The Prostate Cancer Prevention Trial (PCPT) was the first large-scale, long-term randomized, placebo-controlled study designed to evaluate a medicinal agent for reducing the risk of prostate cancer (1). The PCPT was initiated based on multiple lines of evidence available in the early 1990s that suggested that treatment with finasteride—a 5α-reductase inhibitor, which converts testosterone to the more potent androgen dihydrotestosterone—would reduce a man’s risk of developing prostate cancer (2). Participants in the PCPT, who were all aged 55 years or older and had baseline prostate-specific antigen (PSA) levels less than or equal to 3.0 ng/mL, were treated with finasteride (5 mg daily) or a placebo for up to 7 years. Participants were recommended for biopsy if their PSA level (adjusted upward for the suppressive effect of finasteride on serum PSA) at an annual screening exceeded 4.0 ng/mL or if an annual digital rectal examination was abnormal. All participants who had
not been diagnosed with prostate cancer were invited to have a prostate biopsy at the conclusion of the trial.

The primary endpoint of the study was the period prevalence of prostate cancer during the 7 years of treatment in the trial. Approximately 15 months before the anticipated completion of the study, the data and safety monitoring committee terminated the trial, having concluded that it had met its primary objective. The study demonstrated a 24.8% reduction in the period prevalence of prostate cancer with finasteride treatment (3). However, an unanticipated finding was that prostate cancers with a high-grade Gleason score of 7–10 were more common in men treated with finasteride (6.4%) than in men treated with placebo (5.1%).

Four hypotheses have been proposed to explain the finding of increased high-grade disease in the PCPT. One hypothesis is that finasteride induces the development of high-grade prostate cancer by changing the intraprostatic hormonal milieu (3). A second hypothesis is that finasteride alters the histologic appearance of prostate cancers, similar to the effects of androgen deprivation therapy, such that they resemble high-grade cancers (2,4,5). A third hypothesis asserts that finasteride failed to reduce the PSA levels of men who had incipient high-grade cancer at the outset of the study to the same extent that it reduced levels in other participants, with the resulting overadjustment in the PSA level in such men leading to a greater likelihood of biopsy and detection (5).

Indeed, a recent analysis of PCPT data found that the sensitivity of PSA testing for all prostate cancers and for high-grade tumors in particular was higher in the finasteride group compared with the placebo group (6). Finally, the fourth hypothesis postulates that finasteride reduces prostate volume, resulting in disproportionate sampling of the gland upon random needle biopsy as compared with the placebo group (3,5,7,8).

The blinded measurement of prostate gland volume by transrectal ultrasound, which was performed at biopsy on all analyzable PCPT participants either during follow-up or at the end of study, provides a unique opportunity to estimate the impact of increased sampling density on the association of finasteride with high-grade cancer. We used two modeling approaches to adjust for the effect of gland volume on detection of high-grade prostate cancer in the PCPT. Our objective was to estimate the extent to which the excess of high-grade cancer in the finasteride group could be explained by changes in gland volume and thus sampling density at biopsy. The assumptions required for causal inference from analyses adjusting for an intermediate factor affected by treatment, such as sampling density, were considered carefully.

Methods

Study Subjects and Prostate Cancer Clinical Data

Analyses presented in the primary study publication (1) included data for all participants who had had prostate biopsies through a cutoff date of March 19, 2003. The PCPT was coordinated by the Southwest Oncology Group (SWOG). The population used in the statistical analyses of the primary efficacy endpoint (the prevalence of prostate cancer over the 7-year study period) reported in this article is termed the “extended SWOG population” and includes a total of 9898 men, 4775 randomly assigned to finasteride and 5123 randomly assigned to placebo. The extended population includes 838 additional men (407 who received finasteride and 431 who received placebo) who were not included in this original publication because their final outcome status was adjudicated after closure of the dataset used in the original publication (1). The SWOG population, both here and in the original publication, is defined as all participants with known prostate cancer status within 7 years plus 90 days after starting study medication; it therefore includes all participants with an end-of-study biopsy and also those men with biopsy positive for prostate cancer at any time during the study. A total of 301 high-grade cancers were detected in men in the finasteride group (Table 1), 243 of whom had prostate sampling density data and were included in the analysis. In the placebo group, 256 high-grade cancers were identified, of which 209 had sufficient data to be included in the analysis. With the exception of family history of prostate cancer, patients with high-grade cancer for whom volume data were missing had baseline characteristics similar to those of men for whom volume data were available (data not shown).

