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Intraprostatic inflammation is positively associated with serum PSA in men with PSA <4 ng/mL, normal DRE, and negative for prostate cancer

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Abstract

BACKGROUND—Biopsies performed for elevated serum PSA often show inflammatory infiltrates. However, the influence of intraprostatic inflammation on serum PSA in men without biopsy indication and negative for prostate cancer has not been described in detail.

METHODS—We studied 224 men in the placebo arm of the Prostate Cancer Prevention Trial (PCPT) who underwent end-of-study biopsy per trial protocol, had PSA<4 ng/mL, normal digital-rectal examination, and a biopsy negative for cancer. We analyzed data from H&E-stained slides

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containing a mean of 3 biopsy cores. Inflammation measures included the extent (percentage of tissue area with inflammation) and intensity (product of scores for extent and grade) of total, acute, and chronic inflammation in the entire tissue area examined, and by tissue compartment. We calculated median measures of inflammation by pre-biopsy serum PSA tertile (>0–≤0.8, >0.8–≤1.5, >1.5–<4.0 ng/mL). We estimated the association between percentage of tissue area with inflammation and natural logarithm of PSA using linear regression adjusting for age at biopsy.

RESULTS—Median percentage of tissue area with inflammation increased from 2% to 5% to 9.5% across PSA tertiles (P-trend<0.0001). For every 5% increase in tissue area with inflammation, log PSA increased by 0.061 ng/mL (P=0.0002). Median extent and intensity scores increased across PSA tertiles in luminal and intraepithelial compartments for acute inflammation and in stromal and intraepithelial compartments for chronic inflammation (all P-trend≤0.05).

CONCLUSION—In men without clinical suspicion of prostate cancer, greater overall inflammation, luminal and intraepithelial acute inflammation, and stromal and intraepithelial chronic inflammation were associated with higher serum PSA.

Keywords

prostate; inflammation; biopsy; PSA

Introduction

Prostate biopsies performed for elevated serum prostate-specific antigen (PSA), a biomarker commonly used to screen for prostate cancer, often show acute and chronic inflammation.[1–7] Further, the extent or aggressiveness of inflammation in prostate tissue removed during prostatectomy or surgery for benign prostatic hyperplasia has been found to be positively associated with PSA concentrations.[8–11] While the mechanism by which inflammation influences circulating PSA is not completely understood, Irani et al.[11] hypothesized that epithelial cell disruption coupled with inflammation-induced vascular permeability allows PSA to leak into circulation. Extent and intensity of intraprostatic inflammation and location within prostatic tissue compartments (e.g., stromal, intraepithelial, luminal) using a consensus-based scoring system have never been correlated with serum PSA nor studied in men without prostate cancer suspicion. As all previous studies examining this association have done so in men whose biopsies were clinically indicated, the conclusions may have been biased in favor of an association.

We previously reported on intraprostatic inflammation and serum PSA in controls in the placebo arm of the PCPT.[12] Mean PSA measured at the end-of-study biopsy was higher in men who had ≥1 biopsy core (of a mean of 3 evaluated) with inflammation (2.4 vs 1.3 ng/mL, P=0.003), including after excluding men with clinical indication for biopsy (1.7 vs 1.1 ng/mL, P=0.001). Further, PSA increased with increasing number of cores with inflammation (P-trend<0.0001), a finding that persisted after excluding men with clinical indication (P-trend=0.0002). In the cases, in whom the cancer is a source of serum PSA, inflammation was not related to PSA.[12]

Given these prior findings, it was recognized that a more in-depth investigation was needed to better understand the influence of intraprostatic inflammation on PSA in men without prostate cancer, and in which the decision for biopsy was unrelated to the link between inflammation and PSA. If established for this group of men, knowledge of this inflammation-PSA association may improve prostate cancer detection by reducing unnecessary biopsies prompted by PSA elevations due to inflammation, not cancer. For example, information on the link between intraprostatic inflammation and PSA in men without an indication for biopsy along with information from men with elevated PSA due and not due to cancer could be used in the development of a model that partitions contributors – cancer, inflammation etc. – to circulating PSA level. Such a model then could be used to adjust measured PSA concentration for the presence and extent of intraprostatic inflammation for decision-making about re-biopsy in men with elevated PSA but negative for cancer on a first biopsy.

