2016

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*A SWOG-Coordinated Study S9217

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Running title: Intraprostatic inflammation during finasteride treatment

Keywords: Prostate cancer, Inflammation, Finasteride, Prostate-specific antigen, Risk

Financial support: This work was funded by Public Health Service grants P01 CA108964 (IM Thompson, Project 4 EA Platz) and P50 CA58236 (WG Nelson) from the National Cancer Institute. The PCPT is funded by Public Health Service grants U10 CA37429 (CD Blanke) and UM1 CA182883 (IM Thompson/CM Tangen) from the National Cancer Institute.

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Disclosure of Potential Conflicts of Interest:
Teemu J. Murtola has participated in scientific congresses at the expense of Astellas and has received lecture fee from Abbvie and GlaxoSmithKline. William G Nelson has served as paid consultant for GlaxoSmithKline and has received compensation from Merck. The other authors declare that they have no other competing financial interests related to this paper.

Note: The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Word counts

Abstract: 236

Text: 3,529
Number of tables: 4

http://dx.doi.org/10.1158/1055-9965.EPI-15-0987

ABSTRACT

Background: A previous analysis of the placebo arm of the Prostate Cancer Prevention Trial (PCPT) reported 82% overall prevalence of intraprostatic inflammation and identified a link between inflammation and higher-grade prostate cancer and serum PSA. Here we studied these associations in the PCPT finasteride arm.

Methods: Prostate cancer cases (N=197) detected either on a clinically indicated biopsy or on protocol-directed end-of-study biopsy, and frequency-matched controls (N=248) with no cancer on an end-of-study biopsy were sampled from the finasteride arm. Inflammation in benign prostate tissue was visually assessed using digital images of H&E stained sections. Logistic regression was used for statistical analysis.

Results: In the finasteride arm, 91.6% of prostate cancer cases and 92.4% of controls had at least one biopsy core with inflammation in benign areas; $p < 0.001$ for difference compared to placebo arm. Overall, the odds of prostate cancer did not differ by prevalence (OR=0.90, 95% CI 0.44-1.84) or extent (P-trend=0.68) of inflammation. Inflammation was not associated with higher-grade disease (prevalence: OR=1.07, 95% CI 0.43-2.69). Furthermore, mean PSA concentration did not differ by the prevalence or extent of inflammationin either cases or controls.

Conclusion: The prevalence of intraprostatic inflammation was higher in the finasteride than placebo arm of the PCPT, with no association with higher-grade prostate cancer.

Impact: Finasteride may attenuate the association between inflammation and higher-grade prostate cancer. Moreover, the missing link between intraprostatic inflammation and PSA suggests that finasteride may reduce inflammation-associated PSA elevation.

Introduction

A recent analysis in the placebo arm of the Prostate Cancer Prevention Trial (PCPT) indicated a greater prevalence and extent of intraprostatic inflammation in benign prostate tissue of higher-grade prostate cancer cases than controls (1). The PCPT was a placebo-controlled, randomized clinical trial studying whether finasteride, a drug that inhibits the conversion of testosterone into the more potent androgen dihydrotestosterone in the prostate, could decrease the risk of prostate cancer in men initially at low to moderate risk of the disease. Finasteride has been reported to reduce symptoms of type IIIa chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) (2), a condition associated with intraprostatic inflammation, and possibly also those of bacterial prostatitis (3). However, it is currently unknown how finasteride affects the prevalence and extent of intraprostatic inflammation and whether it affects the association between inflammation and prostate cancer risk, including higher-grade disease.

We had 3 *a priori* hypotheses concerning finasteride's effect on intraprostatic inflammation: 1) less inflammation because of a possible reduction of CP/CPPS symptoms during finasteride treatment (2), 2) absolute increase in inflammation in response to finasteride-mediated epithelial cell death and prostate shrinkage (4), or 3) proportional increase in inflammation based on the prostate volume reduction causing the same number of immune cells to cover a larger portion of the remaining prostate tissue.