Statistical Analyses

The relationship of ultrasound-determined prostate volume and number of needle biopsy cores to the detection of high-grade prostate cancer was examined with two analytic approaches. The first was a regression-based approach that is somewhat analogous to the one used to calculate the standardized mortality (or morbidity) ratio (9). This approach, the Peters–Belson method (10), was originally developed by economists and has been used in wage discrimination studies and, more recently, in studies of racial disparities in cancer

CONTEXT AND CAVEATS

Prior knowledge

In the Prostate Cancer Prevention Trial (PCPT), the 5α-reductase inhibitor finasteride reduced the overall incidence of prostate cancer but was associated with an increase in high-grade cancer specifically. However, whether finasteride actually promotes high-grade cancer or rather creates a bias that leads indirectly to the detection of more high-grade cancer has not been clear. One possibility is that finasteride reduces the volume of the prostate, increasing the likelihood that a biopsy sample will contain high-grade cancer.

Study design

In an observational reanalysis of data from the PCPT, several kinds of regression models were used to investigate the contribution of prostate volume and number of cores obtained at biopsy to the increased prevalence of high-grade cancer in the finasteride arm.

Contribution

Adjustment for gland volume and number of cores biopsied (i.e., sampling density) eliminated the differences in high-grade cancer between the two arms.

Implications

The apparent increase in high-grade cancer in the finasteride arm of the PCPT may be an artifact due to sampling density bias.

Limitations

Adjustment for postrandomization variables that are affected by treatment, such as gland volume, can lead to confounding and complicate causal interpretation. Further adjustment for other possible biases could change the results.
screening. This method fits a regression model within a referent group and then uses the fitted model to estimate the number of outcomes expected in a comparator group, had they been members of the referent group. In the analysis reported here, a logistic regression model with high-grade prostate cancer as the outcome was developed on the patients in the PCPT placebo arm, adjusting for the following baseline covariates: age (per year), PSA level (per ng/mL), family history of prostate cancer (first-degree relative, yes versus no), and African American race, as well as for two post-randomization covariates, prostate volume (per cm³) and number of biopsy cores (per six-core increase). The logit of the probability \( \log(P/(1-P)) \) of a participant developing high-grade prostate cancer equals the cross-product of the estimated coefficient vector from this logistic model and the covariate vector. The sum of these probabilities is the expected number of high-grade prostate cancers in men in the finasteride group, had they not received finasteride treatment. Similarity between the expected and observed numbers of high-grade prostate cancers implies no treatment effect. A 95% confidence interval (CI) for the predicted number of cancers in men in the finasteride group, had they not been treated with finasteride, was obtained using the bias-corrected bootstrap method (11). The bootstrap resampled participants 10000 times from the placebo group to update the predicted probabilities of events among those in the finasteride group. The programming was performed in S-Plus 6.1 (Insightful Corp, Seattle, WA).

In the second analytic approach, the dichotomous outcome of high-grade prostate cancer versus its complement (low-grade prostate cancer, ungraded prostate cancer, or no cancer) was modeled using logistic regression to obtain odds ratios (ORs) and their 95% confidence intervals. A dichotomous term for treatment group was included as a covariate. The initial model (model A) included only treatment and baseline covariates (the same as those used in the first approach). The change in the odds ratio for prostate cancer with finasteride versus placebo was then evaluated after fitting an extended model (model B) that included two additional covariates: gland volume and number of needle cores. Similar models were developed that included only participants who underwent end-of-study biopsies and for all prostate cancer as opposed to only high-grade cancer. The interaction between volume and drug treatment was tested in the latter model, with multiplicative interaction terms. The Hosmer–Lemeshow method (12) was used to evaluate model fit. We note that the odds ratio will deviate increasingly from the risk ratio as the prevalence of the outcome and the odds ratio increase (13). In the present analyses, odds ratios provide reasonably close approximations to risk ratios, given the combined effects of outcome prevalence and odds ratio estimates.

To measure the influence of prostate volume on the treatment effect, the proportion of treatment effect explained (PTE) by prostate volume was estimated along with its associated 95% bias-corrected bootstrap (10000 replicates) confidence interval (11,14). The PTE, \( p \), was calculated as

\[
p = 1 - \frac{\beta}{\alpha},
\]

where \( \beta \) is the coefficient for treatment in the model adjusted for volume and \( \alpha \) is the coefficient for treatment in the unadjusted model. The bias-corrected bootstrap confidence interval was calculated by resampling the data with replacement (pseudosamples) and calculating the PTE for each pseudosample. The lower and upper bounds of the confidence interval occur at the 2.5% and 97.5% quintiles, respectively.

