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

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Abstract Finasteride taken for 7 years in the Prostate Cancer Prevention Trial (PCPT) reduced the risk of prostate cancer by 25%, but with an apparent increased risk of high-grade disease. Subsequent analyses found that finasteride biases toward improved prostate cancer detection and accuracy in prostate cancer grading at biopsy. In our first analysis of the present study, we accounted for these biases in estimating the effect of finasteride on the risk of overall and high-grade prostate cancer. This analysis used PCPT data that included 3-month longer collection of endpoints than in the original report with observed prostate cancer rates of 22.9% (4.8% with high grade; placebo) versus 16.6% (5.8% with high grade; finasteride). Based on these updated results, the bias-adjusted prostate cancer rates are estimated to be 21.1% (4.2% high grade; placebo) and 14.7% (4.8% high grade; finasteride), a 30% risk reduction in prostate cancer [relative risk (RR), 0.70; 95% confidence interval (95% CI), 0.64-0.76; $P < 0.0001$] and a nonsignificant 14% increase in high-grade cancer (RR, 1.14; 95% CI, 0.96-1.35; $P = 0.12$) with finasteride. We then estimated rates of high-grade prostate cancer based on an analysis that incorporated grading information from radical prostatectomies in 500 subjects diagnosed with cancer. The resulting estimates were high-grade cancer rates of 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. Our third analysis examined the impact of biopsy sensitivity on the relative risk of high-grade prostate cancer and found that differential sensitivity of biopsy between the treatment arms can have a significant impact on risk ratio estimates. These collective results suggest that the observed, unadjusted higher risk of high-grade disease with finasteride seems to have been due to facilitated diagnosis resulting primarily from increased biopsy sensitivity with finasteride. Therefore, men undergoing regular prostate cancer screening or who express an interest in cancer prevention should be informed of the opportunity to take finasteride for preventing prostate cancer.

One in seven men in the United States is expected to be diagnosed with prostate cancer in his lifetime primarily because of aggressive screening. The effect of screening on morbidity and mortality is uncertain, and the human and economic cost of prostate cancer treatment is substantial. These circumstances make preventing this common disease an attractive public health strategy (1–3). The Prostate Cancer Prevention Trial (PCPT) tested the ability of finasteride, a selective inhibitor of 5α-reductase type 2, to reduce the risk of prostate cancer. The independent Data and Safety Monitoring Committee recommended closure of the PCPT 15 months early because of overwhelming evidence that the primary end point had been reached: Finasteride had reduced the risk of prostate cancer by 25% (4). Concurrently, finasteride apparently had increased the risk of high-grade disease. Although high-grade tumors were a relatively small proportion of all detected tumors in the finasteride group, the potentially increased risk of aggressive disease and an unfavorable editorial accompanying the initial publication led to a general lack of acceptance of finasteride for cancer prevention (5). In the United States, early detection and treatment remain the primary focus for controlling this disease.

Since the initial publication of primary PCPT outcomes, analyses of these contrasting conclusions have continued, as has a widespread debate on finasteride for prostate cancer prevention. We now know that finasteride enhances the detection of prostate cancer through the following effects on the performance characteristics of for-cause biopsies (see "Materials and

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Methods" section for definition): (*a*) improved sensitivity of prostate-specific antigen (PSA) for overall and high-grade cancer detection, (*b*) improved sensitivity of digital rectal examination (DRE) for cancer detection, and (*c*) more accurate grading of high-grade prostate cancer (5, 6). Although these three detection biases would be expected to lead to cancer overdetection in study subjects receiving finasteride, there was a counteracting bias for greater cancer detection in the placebo group because these men more commonly underwent biopsy.

To better understand the cumulative effect of these biases on prostate cancer detection in the PCPT, we conducted three analyses. First, we analyzed the effect of finasteride on overall and high-grade prostate cancer in all study participants including those who did not have (but were eligible for) an end point determination. This analysis accounted for the selection biases of finasteride in improving detection of cancer by for-cause biopsies. Second, we estimated the true prevalence of high-grade prostate cancer among men with biopsy-detected cancer based on the subset of patients who underwent radical prostatectomy (which is more definitive than is biopsy for cancer grade, especially when comparing grades between the finasteride and placebo groups). Third, we examined the effect of imperfect biopsy sensitivity for prostate cancer on the prevalence of high-grade prostate cancer within each study arm and on the overall risk reduction associated with finasteride.