Thus, we performed a case-control study nested in the finasteride arm of the PCPT to evaluate the association between intraprostatic inflammation and prostate cancer risk during finasteride treatment. A unique feature of PCPT was that all men underwent annual prostate-specific antigen (PSA) screening and digital-rectal examination (DRE), and men not diagnosed with prostate cancer by the end of the 7-year follow-up period were asked to undergo an end-of-study prostate biopsy irrespective of whether they had a clinical

indication, that is, suspicion of prostate cancer (5). Consequently, tissue was available from both prostate cancer cases and from cancer-free controls.

Materials and Methods

Study population and design

We studied a subset of men who participated in the multisite PCPT (5). The trial included men who were ≥55 years; had no abnormalities detected on DRE and had PSA value ≤3 ng/mL and no to moderate lower urinary tract symptoms (American Urological Association Symptom Index <20) at baseline. A total of 18,882 men were enrolled in the trial between 1993 and 1997 and were randomized to receive finasteride (5 mg/day) or placebo for 7 years. At trial entry, participant weight and height were measured for calculation of body mass index (BMI; kg/m^2). Additionally, participants completed a questionnaire, which included questions on demographics, lifestyle, and medical factors, such as cigarette smoking history, first-degree family history of prostate cancer, and history of diabetes.

During follow-up, participants were screened annually for prostate cancer by PSA and DRE. The PSA threshold for prostate biopsy was 4 ng/mL. To ensure equal percentage of prostate biopsies in both study arms, the measured PSA values were initially doubled for finasteride-treated men, and from the beginning of the fourth year in the study a multiplying factor of 2.3 was used. If either PSA or DRE was abnormal, men were recommended for prostate biopsy. Cancers detected on a biopsy done for clinical suspicion of prostate cancer were termed “for-cause" biopsy detected cases. To catch cancer cases missed because of finasteride’s PSA lowering effect, all men in both arms of the trial who were not diagnosed with prostate cancer during the trial were requested to undergo prostate biopsy after seven years on the trial irrespective of their PSA

concentration or DRE status (5). Cancers detected on these biopsies were considered to be for-cause biopsy detected if the man had an elevated PSA or abnormal DRE, otherwise, these cancers were considered to be end-of-study biopsy detected.

Pathologic evaluation of the prostate biopsy cores, including evaluation of Gleason sum, was confirmed at the Prostate Diagnostic Laboratory at the University of Colorado; pathologists were blinded to the trial arm and exposure information (5).

Adherence (whether the participant was on or off finasteride) and compliance to finasteride (the proportion of doses used) were checked biannually at research visits for reissuing of medication and counting of remaining finasteride doses (5).

The PCPT was approved by the institutional review boards at each trial site. This study on inflammation was approved by the Johns Hopkins Bloomberg School of Public Health Institutional Review Board and by the Colorado Multiple Institutional Review Board.

Prostate cancer cases and controls

To create a case-control study for evaluation of intraprostatic inflammation we used a sub-sample of a previously developed case-control study nested in the PCPT that included all 1,809 eligible men diagnosed with prostate cancer (cases) either on for-cause or end-of-study biopsy, and a sample of 1,809 men who were negative for prostate cancer on end-of-study biopsy (controls) (6). To enrich the population for non-white men, all 372 non-white men were included in the control group, and 1,437 men were sampled from the white men without prostate cancer to achieve the target of 1,809 controls. Controls were frequency matched to cases on age at baseline, first-degree family history of prostate cancer at baseline, and treatment arm.

For the inflammation study 197 cases from the finasteride arm of the PCPT were selected from the larger case-control population. To enhance statistical efficiency, we

sampled approximately equal numbers of cases by grade (Gleason sum ≤6; or 7-10) and biopsy indication (for-cause, end-of-study). Additionally, 248 controls who did not have cancer at end-of-study biopsy were sampled from the finasteride arm.