To estimate the association between treatment and both low- and high-grade cancer simultaneously, we fit polytomous logistic models with low-grade, high-grade, and ungraded cancer as the outcomes and no cancer as the referent group (12). Models and covariates (model A compared with model B, with the addition of control for gland volume and number of needle cores) paralleled those in the binary logistic regression analyses. All analyses were performed using S-Plus 6.1; all \( P \) values were two-sided.

## Results

Our analysis of the primary study endpoint—i.e., the prevalence of prostate cancer over the 7-year study period—in the extended SWOG population was consistent with the results originally reported from the PCPT (1). That is, prostate cancer was detected in 2153 (21.8%) of the 9898 men: 879 (18.4%) of the 4775 men treated with finasteride \( 5 \) mg daily and 1274 (24.9%) of the 5123 men in the placebo group, for a 26.0% (95% CI = 19.5% to 32.5%) reduction in prevalence of prostate cancer over the 7-year study period. An excess of high-grade cancers observed in the finasteride group in the extended population was similar to the original findings—that is, the prevalence of high-grade cancer in the finasteride and placebo groups was 6.3% (301 of 4775 men) and 5.0% (256 of 5123 men), respectively (difference = 1.3%, 95% CI = 0.4% to 2.2%; \( P = .005 \)). In both treatment arms, similar numbers of participants were diagnosed with prostate cancer using for-cause and end-of-study biopsies, yet the majority of high-grade tumors were diagnosed with for-cause biopsies. Prostate cancers detected in the entire trial population were stratified by treatment, Gleason score, and method of diagnosis, that is, either during follow-up (i.e., in for-cause biopsies) or at the end of study (Table 1).

Among the extended SWOG population, 4285 of the 4775 men in the finasteride group and 4591 of the 5123 men in the placebo group had prostate volume measurements (Fig. 1). These numbers exclude one and four participants (in finasteride and placebo groups, respectively) who had prostate volumes that were considered to be out of range (\( \geq 200 \) cm³). Among all study participants, median prostate volumes were 25.1 cm³ in the finasteride arm and 33.5 cm³ in the placebo arm. Among participants who had an end-of-study biopsy revealing cancer, median prostate volumes were 24.4 cm³ in the finasteride arm and 31.9 cm³ in the placebo arm, whereas among participants with cancer detected during follow-up (i.e., in for-cause biopsies) median prostate volumes were 25.8 and 34.4 cm³, respectively. Thus, median prostate volume in the finasteride group, as assessed by transrectal ultrasound, was 25% lower than that in the placebo group among all participants, 23% lower among those diagnosed with prostate cancer, and 27% lower among those without prostate cancer (Fig. 1). Because similar numbers of biopsy cores were obtained in both treatment groups (median of 6.0 cores per biopsy in both groups), the mean sampling density (biopsy cores/cm³) was 27% greater in the finasteride group than in the placebo group among all participants with prostate cancer (0.33 versus 0.26 cores/cm³ in the finasteride and
placebo groups, respectively) and 38% greater in the finasteride group than in the placebo group among all participants with high-grade prostate cancer (0.32 versus 0.23 cores/cm³ in the finasteride and placebo groups, respectively).

As expected, older age, African American race, family history of prostate cancer, and baseline PSA value were positively associated with detection of high-grade prostate cancer in the logistic model (Table 2), although the association for family history was not statistically significant. Among patients in the placebo group, prostate volume was inversely related to the likelihood of detecting high-grade prostate cancer. Thus, the likelihood of detecting high-grade cancer decreased as the volume increased (per 10 cm³ increase, OR = 0.81; 95% CI = 0.74 to 0.90), that is, the risk for detection of high-grade cancer decreased by 19% for each 10 cm³ increase in prostate volume.

The logistic model developed on the placebo group of the extended SWOG population (Table 2) was then used to calculate the expected number of high-grade tumors in the finasteride group based on gland volume, number of biopsy cores, and other covariates (Fig. 2). The expected number is the sum of the individual probabilities of high-grade cancer for members of the finasteride group, had they been assigned to the placebo group. The actual number of high-grade tumors in the finasteride group (n = 243) was similar to the number predicted by the model (n = 239, bias-corrected 95% CI = 203 to 276). The similarity between observed and predicted cases of high-grade prostate cancer was consistent across different prostate volumes (Fig. 2).