Materials and Methods

The PCPT randomized 18,882 eligible men to receive either placebo or finasteride for 7 years and to be followed for 7-year period prevalence of prostate cancer. Prostate biopsy was done either due to an abnormal 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). A biopsy associated with either an abnormal DRE or elevated PSA is referred to as a for-cause biopsy. 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 data set 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 data set we use for the present analyses.

For the present analyses, a man was defined to have an end point if he had an interim diagnosis of prostate cancer or if he underwent an end-of-study biopsy within 90 d of his 7-y anniversary of his randomization or by June 23, 2003 (whichever came first). Due to early closure of the study, 15,990 (85%) of the 18,882 men were assessable for the endpoint. End points were observed in 5,223 men on the placebo arm and 4,958 men on the finasteride arm for a total of 10,182 (64%) of the 15,990 men. A 60% compliance rate for end point ascertainment was specified in the protocol design assumptions. For the purposes of this article, we will consider the sample size of the study to be the 15,990 men who reached their 7-y anniversary when the study was reported and unblinded. High-grade prostate cancer was defined as a Gleason score of ≥ 7.

Predicting prostate cancer prevalence if all subjects had an end point

It is likely that men who did not have an end point evaluated have a different underlying probability of prostate cancer than those who did have an end point evaluated. To estimate the cancer prevalence if all subjects had an end point, a reasonable and often used assumption is that there are measured study covariates, which both explain the differences between men with and without end points 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 end point evaluated and one without, the outcome data from the man with the evaluated end point inform the cancer status for the man without the end point evaluation.

An approach that uses this assumption and can be used to estimate the prevalence of prostate cancer and high-grade disease is the inverse probability of censoring weighted estimation (12). Use of this analysis approach is a two-step process; the first step is to estimate the probability of having an end point 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 end point, using the inverse of the probabilities from the first step as weights.

To estimate the probability of having an end point 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 end point and (*b*) having a diagnosis of prostate cancer. The baseline covariates that were included in these analyses were treatment arm, age, ethnicity/race, PSA 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 DRE 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 end point evaluated. The same weights and approach were used to estimate the prevalence of biopsy-detectable high-grade cancers in each treatment arm.

Predicting high-grade prostate cancer by integrating prostatectomy data

The previous analysis attempts to account for selection bias between the treatment arms on which participants have a study end point 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 done 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 done and data were available on 500 of 2,017 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.

Effect of differential biopsy sensitivity on disease prevalence

The first two analyses addressed biases related to imperfect ascertainment of biopsy end points 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 end points 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

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

These analyses use the assumption that biopsy perfectly detects cancer, although there is substantial evidence that (*a*) biopsy operating characteristics are less than perfect and (*b*) the operating characteristics are improved under finasteride. The final analysis addressed the effect 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 (the probability of cancer given a positive biopsy equals 1.0; ref. 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 used 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. Because 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.).

Results

Table 1 presents a comparison of the characteristics of men with and without a study end point. Characteristics determined to be associated with a reduced odds of having an end point were randomization to finasteride (RR, 0.89) and older age (OR [odds ratio], 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 end point. Whereas PSA at randomization was marginally associated with an increased odds of observed end point (RR, 1.14; $P < 0.0001$), the association was no longer significant after adjusting for other covariates ($P = 0.6$).

Predicting prostate cancer prevalence if all subjects had an end point

Prostate cancer prevalence results from the analyses accounting for nonrandom missing biopsy results are presented in Table 2. The observed rates of prostate cancer for the 5,223