Assessment of inflammation in benign prostate tissue from biopsies

The H&E stained slides of the prostate biopsies used for prostate cancer diagnosis during the PCPT were reviewed for inflammation. For each man, 6-10 needle biopsy cores were usually taken. Multiple cores were mounted on each slide. We sampled a median of 2 slides per man, yielding, on average, 3.3 biopsy cores per man. Cores were mainly from the apex or mid-gland.

In both cases and controls, we evaluated inflammation in only the benign areas of the biopsy cores. To blind the pathologist to case-control status, all areas of adenocarcinoma (cases) and arbitrary benign areas on cores without cancer (cases and controls) were masked with ink on the slide cover slips (1). We used the Aperio ScanScope slide scanner (Aperio, Vista, CA) to digitally image the H&E stained slides. Slide images were uploaded into the Spectrum Digital Pathology Information Management System (Aperio, Vista, CA) and were visually reviewed for inflammation online using the Aperio ImageScope Viewer Software package.

Assessment of inflammation in benign tissue in the PCPT has been described in detail previously (1). In short, the following aspects were evaluated: 1) the presence of any inflammatory cells, any acute inflammatory cells (e.g., polymorphonuclear cells), and any chronic inflammatory cells (e.g., cells with an appearance consistent with that of lymphocytes and macrophages) in the benign tissue for each biopsy core on each slide; 2) the proportion of the total benign (unmasked) biopsy core area per slide that had involvement of any inflammatory cells, either acute inflammatory cells, or chronic

inflammatory cells; and 3) an inflammation score using a modified version of the histopathological classification system developed by Nickel et al. (7). For the latter, the extent (1=focal, 2=multifocal, 3=diffuse) and grade (1=mild, 2=moderate, 3=severe) of inflammation present was recorded separately for the luminal, intraepithelial, and stromal compartments of the benign prostate tissue on each slide. All of the images for this study were reviewed by a single pathologist (BG), who was trained to score inflammation using these methods.

Statistical analysis

We used linear regression with model adjustment for baseline age, family history of prostate cancer, and race to calculate adjusted means and proportions for population characteristics, measures of inflammation, serum PSA, and adherence and compliance to finasteride use. Logistic regression with the same model adjustments was used to evaluate statistical significance of the differences between cases and controls.

We used logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI) of prostate cancer overall, and separately for higher-grade (Gleason 7-10) and lower-grade (Gleason 6 or less) prostate cancer by inflammation prevalence (i.e., at least one biopsy core with inflammation) and extent (i.e., none, some, or all cores with inflammation). We adjusted for age, family history of prostate cancer, and race. We performed separate analyses for all men (intention-to-treat analysis) and for men on finasteride at the time of biopsy to evaluate the biological effect. In further sensitivity analyses we evaluated the influence of PSA concentration, Gleason sum and compliance to finasteride (≤75% vs. >75% of the assigned finasteride doses used) on these associations.

Logistic regression was performed using IBM SPSS statistics 20 statistical software (Chicago, Illinois, USA). Adjusted means were estimated using STATA version 12 (StataCorp LP, College Station, Texas, USA). All statistical tests are two-sided.

Results

Study Population Characteristics

Due to frequency matching in the parent nested case-control study, the median age at the trial baseline and the prevalence of family history of prostate cancer were similar between cases and controls (Table 1). The proportion of non-white men was higher among controls due to their oversampling in controls. After adjusting for age, family history, and race, the prevalence of smoking and diabetes, and the median BMI and mean prostate volume were comparable in cases and controls. The median PSA was higher among prostate cancer cases compared to controls both at baseline and at the time of biopsy, with the highest concentration observed in men subsequently diagnosed with higher-grade prostate cancer (Table 1). As expected given their randomization to the finasteride arm, PSA concentration decreased between baseline (before finasteride treatment) and biopsy (after 7 years of treatment) most among controls, but also among prostate cancer cases, with the exception of higher-grade cases in whom the mean PSA concentration increased compared to baseline despite finasteride. Adherence and compliance to finasteride use were lower in cases compared to controls, being lowest in men diagnosed with lower-grade prostate cancer (Table 1).