In an alternative analysis, binary logistic models were developed using both the placebo and finasteride groups, with an outcome variable of high-grade prostate cancer versus all other outcomes (Table 3). In model A, adjusted for baseline covariates only, the odds ratio for detection of high-grade prostate cancer in men in the finasteride versus placebo groups was 1.27 (95% CI = 1.05 to 1.54). However, when the model was further adjusted for prostate volume and number of biopsy cores (i.e., sampling density; model B), the association between finasteride and high-grade prostate cancer disappeared (OR = 1.03, 95% CI = 0.84 to 1.26), whereas the odds ratios for other covariates remained unchanged. No interactions were found between volume and treatment group in this model. An analogous set of models was developed for the subgroup of participants who underwent end-of-study biopsies only. In this subgroup, the odds ratio for high-grade cancer in the finasteride

**Table 1. Distribution of Gleason scores at the time of diagnosis by treatment group in the Prostate Cancer Prevention Trial**

<table>
<thead>
<tr>
<th>Gleason score</th>
<th>All cancers, n (%)</th>
<th>Cancers diagnosed in biopsies performed for cause, n (%)</th>
<th>Cancers diagnosed in end-of-study biopsies, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Finasteride, n = 4775</td>
<td>Placebo, n = 5123</td>
<td>Finasteride, n = 4775</td>
</tr>
<tr>
<td>2–6 (low)</td>
<td>532 (11.1) 945 (18.4)</td>
<td>301 (6.3) 256 (5.0)</td>
<td>41 (0.9) 59 (1.2)</td>
</tr>
<tr>
<td>7–10 (high)</td>
<td>461 (10.0) 141 (2.7)</td>
<td>75 (1.5) 62 (1.2)</td>
<td>46 (1.0) 62 (1.2)</td>
</tr>
</tbody>
</table>

* The extended Southwest Oncology Group population was analyzed; this population included participants for whom sampling density data were unavailable.
† Includes cancers diagnosed in biopsies performed for cause either during the study or at the end of the study.
‡ Excludes cancers diagnosed in biopsies performed for cause at the end of the study.

**Table 2. Odds ratios (and 95% confidence intervals) for high-grade prostate cancer compared with no high-grade prostate cancer (i.e., low-grade or ungraded prostate cancer or no prostate cancer) in the placebo group of the Prostate Cancer Prevention Trial**

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at biopsy (per 10 yr)</td>
<td>1.45 (1.12 to 1.87)</td>
</tr>
<tr>
<td>Race (African American vs other)</td>
<td>2.60 (1.44 to 4.69)</td>
</tr>
<tr>
<td>Family history of prostate cancer (first-degree relative, yes vs no)</td>
<td>1.31 (0.91 to 1.87)</td>
</tr>
<tr>
<td>Baseline PSA (per ng/mL increase)</td>
<td>2.36 (1.95 to 2.85)</td>
</tr>
<tr>
<td>Gland volume (per 10 cm² increase)</td>
<td>0.81 (0.74 to 0.90)</td>
</tr>
<tr>
<td>Number of biopsy cores (per six-core increase)</td>
<td>1.99 (1.29 to 3.05)</td>
</tr>
</tbody>
</table>

* The odds ratios and 95% confidence intervals come from a logistic regression model that was based on the extended Southwest Oncology Group population. A total of 209 events and 4330 nonevents were included in the model; 584 observations were excluded due to missing values. The regression model was adjusted for all variables shown in the table. OR = odds ratio; CI = confidence interval; PSA = prostate-specific antigen.
Regression models were used to predict the number of high-grade tumors in the finasteride group of the Prostate Cancer Prevention Trial. The logistic regression model developed on the placebo group of the extended Southwest Oncology Group population was used to predict the number of high-grade tumors in the finasteride group of this population based on the Peters–Belson approach (10) for different prostate volumes.

Group compared with the placebo group was 1.07 (95% CI = 0.80 to 1.42) in a model adjusting for baseline variables. However, after additional adjustment for sampling density, the OR was 0.89 (95% CI = 0.66 to 1.21). For the analysis of the proportion of treatment effect explained by prostate volume (14), we included all participants with nonmissing data (4576 in the placebo and 4251 in the finasteride group). The proportion of treatment effect explained by volume was estimated to be 89% (bias-corrected 95% CI = 40% to 100%).