Table 1. Comparison of men with and without endpoint evaluated

N (%) / mean ± std	End point evaluated		OR* (95% CI)	*P**
	No n = 5,809	Yes n = 10,181		
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 (reference)	
Age at randomization†	63.4 ± 5.9	62.9 ± 5.4	0.98 (0.97-0.99)	<0.0001
Race				
White	5,297 (91%)	9,483 (93%)	1.37 (1.21-1.55)	<0.0001
Other	512 (9%)	699 (7%)	1.0 (reference)	
Family history of PCA				
Yes	782 (13%)	1,698 (17%)	1.23 (1.12-1.35)	<0.0001
No	1,200 (79%)	383 (77%)	1.0 (reference)	
PSA at randomization‡	63.4 ± 5.9	62.9 ± 5.4	0.99 (0.94-1.04)	0.59
Prior negative study biopsy				
Yes	463 (8%)	1,349 (13%)	1.60 (1.43-1.80)	<0.0001
No	5,345 (92%)	8,833 (87%)	1.0 (reference)	<0.0001
Biopsy prompt for elevated PSA				
Yes	69 (1%)	803 (8%)	6.80 (5.32-8.84)	<0.0001
No	5,739 (99%)	9,381 (92%)	1.0 (reference)	
Biopsy prompt for suspicious DRE				
Yes	82 (1%)	830 (8%)	5.66 (4.52-7.18)	<0.0001
No	5,726 (99%)	9,352 (92%)	1.0 (reference)	

*From a multivariable logistic regression model with endpoint evaluated (yes/no) as the outcome, adjusting for other factors in Table 1. OR = odds ratio, CI = confidence interval.

†The OR represents the difference in odds of endpoint comparing men 1-year apart in age.

‡OR for each 1-unit increase in PSA level.

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

	Placebo arm *n* = 8,024	Finasteride arm *n* = 7,966	RR (95% CI)	*P*-value
Prostate cancer				
Estimate of overall prevalence	1,693 (21.1%)	1,171 (14.7%)	0.70 (0.64-0.76)	<0.0001
Observed	1,194 (22.9%)	823 (16.6%)	0.72 (0.67-0.79)	<0.0001
High-grade cancer				
Estimate of overall prevalence	337 (4.2%)	382 (4.8%)	1.14 (0.96-1.35)	0.12
Observed	252 (4.8%)	288 (5.8%)	1.21 (1.02-1.42)	0.02

men in the placebo group and 4,959 men in the finasteride group with an end point 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 8,024 men in the placebo group would have been 21.1% and in the 7,966 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 end point evaluated were slightly less likely to have prostate cancer. Similarly, whereas 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 versus 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 nonsignificant 14% increased risk ($P = 0.12$).

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. Whereas treatment group,

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

	No prostatectomy *n* = 1,517	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 (reference)	
Age at randomization	64.6 ± 5.6	61.1 ± 4.2	0.86 (0.84-0.88)	<0.0001
			1.0 (reference)	
Race				
White	1,403 (92%)	466 (93%)	1.41 (0.94-2.16)	0.11
Other	114 (8%)	34 (7%)	1.0 (reference)	
Family history of prostate cancer				
Yes	317 (21%)	117 (23%)	1.02 (0.78-1.31)	0.90
No	1,200 (79%)	383 (77%)	1.0 (reference)	
PSA at randomization	1.6 ± 0.8	1.7 ± 0.7	1.25 (1.07-1.82)	0.006
			1.0 (reference)	
Prior negative biopsy				
Yes	206 (14%)	67 (13%)	1.05 (0.76-1.44)	0.78
No	1,311 (86%)	433 (87%)	1.0 (reference)	
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 (reference)	
Biopsy prompt for DRE				
Yes	281 (19%)	123 (25%)	1.69 (1.30-2.18)	<0.0001
No	1,236 (81%)	377 (75%)	1.0 (reference)	
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 (reference)	