Prevalence and Extent of Inflammation in Benign Prostate Tissue in Controls

The prevalence and extent of inflammation was examined for all patients in the finasteride arm (Table 2, All men) as well as for those who were actively taking finasteride at the time of biopsy (Table 2, Men on finasteride at time of biopsy) The prevalence of inflammation among controls (men without cancer on end of study biopsy) was 92.4% for all men in the finasteride arm, and 93.5% in men on finasteride at the time of biopsy (Table 2). Most of the inflammation present was chronic (313 men, 70.3%); of these men, 131

(41.9%) had grade 3 chronic inflammation. In contrast, acute inflammation was observed only in 34 men (7.6%); of these men, 1 (2.9%) had grade 3 acute inflammation. Interestingly, the prevalence and extent of inflammation was higher in the finasteride arm (present study) in the control group (without cancer) than in the placebo arm. For example, in the controls the number of men with at least one core with inflammation (92.4% on finasteride vs. 78.2% not on finasteride; p = <.001), and the mean of mean percentage of tissue area with inflammation (16.4% in the finasteride arm vs. 11.5% in the placebo arm; p = <.001) were both significantly higher in the finasteride arm.

Inflammation and Prostate Cancer Risk

Unlike in the placebo arm (1) no difference in prevalence or extent of inflammation was observed between cases and controls overall (Table 2) or by location (intraluminal, stromal or epithelial, data not shown) in the finasteride arm. The exception was a lower mean percentage of biopsy cores with inflammation, a measure of extent, in lower-grade cases compared to controls in the intention-to-treat analysis. However, the difference was no longer significant in men on finasteride at the time of biopsy.

Overall, unlike in the placebo arm there were no statistically significant associations between prevalence or extent of inflammation and the odds of prostate cancer either in the intention-to-treat analysis or among men on finasteride (Table 3). An increasing extent of inflammation was associated with a decreasing odds of lower-grade disease (P-trend 0.03), but only in the intention-to-treat analysis.

Inflammation and PSA Concentration

Serum PSA concentration at the time of biopsy did not differ by the prevalence or

extent of inflammation in either cases or controls (Table 4). This is also in contrast to findings in the placebo arm (1). The exception was a higher PSA concentration among men with at least one biopsy core with inflammation compared to men with no biopsy cores with inflammation among those on finasteride at the time of biopsy (P=0.05).

Having inflammation in all biopsy cores (versus none) was non-significantly inversely associated with prostate cancer in both men with lower (PSA ≤2 ng/ml, OR 0.73, 95% CI 0.27-2.00) and higher (PSA >2 ng/ml, OR 0.50, 95% CI 0.09-2.88) corrected PSA concentration. For higher-grade cancer the pattern of association was different from overall; the OR for having inflammation in all biopsy cores was above 1.0 for men with PSA >2 ng/ml (OR 1.17, 95% CI 0.17-8.25), but less than 1.0 for men with PSA at ≤2 ng/ml (OR 0.83, 95% CI 0.21-3.28).

Estimated effect of prostate volume shrinkage on intraprostatic inflammation

The overall prevalence of intraprostatic inflammation in the PCPT finasteride arm was higher compared to the placebo arm (1); the proportion of men with at least one biopsy core with inflammation was 92.4% vs. 78.2% in the controls and 91.2% vs. 86.2% in prostate cancer cases, respectively. Also, the mean extent of inflammation (mean of the mean percentage of tissue area with inflammation) was 5.5% higher in the PCPT finasteride arm (16.7%) compared to the placebo arm (11.2%) (1). Because finasteride treatment decreases prostate volume, we calculated how much the extent of inflammation would increase due to volume reduction if we assume that the absolute amount of inflammation-affected tissue would remain constant in the prostate. The median prostate volume was 15% lower in the finasteride arm compared to the placebo arm (25.1 vs. 29.5 cm^3, respectively). Therefore, the absolute volume of inflamed tissue in a 30 cm^3 prostate in a man before finasteride treatment is assumed to be 11.2% x 30 cm^3 = 3.36 cm^3. If the