We also applied the binary logistic approach to the primary endpoint of the study (i.e., the 7-year prevalence of any prostate cancer). In this analysis, the odds ratio for any prostate cancer in men in the finasteride group compared with the placebo group was 0.68 (95% CI = 0.62 to 0.75) when adjusting for baseline variables alone. Additional adjustment for volume and number of cores yielded an odds ratio of 0.55 (95% CI = 0.49 to 0.62), showing that the effect of sampling density bias was not restricted to high-grade cancer.

We next developed polytomous models, which allow low-grade, high-grade, and ungraded cancer as separate possible outcomes, both with and without adjustment for sampling density (Table 4; results are shown for low- and high-grade cancer only). In these models, adjustment for sampling density lowered the odds ratio for low-grade cancer compared with no cancer in men treated with finasteride compared with men treated with placebo from 0.56 (95% CI = 0.49 to 0.63) after adjustment for baseline variables to 0.47 (95% CI = 0.41 to 0.54). Sampling density adjustment reduced the odds ratio for high-grade cancer compared with no cancer in the finasteride group from 1.14 (95% CI = 0.94 to 1.38) after adjustment for baseline variables to 0.88 (95% CI = 0.72 to 1.09). Again, the odds ratios for other covariates in these models remained unchanged.

**Discussion**

The substantial reduction in overall prostate cancer prevalence that was attributable to finasteride in the PCPT (1) is consistent with evidence (2) that androgens influence the development of this common tumor. However, the excess of high-grade cancer seen in the finasteride group precluded any simple interpretation regarding the clinical and public health significance of this trial; as a result, the American Society for Clinical Oncology and the American Urologic Association have recently decided to jointly develop clinical practice guidelines on the use of finasteride for the prevention of prostate cancer (15). A direct causal explanation for this excess—in which finasteride selectively promotes the growth of higher grade cancers while suppressing the growth of lower grade ones—has some degree of biologic plausibility (16). Aggressive prostate cancer has been reported in men with low serum testosterone, and in certain contexts growth-inhibitory effects due to excess androgen action on the prostate have been observed (17,18). It should be noted, however, that long-term administration of finasteride to rats at doses more than 100 times the systemic exposure of humans administered 5 mg per day failed to increase epithelial cell proliferation or induce malignant change in the prostate (19). Sampling bias due to shrinkage of the prostate and a resulting increase in the sampling density (the number of biopsy cores per unit of prostate volume in the finasteride arm) is one of several other hypotheses that have been suggested to explain the disproportionate increase in high-grade cancers in the finasteride arm of the PCPT. Finasteride-group participants in the PCPT experienced a 25% reduction in gland volume compared with that in placebo-group participants, a reduction that is similar to that
Table 4. Odds ratios (and 95% confidence intervals) for low- and high-grade prostate cancer (compared with no cancer) associated with finasteride use and other risk factors from polytomous logistic regression models: effect of adjustment for sampling density of the prostate at biopsy*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Model A (adjusted for baseline covariates only)</th>
<th>Model B (adjusted for baseline and sampling density covariates)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Low-grade cancer, OR (95% CI)</td>
<td>High-grade cancer, OR (95% CI)</td>
</tr>
<tr>
<td>Finasteride vs placebo</td>
<td>0.56 (0.49 to 0.63)</td>
<td>1.14 (0.94 to 1.38)</td>
</tr>
<tr>
<td>Age at biopsy (per 10 y)</td>
<td>1.24 (1.11 to 1.39)</td>
<td>1.54 (1.30 to 1.83)</td>
</tr>
<tr>
<td>African American vs other</td>
<td>1.59 (1.17 to 2.15)</td>
<td>2.53 (1.69 to 3.79)</td>
</tr>
<tr>
<td>Family history of prostate cancer (first-degree relative, yes vs no)</td>
<td>1.45 (1.24 to 1.70)</td>
<td>1.40 (1.09 to 1.78)</td>
</tr>
<tr>
<td>Baseline PSA (per ng/mL increase)</td>
<td>1.54 (1.42 to 1.68)</td>
<td>2.29 (2.02 to 2.60)</td>
</tr>
<tr>
<td>Gland volume (per 10 cm³ increase)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Number of biopsy cores (per six-core increase)</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

* The models were based on the extended Southwest Oncology Group population. A total of 452 events and 8375 nonevents were included in the models; 1071 observations were excluded due to missing values. The regression models were adjusted for all variables shown. OR = odds ratio; CI = confidence interval; PSA = prostate-specific antigen.

observed in randomized trials of finasteride for treatment of benign prostatic hyperplasia (20,21), whereas the number of needle cores at biopsy was equivalent between the finasteride and placebo groups. The analyses presented here show that adjustment for changes in gland volume due to the drug could account for essentially all of the observed association between finasteride assignment and high-grade cancer.