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

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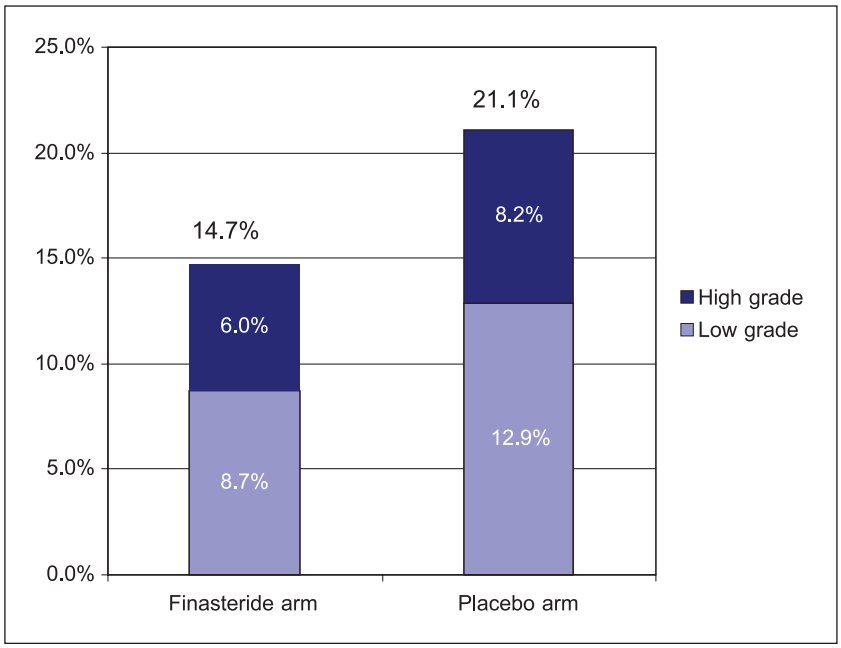

Fig. 1. Estimated actual fractions of total subjects with low-grade and high-grade cancer using prostatectomy data.

family history, White race, a prior negative study biopsy, and high-grade cancer on biopsy did not have a significant effect on whether a prostatectomy was done and the results were available, younger age, PSA at randomization, and 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 (for-cause biopsies) were interim biopsies. It follows, for interim biopsies, that there was a longer time observed postdiagnosis to both have a prostatectomy and to observe and obtain the prostatectomy results.

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

The estimated risk reduction with finasteride for Gleason ≤6 is 34% [RR, 0.66; 95% confidence interval (95% CI), 0.55-0.80; $P \leq 0.0001$] and for Gleason ≥7 is 27% (RR, 0.73; 95% CI, 0.56-0.96; $P = 0.02$).

Effect 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 effect on prostate volume.

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

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

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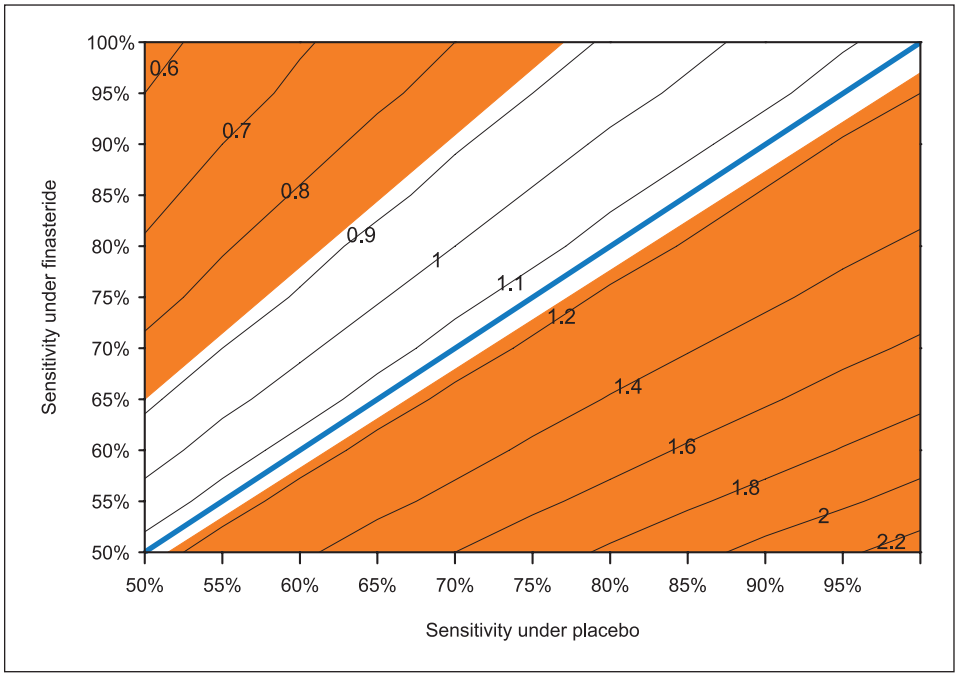

Fig. 2. Risk ratios for high-grade prostate cancer under imperfect sensitivity of biopsy to detect high-grade cancer with placebo and finasteride.

the sensitivity for high-grade prostate cancer is 80% for the finasteride arm and 70% for the placebo arm, the resulting actual risk of high-grade disease on biopsy would be 6% for both, equal to no difference in high-grade prostate cancer prevalence on biopsy. Alternatively, if the sensitivity for prostate cancer is 80% in the finasteride arm 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.