prostate volume decreased by 15%, the new volume would be 0.85 x 30 cm^3 = 25.5 cm^3. Therefore, the extent of the same amount of inflamed tissue in lower volume prostate would be 3.36 cm^3/25.5 cm^3=13.1%, which is 1.9% higher than the assumed original extent of 11.2%. Thus, the expected percentage of tissue with inflammation that would be due to gland shrinkage (13.1%) is lower than the observed extent (16.7%).

Discussion

In the finasteride arm of the PCPT, we observed a high prevalence and extent of inflammation in benign prostate tissue, but did not observe any association between intraprostatic inflammation and the risk of total or higher-grade prostate cancer. Further, intraprostatic inflammation was not associated with serum PSA concentration in these finasteride-treated men. Previously published results from the PCPT placebo arm reported 86% and 78% prevalence of intraprostatic inflammation among prostate cancer cases and controls, respectively, with highest prevalence being observed in cases with higher-grade disease(1). We show that in the finasteride arm the overall prevalence of intraprostatic inflammation was higher, the observed positive association with risk of total and higher-grade cancer was fully attenuated, and the observed positive association between finasteride-associated inflammation and PSA was missing.

Finasteride treatment induces both apoptosis and a reduction in cellular volume (hormonal atrophy) in the prostate (8), which leads to overall prostate volume reduction. Androgens and androgen deprivation therapy influence the immune system both systemically (9) and locally (10). Local prostate effects are characterized by an increased number of macrophages, dendritic cells, and T-cells in the tissue (10). Androgen ablation makes normally tolerant T-cells recognize prostate antigens and proliferate in response to them (4). Although we did not assess specific types of inflammatory cells present, the markedly elevated prevalence of intraprostatic inflammation in the finasteride arm relative to the placebo arm suggests that similar effects result also from local androgen inhibition in the prostate in response to 5α-reductase inhibition. This is supported by an even higher prevalence of inflammation in men still on finasteride at the time of biopsy.

To determine whether the hypothesis of absolute or proportional increase in inflammation is more likely, we considered the possible effect of prostate volume reduction

during finasteride treatment on extent of inflammation. This analysis indicated that while some of the increase in inflammatory cells could be the result of gland shrinkage, the estimated increase in inflammation extent due to overall volume decrease by finasteride does not entirely explain the greater extent of intraprostatic inflammation in finasteride-treated men compared to the placebo arm. Instead, our findings suggest that finasteride treatment induces intraprostatic inflammation as has been previously reported for other types of androgen deprivation (9,10).

Unlike in the previous study in the PCPT placebo arm (1), we did not observe an association between intraprostatic inflammation and risk of prostate cancer overall or higher-grade disease in the finasteride arm. This may be because the high prevalence of inflammation in finasteride-treated men makes comparisons underpowered given our sample size, or because chronic finasteride-associated inflammation is not a prostate cancer risk factor as it is in placebo-treated men. The latter notion is supported by the lack of an association between finasteride-associated inflammation and PSA level; inflammation induced by finasteride treatment may not cause such damage to prostate epithelial cells that would allow PSA to leak into circulation, or finasteride treatment may attenuate the cytotoxic effects of inflammation. The immune cells induced to infiltrate the prostate during finasteride therapy may not be pro-carcinogenic; in fact they may be anti-tumorigenic (10). Inflammation observed in the placebo arm may also reflect more long-standing and etiologically relevant inflammation, whereas finasteride-induced inflammation could have started only after PCPT randomization, at maximum seven years earlier. Further research will be needed to clarify which of these speculations, if any, is explanatory.