This conclusion came from two related regression modeling approaches. In the first approach, the observed number of high-grade cancers in the finasteride group was found to be similar to the number predicted based solely on the modeled relationship of baseline factors and gland sampling density to high-grade cancer in the placebo group. This type of analysis highlights the fact that the inverse relationship of gland volume to high-grade cancer detection exists independently of any drug effects. In fact, this approach differs from logistic regression in that it does not produce odds ratio estimates and explicitly assumes that the relationship of sampling density to cancer prevalence is the same in both treatment groups.

In the second approach, which used binary and polytomous logistic regression models encompassing both treatment groups, the relative odds for high-grade cancer between the finasteride and placebo group was approximately 1.0 after adjustment for volume was included. It is important to note that there was no evidence in these models of an interaction between treatment group and gland volume. That is, the association of volume with risk of high-grade cancer did not differ between treatment groups, as could have occurred, for example, due to differential effects of finasteride on volume of the peripheral as opposed to the central or transitional zones of the prostate. Different relationships of gland volume to risk of high-grade disease in the drug versus placebo groups would also have reduced the validity of predictions based on the placebo group alone, such as those employed in the first analytic approach. The polytomous model allows for the effect of finasteride on low- and high-grade cancer to be evaluated both simultaneously and separately. It therefore allows for the possibility, as suggested by the original trial analyses (1), that finasteride might have different, and even opposing, biologic effects on the risks of high- and low-grade tumors. The results from the polytomous models indicated that, after adjustment for sampling density, finasteride was associated with an even stronger reduction in low-grade cancer than was seen without such adjustment and with a small but non-statistically significant reduction in the risk for high-grade cancer.

Previous studies have demonstrated a higher probability for detection of prostate cancer of any grade in smaller prostate glands (22,23). In an early analysis of more than 1000 consecutive needle biopsies, prostate cancer was detected in 38% of prostates whose volume was below 50 cm³ compared with only 23% of those with volumes above 50 cm³; these differences in the cancer detection rate remained statistically significant after adjustment for age, PSA level, and digital rectal examination findings (22). The inverse relationship between gland volume and the likelihood of prostate cancer detection on random biopsy was also recognized early on by investigators who proposed using PSA density (serum PSA concentration per unit gland volume) as a method to improve the validity of PSA screening (24). More recently, evidence has emerged to indicate that the detection of high-grade cancer in particular is sensitive to gland volume and sampling density. For example, higher sampling density, such as that achieved by an 18-core biopsy, has been shown to reduce the occurrence of undergrading on biopsy relative to prostatectomy (25). Furthermore, an analysis of 369 prostatectomy cases in Canada (8) found that, although patients with gland volumes in the highest quartile were 58% less likely to have high-grade cancer on biopsy than patients with volumes in the lowest quartile, there was no association between volume and tumor grade at surgery in the same patients, consistent with the idea that high-grade cancer is more completely ascertained at biopsy in small glands. Application of a revised Gleason scoring system (26) in the PCPT, which incorporated the worst Gleason grade observed in the biopsy as one of the components in the final Gleason score regardless of its abundance in the specimen, may have further enhanced this bias because, intuitively, it seems more likely that a small amount of high-grade tissue would be encountered in a smaller gland than in a larger gland, given an equal number of biopsy cores.
Bias due to sampling density should affect detection of low-grade cancers as well as high-grade ones. Indeed, such an outcome was apparent in PCPT because adjustment for gland volume and number of biopsy cores statistically significantly reduced the odds ratio for risk of all prostate cancer from 0.68 to 0.55. Although this result implies that overall gland shrinkage affects the detection of low- and high-grade cancer approximately equally, future studies may reveal whether finasteride reduces the volume of cancer itself and, if so, whether this effect differs by tumor grade. For example, if finasteride reduces the volume of low-grade cancer more than it reduces that of high-grade cancer, one would expect to see relatively larger bias due to sampling density when estimating the drug’s association with high-grade cancer. In any event, volume bias has probably led to some degree of underestimation of finasteride’s effects on total prostate cancer prevalence even as it caused overestimation of the risk of high-grade cancer.

