well as a decrease in urinary symptoms and complications of an enlarged prostate against the potential side effects. Although established side effects of finasteride include reduced sexual function,

the present analyses lead us to conclude that men 55 years or older can remove the perceived increased risk of high-grade prostate cancer from their consideration of the adverse effects of finasteride. We found no evidence that finasteride induced high-grade disease but that there may have been an actual reduction in risk.

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