The lack of an association between finasteride-associated inflammation and PSA also has implications for the accuracy of PSA as a tumor marker. If benign causes of PSA

elevation, such as intraprostatic inflammation, are removed by finasteride treatment, the performance of PSA would be enhanced as a prostate cancer tumor marker. Concordantly, an earlier PCPT analysis reported improved sensitivity of PSA to detect prostate cancer during finasteride treatment (11). In the current analysis, PSA was decreased at prostate biopsy as compared with the baseline level obtained before starting finasteride, except in those later diagnosed with higher-grade cancer. This observation suggests that PSA elevation is more specific to higher-grade prostate cancer during finasteride therapy.

We observed a possible inverse association between extent of finasteride-associated inflammation and risk of lower-grade prostate cancer. This finding was not explained by differing likelihood of a prostate biopsy as the association was also inverse even in men with a low corrected PSA (≤2 ng/ml). We also observed that lower-grade cases had a lower prevalence and extent of inflammation than controls; these differences were attenuated when restricting to men on finasteride at the time of biopsy.

Our study has several unique strengths. Prostate cancer screening and diagnosis were standardized by the PCPT study protocol, and tumor diagnosis and Gleason sum were confirmed by central pathological review. The pathologist who assessed inflammation in all biopsy cores was trained to evaluate inflammation by a consensus-developed system (7), and was fully blinded to case-control status and treatment arm, which reduces the potential for observation bias. We also had the unique opportunity to evaluate the association between intraprostatic inflammation and prostate cancer risk in men with very low PSA, allowing evaluation of biological effects in the prostate without the possible detection bias due to inflammation affecting PSA level and likelihood for prostate biopsy.

Our study also has some limitations. Although PCPT was a prospective randomized trial, our current nested case-control study was a retrospective analysis. Inflammation in prostate cancer tissue was evaluated only at one time-point (time of biopsy) and we could not evaluate time trends in intraprostatic inflammation during finasteride usage. Further, we could not determine whether inflammation in benign tissues of cancer cases was due to the tumor or vice versa. Prostate biopsies are taken mainly from the peripheral zone of the prostate where malignancy usually occurs. We could not determine whether inflammation in central areas (e.g. the transition zone) of the prostate is associated with prostate cancer risk. Participants of the PCPT trial were selected to be men with low risk of prostate cancer at baseline, and were screened yearly for the entire duration of the trial. Thus, we could not evaluate associations between inflammation and metastatic prostate cancer at diagnosis or prostate cancer death. Finally, due to low number of non-white men we could not evaluate the association between intraprostatic inflammation and prostate cancer separately by race.

In conclusion, we found that men using finasteride have an increased prevalence and extent of intraprostatic inflammation compared to men not using finasteride. Nevertheless, finasteride-associated inflammation was not associated with risk of higher-grade prostate cancer or PSA in contrast to findings in the PCPT placebo arm. Finasteride may improve the accuracy of PSA as a tumor marker, if it does indeed minimize PSA elevation due to inflammation. Future studies will need to address whether increased inflammation in finasteride-treated men is due to sustained cell death and hormonal atrophy in prostate tissue, and whether intraprostatic inflammation is associated with metastatic or fatal prostate cancer.

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Table 1. Characteristics* of prostate cancer cases and controls**, finasteride arm, Prostate Cancer Prevention Trial