In the PCPT, high-grade cancers were detected far more commonly during follow-up (i.e., in for-cause biopsies) than at the end of the study (335 versus 202) and the excess of high-grade cancers in the finasteride group was confined almost entirely to cancers detected during for-cause biopsies. However, if volume affects the likelihood of detecting high-grade cancer, this bias should also occur to some extent in the end-of-study biopsies. In fact, we did observe a decrease in the odds ratio for high-grade cancer among participants receiving end-of-study biopsies once volume was added to the model, although the extent of this decrease could not be ascertained with precision due to small numbers. The stronger association of finasteride with high-grade cancer during follow-up could be partially explained by greater volume bias, given that the difference in median gland volume between the treatment arms was 9.3 cm³ for for-cause biopsies versus only 7.5 cm³ in end-of-study biopsies. However, another explanation could be that finasteride accelerates the detection of high-grade cancers during early follow-up by failing to cause the expected decline in PSA, an effect similar to the finasteride challenge that some have suggested might be used to unmask cancer in some patients (27). Suggestive evidence for this phenomenon is seen in the polytomous models presented here, in which the independent association of baseline PSA with high-grade cancer is statistically significantly greater than its association with low-grade cancer.

This study has several strengths. One is that men in the placebo and treatment groups had similar baseline characteristics and identical follow-up regimens. Relative to observational databases, all transrectal ultrasound and biopsies in the study were performed using standardized methods, and all pathology samples were examined and graded in a single central pathology laboratory. On the other hand, the study does have some weaknesses, including that the analyses described here were not specified before unblinding of the study results. However, we should note that the designers of the PCPT anticipated the possibility that the effect of finasteride on prostate volume might introduce an ascertainment bias (28), even though empirical evidence regarding this potential bias became available only after the study was initiated (22,23,25,29). Consequently, in November 2000 the PCPT Steering Committee attempted to address this potential bias by requiring that all end-of-study biopsies consist of a minimum of three cores from each side of the prostate and that biopsy needles be directed more laterally to preferentially sample the peripheral zone, where most cancers arise. Many of the for-cause biopsies were conducted before this recommendation, and the main results presented here show that this recommendation was of limited effect in reducing the volume bias.

Another possible limitation of this study is that although debate exists as to whether finasteride preferentially reduces the volume of the transition (periurethral) zone compared with that of the peripheral zone, data on the volume of these zonal compartments were not available in the PCPT. In any case, these volume estimates, if determined by ultrasound, would have been of questionable reliability, especially in a national study with numerous clinical sites. One relatively recent study, which used serial magnetic resonance imaging and tissue morphometric analysis, found that with prolonged use of finasteride, transition and peripheral zone volumes were reduced proportionately (30). If, as some studies suggest, finasteride does cause a greater reduction in transition than does peripheral zone volume, the sampling density bias due to the drug would be accentuated because inadvertent sampling of the transition zone would be even less likely (31). It should be noted that men with benign prostatic hyperplasia due to a greatly enlarged transition zone volume were likely to be underrepresented in the PCPT because the entry criteria excluded men with elevated PSA levels or urinary symptom scores. Although information on volume would have permitted a more nuanced evaluation of the sampling density bias due to finasteride, we do not believe that the lack of this information alters our basic conclusion, especially because total gland volume had an equivalent association with detection of prostate cancer (both low- and high-grade) in the placebo and finasteride groups.