Using these data, Figs. 2 and 3 present the risk ratios under all pairs of sensitivity of prostate biopsy (for finasteride and placebo) to detect high-grade cancer. Beginning with Fig. 2, the reader's attention is directed first to the thicker 45-degree 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 ~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, whereas 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 <1 represent values where the 95% CI excludes 1 where we would conclude that finasteride is protective against high-grade cancer; conversely, the lower shaded region with risk ratios >1 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% CI around the relative risk estimate includes 1, and we would conclude that there is no significant difference in high-grade cancer rates between the treatment arms.

Figure 2 shows 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 shows that small differences in biopsy sensitivity between the treatment arms could explain the observed increased risk of high-grade cancer with finasteride.

Figure 3 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 Fig. 2, the white area represents the region where the 95% CI around the relative risk estimate includes 1 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% and 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 >85% on the placebo arm and 25% to 30% in the finasteride arm, values strongly contradicted by the observed prostatectomy data.

Discussion

Although finasteride significantly reduced the risk of prostate cancer in the PCPT (by 25% in the initial report), it was not generally accepted for prostate cancer prevention because of the observed higher risk of high-grade tumors. Since the original PCPT report in 2003, investigators have uncovered the

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following biases in cancer detection caused by finasteride: a shift in the receiver operating characteristics curve of PSA, enhanced detection of overall and high-grade prostate cancer, and increased sensitivity of DRE for cancer detection and increased sensitivity of biopsy for high-grade cancer detection, all of which were statistically significant (6–8). These three biases of finasteride were accompanied by a greater likelihood of biopsy in the PCPT placebo group, a placebo bias.

The present analyses systematically controlled for these and other factors in estimating the true rate of cancer in the two study groups. Multiple factors, including baseline and annual-visit characteristics of participants, significantly influenced whether a man underwent the end-of-study biopsy required by the PCPT primary end point. Older age and finasteride lowered the likelihood of biopsy; race (White), family history of prostate cancer, and an interim prostate biopsy recommendation increased biopsy likelihood.

Our first analysis incorporated adjustments for all of the aforementioned biases in showing 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 end point determination (Table 2). Estimated overall prostate cancer rates were 14.7% (finasteride) and 21.1% (placebo) in the entire population and 16.6% (finasteride) and 22.9% (placebo) in men with actual end points. High-grade prostate cancer estimates were 4.8% (finasteride) and 4.2% (placebo) in the entire population and 5.8% (finasteride) and 4.8% (placebo) in men with actual endpoints. While estimates of prostate cancer prevalence were not substantially different from the observed data, accounting for PSA and DRE biases did result in a now-significant estimate of increased risk of high grade disease with finasteride.

The second analysis incorporated the finding of the increased sensitivity of biopsy for detecting high-grade prostate cancer in finasteride-treated men diagnosed with cancer. We extended the changes from biopsy grade (of prostate cancer) to prostatectomy grade (calculated in the subset of men who had a prostatectomy) to the entire PCPT population. The resulting rates, or "true" rates, of high-grade disease in this analysis were 8.2% (placebo) and 6.0% (finasteride), a 27% relative risk reduction. This outcome suggests that it was highly unlikely that finasteride actually increased the risk of high-grade cancer in the PCPT (Fig. 1).

The third and final analysis incorporated biopsy sensitivity across a range of plausible values. Biopsy sensitivity for high grade disease is lower under placebo than under finasteride, as has been shown previously (8). As shown in Fig. 2 and Table 4, different ranges of biopsy sensitivity for high-grade cancer resulted in either a null or a reduced relative risk in the finasteride group for high-grade cancer. Limiting the analysis to gleason grade 8-10, prevalence estimates were 0.8 % in the placebo arm and 1.0% in the finasteride arm, a clinically insignificant difference and imprecise given very small numbers of cases. This analysis shows how small differences in biopsy sensitivity between the study arms could result in the apparent finasteride-associated increase in high grades on biopsy that was reported in 2003 (4).