	Controls	Prostate cancer cases		
		Total	Lower grade (Gleason 6 or less)	Higher grade (Gleason 7-10)
N	248	197	97	100
Mean age at baseline (years)	64	64	64	65
Mean age at biopsy (years)	74	71	71	72
Non-white; n (%)	60 (24.2)	21 (10.7)#	10 (10.3)#	11 (11.0)#
Family history; n (%)	53 (21.4)	41 (20.8)	22 (22.7)	19 (19.0)
Cigarette smoking history; n (%)				
Current	16 (6.5)	11 (5.6)	3 (3.1)	8 (8.0)
Former	144 (58.1)	120 (60.9)	57 (58.8)	63 (63.0)
Never	88 (35.5)	66 (33.5)	37 (38.1)	29 (29.0)
Mean pack-years smoked, current and former smokers	13.8	14.4	14.4	14.6
Mean body mass index (kg/m^2)	27.9	27.5	27.3	27.7
History of diabetes; n (%)	16 (6.5)	10 (5.1)	4 (4.1)	6 (6.0)
Mean prostate volume (cc)	27.3	26.2	26.1	26.4
Mean PSA***				
Concentration at baseline (ng/mL)	1.10	1.50#	1.43#	1.56#
Concentration at biopsy (ng/mL)	0.54	1.28#	1.28#	1.49#
Mean annual change in PSA (ng/mL/year)	-0.62	-0.07#	-0.30#	0.16#
Adherence to finasteride use; n (%)	231 (93.1)	170 (86.3)#	82 (84.5)#	88 (88.0)
Mean compliance with finasteride treatment (%)	91.8	85.5	82.5	88.4

*For all characteristics except baseline age, family history of prostate cancer, and race, values were calculated by generalized linear models (linear for adjusted proportions and means and logistic for P-values) adjusting for baseline age, family history, and race.
**In the parent nested case-control study, cases and controls were frequency matched on baseline age and family history. All non-white controls were sampled. For this tissue-based study, cases were sampled from the finasteride arm of the trial so that half were higher grade (Gleason sum ≥7) and half were lower grade (Gleason sum <7), and of these half were detected on a biopsy performed for an elevated PSA or an abnormal digital-rectal examination (for-cause biopsy) and half were detected on a biopsy performed at the end of the trial per trial protocol (end-of-study biopsy). Controls were sampled from men who were negative for prostate cancer on the biopsy performed at the end of the trial per protocol.
*** Uncorrected PSA concentrations (see Methods)
#P<0.05 compared with controls.

Table 2. Prevalence and extent* of inflammation assessed in benign prostate tissue from biopsy cores in prostate cancer cases overall and by grade and controls**, finasteride arm of the Prostate Cancer Prevention Trial

	All men				Men on finasteride at the time of biopsy			
	Controls	Prostate cancer cases			Controls	Prostate cancer cases		
		Total	Grade			Total	Grade	
			Lower grade	Higher grade			Lower grade	Higher grade
N	248	197	97	100	231	170	82	88
At least one biopsy core with inflammation (%)***	92.4*****	91.6*****	90.2	92.7	93.5	92.9	93.9	92.0
Mean of the percentage of biopsy cores with inflammation***	71.0	67.7	62.1#	73.0	72.0	70.3	66.7	73.7
Mean of the mean percentage of tissue area with inflammation****								
Overall	16.4	17.0	14.6	19.0	16.8	17.8	15.3	20.1
In men with at least one biopsy core with inflammation	17.7	18.5	16.3	20.4	18.0	19.1	16.3	21.8

*From generalized linear models (linear for adjusted proportions and means, logistic for P-values) adjusting for baseline age, family history of prostate cancer, and race.

** In the parent nested case-control study, cases and controls were frequency matched on baseline age and family history of prostate cancer. All non-white controls were sampled. For this tissue-based study, cases were sampled from the finasteride arm of the trial so that half were higher grade (Gleason sum ≥7) and half were lower grade (Gleason sum <7), and of these half were detected on a biopsy performed for an elevated PSA or an abnormal digital-rectal examination (for-cause biopsy) and half were detected on a biopsy performed at the end of the trial per trial protocol (end-of-study biopsy). Controls were sampled from men who were negative for prostate cancer on the biopsy performed at the end of the trial per protocol.

***For each man, the denominator is total number of biopsy cores evaluated.

****For each man, the denominator is total benign tissue area across all biopsy cores evaluated on each of the man's slides.

***** The prevalences in the PCPT placebo arm were 78.2% in controls and 86.2% in cases (1).

#P≤0.05 compared with controls.