Because the findings presented here come from an observational (cohort) analysis derived from randomized trial data, some important additional caveats must be considered. Adjustment for postrandomization variables that are affected by treatment, such as gland volume, can reintroduce confounding bias and complicate causal interpretation (32). In this context, the total effect of finasteride on prostate cancer risk can be viewed as the net result of two causal pathways: an indirect effect going through gland volume as an intermediate and a direct (i.e., biologic) causal effect. Standard multivariable adjustment for gland volume, as we have done, can decompose these effects and produce a valid estimate of the direct causal effect of the drug at a given gland volume, under two assumptions (33,34). The first assumption is that the amount of residual confounding of the total effect (direct and indirect) of finasteride on prostate cancer risk is acceptably small. This assumption is not unreasonable in the PCPT because both measured and unmeasured confounders were balanced at baseline by randomization. In general, an observational analysis that adjusts for an intermediate variable in the context of a randomized trial has a greater chance of meeting this criterion of minimal residual confounding than similar analyses done within a cohort or case–control study. The second assumption is that no important variables that affect both gland volume and prostate cancer risk and hence could confound their relationship have been ignored. Although the existence of such factors cannot be ruled out, no known biologic factors meet these criteria. In addition, three requirements must be met for an ignored variable to explain the results we observed in this...
instance. First, this variable must be associated with gland volume and prostate cancer risk in the same direction because a positive association with one and negative association with the other would lead to an overestimate, rather than an underestimate, of the direct effect. Because the existence and nature of any ignored but important variable are unknown, we cannot infer any direction for these associations based on prior knowledge. Therefore, approximately half of the time the direct effect will be overestimated, and, if there are many such variables, their net effect will probably be small. Second, confounding that is introduced by this postrandomization variable must be large enough to change the direct causal effect estimate for finasteride and high-grade cancer from nonstatistically significantly negative to statistically significantly positive. Third, this confounding must be large enough to overcome the effect of measurement error in ascertaining gland volume, an effect that is likely to be considerable, given that numerous observers took measurements from two-dimensional ultrasound images. This measurement error would attenuate the estimated magnitude of the indirect effect of finasteride that is mediated through gland volume. Given more precise estimation of gland volume, the direct effect component would be even smaller.

In light of these considerations, any residual bias in the treatment-and volume-adjusted direct effect estimate must be attributable to unmeasured and presumably unknown confounders. Thus, the risks involved in making a causal interpretation of our results are the same risks involved in interpreting any observational study because no observational study can be guaranteed to be free of unmeasured confounding. Judgments regarding the validity of any causal conclusion from an observational study therefore depend on the fit of the data to a well-defined biologic hypothesis versus the fit to alternative hypotheses (35). In this instance, our hypothesis regarding sampling density bias fits with the data, has biologic plausibility that is supported by findings from other studies, and is interpretable as a causal factor under well-defined and reasonable assumptions. Conversely, we are not aware of competing explanations in which gland volume does not play a substantial role that have these characteristics. Efforts are being directed at developing new statistical methods—such as principal stratification and instrument variable techniques—that estimate direct causal effects while also accounting for intermediate variables and unmeasured confounding (36–40); such methods might provide interesting opportunities for future analyses of the PCPT data, although each approach has its own set of required assumptions. For example, for principal stratification analysis to be feasible for the data analyzed here, the effects of missing data and noncompliance must be ignorable, gland volume must be viewed as a dichotomized variable, and gland volume must be predicted accurately by the available data.

It is possible that with further adjustment for the contribution of other potential biases—especially the effect of finasteride on PSA levels—an inverse or protective association between finasteride and both high- and low-grade cancer might emerge. However, even if it were established that finasteride reduces the prevalence of lower grade prostate cancer but has no effect on high-grade cancer, the clinical and public health implications could still be substantial. Because most men in the United States with localized, low-risk cancer opt for surgery or radiation therapy, a large number of men could be spared the morbidity and expense of this treatment (41). In addition, even though the risks of death from prostate cancer are lower among men with Gleason grade 6 or less compared with men with higher grade prostate cancer, the predominance of lower-grade tumors during the PSA screening era means that such tumors make a large contribution to the total prostate cancer deaths on a population level. If our conclusion that finasteride accelerates the detection of high-grade cancer yet may not promote its development is correct, then the implications regarding the clinical impact of this drug are quite favorable. The occurrence of lower-grade tumors of questionable clinical significance would be reduced, and the early detection of more serious tumors would be enhanced.

The null relationship between finasteride and high-grade cancer that we observed in the PCPT after adjustment for gland volume must be interpreted cautiously and does not allow us to recommend definitive changes in clinical practice. Analyses pertinent to other hypotheses regarding the excess of high-grade cancer in PCPT are ongoing, and some recent publications have suggested that this excess was not caused by overgrading due to incidental effects of finasteride on tumor histology (42–44). A recent consensus meeting on the clinical implications of the PCPT concluded that the increase in high-grade cancer was probably attributable to detection bias (45). The REDUCE trial of the 5α-reductase inhibitor dutasteride is scheduled to be completed in the next few years (46) and is likely to provide information of great importance on the safety and efficacy of 5α-reductase inhibitors for the primary prevention of prostate cancer. The modeling approaches we have used may be applicable in that trial as well.

References