Limitations of these analyses include an 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 the weights were modeled correctly and included all relevant information, and assumptions that all study participants diagnosed with cancer could have had a prostatectomy. It should be noted, however, that confounding factors would only have an effect if they related to having both an end point and prostate cancer. A major limitation of all estimates is inherent with the prostate biopsy itself, which only samples the prostate. The majority of PCPT men had a six-core biopsy, which would be expected to have missed

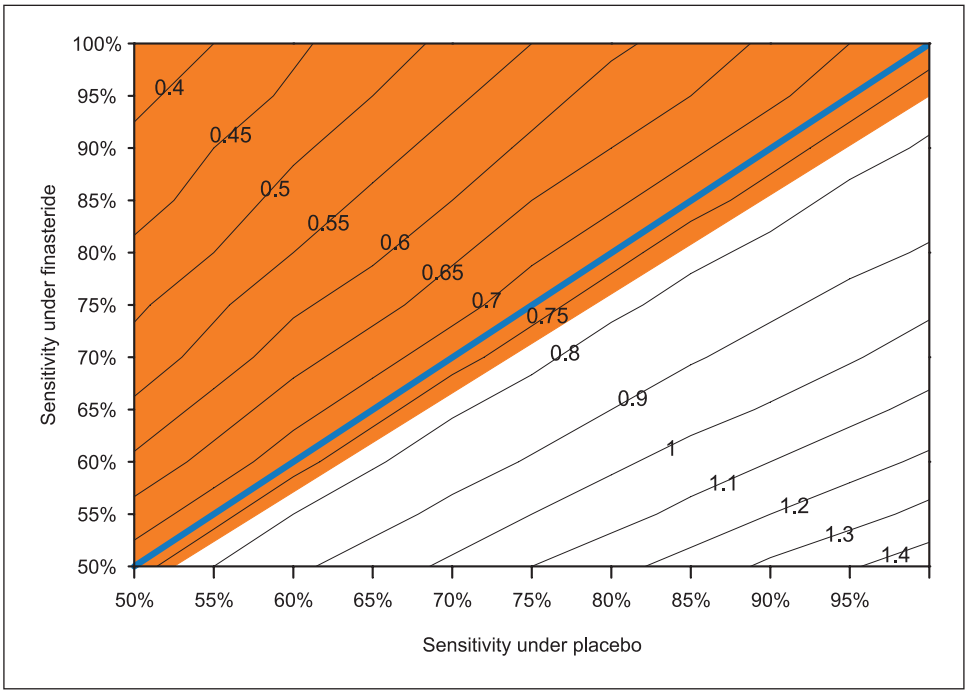

Fig. 3. Risk ratios for sensitivity to biopsy incorporating the prostatectomy data.

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many cancers that would have been detected with currently more standard 10- to 12-core biopsies. The advantage of the six-core biopsy, however, was in detecting cancers that were more likely to be clinically significant (versus detection with 10- to 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 United States. Second, the prevented cancers in the PCPT have been evaluated for, and found to have, a substantial proportion of clinically significant tumors (15). Even men with less consequential low-grade prostate cancers frequently seek and receive treatment. This treatment has the consequences of high expenses, risk of sexual, urinary, and bowel side effects, and an emotional toll on patients and families from lifetime follow-up surveillance for prostate cancer recurrence (16).

The last consideration, and most relevant to the debate about finasteride prevention, is the benefit-risk ratio of the agent. Men must weigh the established benefits of a 25% reduction in prostate cancer (estimated to be 30% in the present analysis), decreased urinary symptoms, and decreased complications of an enlarged prostate against the established side effects, which include reduced sexual function. We found no evidence that finasteride increased the risk of high-grade prostate cancer in the PCPT. Therefore, we conclude that men 55 years or older have no need to be concerned about an increased risk of high-grade prostate cancer with finasteride.

Disclosure of Potential Conflicts of Interest

P.J. Goodman: GlaxoSmithKline consultant; M.S. Lucia: GlaxoSmithKline consultant and commercial research grant; C.A. Coltman: Seno Medical consultant. The other authors disclosed no potential conflicts of interest.

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