Table 3. Association* between inflammation assessed in benign prostate tissue from biopsy cores and prostate cancer risk, overall and by grade, finasteride arm, Prostate Cancer Prevention Trial

	Prostate cancer cases, all			Prostate cancer cases, men on finasteride at the time of biopsy		
	Total	Lower grade	Higher grade	Total	Lower grade	Higher grade
N	197	97	100	170	82	88
At least one biopsy core with inflammation						
OR	0.90	0.75	1.07	0.93	1.03	0.79
95% CI	0.44-1.84	0.32-1.75	0.43-2.69	0.42-2.08	0.35-3.02	0.31-2.06
Extent of biopsy cores with inflammation						
Zero cores						
OR	1.00	1.00	1.00	1.00	1.00	1.00
95% CI	Reference	Reference	Reference	Reference	Reference	Reference
Some cores						
OR	1.00	0.97	1.00	1.00	1.30	0.72
95% CI	0.48-2.09	0.40-2.32	0.38-2.58	0.44-2.31	0.43-3.91	0.27-1.93
All cores						
OR	0.80	0.52	1.16	0.86	0.76	0.87
95% CI	0.38-1.68	0.21-1.30	0.45-3.00	0.37-1.98	0.25-2.34	0.33-2.34
P-trend	0.68	0.03	0.57	0.49	0.13	0.77

*From a logistic regression model adjusting for the matching factors (baseline age and family history of prostate cancer) and for oversampling of non-white controls. In the parent nested case-control study, cases and controls were frequency matched on baseline age and family history of prostate cancer. All non-white controls were sampled. For this tissue-based study, cases were sampled from the finasteride arm of the trial so that half were higher grade (Gleason sum ≥7) and half were lower grade (Gleason sum <7), and of these half were detected on a biopsy performed for an elevated PSA or an abnormal digital-rectal examination (for-cause biopsy) and half were detected on a biopsy performed at the end of the trial per trial protocol (end-of-study biopsy). Controls were sampled from men who were negative for prostate cancer on the biopsy performed at the end of the trial per protocol.

Table 4. Mean serum PSA concentration at biopsy* by prevalence and extent of inflammation assessed in benign prostate tissue from biopsy cores in the controls and prostate cancer cases, finasteride arm, Prostate Cancer Prevention Trial

	All men						Men on finasteride at the time of biopsy					
	At least one biopsy core with inflammation		P	Extent of biopsy cores with inflammation		P-trend**	At least one biopsy core with inflammation		P	Extent of biopsy cores with inflammation		P-trend**
	No	Yes		Some	All		No	Yes		Some	All	
CONTROLS												
Total (N)	19	229		115	114		15	216		107	109	
Mean PSA at biopsy (ng/ml)***	0.56	0.60	0.51	0.58	0.61	0.34	0.38	0.55	0.05	0.55	0.55	0.22
Without indication for biopsy (N)	16	217		110	107		13	206		104	102	
Mean PSA at biopsy (ng/ml)***	0.59	0.58	0.74	0.58	0.58	0.53	0.39	0.54	0.06	0.55	0.52	0.48
CASES												
Total (N)	16	181		99	82		12	158		83	75	
Mean PSA at biopsy (ng/ml)	1.33	1.54	0.58	1.61	1.46	0.74	1.10	1.40	0.41	1.50	1.28	0.60
Detected on a for-cause biopsy (N)	8	90		48	42		6	82		43	39	
Mean PSA at biopsy (ng/ml)***	1.67	2.12	0.43	2.29	1.91	0.57	1.23	1.88	0.29	2.14	1.58	0.34
Detected on an end-of-study biopsy (N)****	8	91		51	40		6	76		40	36	
Mean PSA at biopsy (ng/ml)***	0.99	0.97	0.92	0.96	0.99	0.90	0.98	0.88	0.63	0.81	0.95	0.55

*From linear regression models adjusting for age at baseline.
**Across no (zero), some, all biopsy cores with inflammation. Reference is men with “No” (zero) biopsy cores with inflammation.
*** Uncorrected PSA concentrations (see Methods)
****Without an indication for biopsy.