For this reason, in this current study we undertook a more detailed assessment of the association of extent and intensity of acute and chronic inflammation in biopsies in the luminal, intraepithelial, and stromal compartments with serum PSA in men who underwent an end-of-study prostate biopsy. This unique cohort had a PSA concentration lower than the usual prompt for biopsy and a normal prostate digital-rectal examination but underwent a prostate biopsy as part of the trial protocol, and had no evidence of prostate cancer on biopsy. The inflammation that we studied in these biopsies might be classified as group IV (asymptomatic inflammatory prostatitis) using the National Institute of Health (NIH) consensus classification,[13] although the consensus classification scheme did not explicitly consider inflammation observed in biopsies in men without indication for prostate tissue removal. Based on our prior work,[12] we hypothesized that intraprostatic inflammation would be positively associated with circulating PSA concentration even in men without an indication for prostate biopsy.

Materials and Methods

Study design and population

We conducted a cross-sectional analysis among men randomized to the placebo arm of the PCPT.[14] The investigators previously developed a nested case-control study that included all 1,809 prostate cancer cases from the treatment and placebo arms and an equal number of controls who had an end-of-study biopsy negative for cancer.[15] We previously used a subset of this nested case-control study to investigate inflammation and prostate cancer. The subset included 209 controls who were sampled from the placebo arm.[12] For the current analysis, we excluded 23 of 209 controls as they had a clinical indication at the end-of-study biopsy (PSA ≥4 ng/mL and/or abnormal DRE).

From the PCPT nested case-control study, we also previously selected 38 men who never had an elevated serum PSA or abnormal DRE during the trial (i.e., never had a clinical indication for biopsy during the PCPT) and did not have a diagnosis of high-grade prostatic intraepithelial neoplasia or prostate cancer on the end-of-study biopsy. In the current analysis, we included the 186 controls plus these 38 men, for a total of 224 men without

clinical indication for prostate biopsy (i.e., PSA <4 ng/mL and normal DRE) and negative for prostate cancer on the end-of-study biopsy.

The Institutional Review Boards at the participating trial sites approved the PCPT. Trial participants provided consent for use of their biospecimens and data for future studies. The Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health and the Colorado Multiple Institutional Review Board approved the PCPT inflammation study.

Assessment of intraprostatic inflammation

For the current analysis, we used data from our prior review of intraprostatic inflammation in controls.[12] A single pathologist reviewed digital images of H&E-stained sections of a mean of 3 biopsy cores (of the 6–10 for feasibility as previously described[12]) per man. Typically, more than one core was mounted on a slide. For each slide, the percentage of the total evaluated tissue area with inflammation involvement was visually estimated as a measure of extent. In each tissue compartment (intraepithelial, luminal, stromal) extent and grade of total, acute (e.g., polymorphonuclear cells), and chronic (e.g., cells with an appearance consistent with that of lymphocytes and macrophages) inflammation were scored using a slight modification of Nickel et al.[16] Grade, defined as inflammatory cell density, was visually scored as 1=mild, 2=moderate, and 3=severe. The measure of extent was visually scored for each grade present as 0=none, 1=mild (<10% of tissue area involved by inflammatory cells), 2=multifocal (≥10% but <50%), 3=diffuse (≥50%). Separately for each tissue compartment, acute and chronic inflammation intensity scores were calculated as sum across grade of the product of grade and extent score for that grade.

Statistical analysis

When more than one slide was available for a man, we used mean (i.e., sum of extent or intensity score across slides divided by number of slides) and maximum (extent or intensity score from the slide with the highest score) extent and intensity score of inflammation. We divided the distribution of PSA measured in the controls at the end-of-study biopsy into tertiles (cutpoints: 0.8, 1.5 ng/mL); we selected tertiles based on sample size. We calculated age-adjusted means or prevalences of the men's characteristics by PSA tertile using generalized linear models, specifically linear for adjusted means and proportions and logistic for P-trends. We determined mean, median, and interquartile range of mean or maximum extent and intensity of inflammation by PSA tertile. We tested for trend across tertile-specific medians using the Cuzick test.[17] We used the natural logarithm of serum PSA to achieve normality. We estimated the increase in log PSA per 1% increase in mean and maximum percentage of tissue area with inflammation overall, in men without a prior negative biopsy, and in men below and at or above the median prostate volume using linear regression and adjusting for age at biopsy. Statistical tests were 2-sided and $P<0.05$ was considered statistically significant. We performed the analyses using SAS version 9.3 (Cary, NC), R version 3.0.2, and STATA version 12 (StataCorp LP, College Station, Texas, USA).

Results

Median serum PSA at biopsy was 0.56, 1.18, and 2.46 ng/mL in the lowest, middle, and highest PSA tertile at biopsy (P-trend<0.0001); by design all of the men had PSA <4 ng/mL. Age at baseline and biopsy and age-adjusted characteristics, including BMI, did not significantly differ across PSA tertiles at biopsy, with the exception of higher PSA at baseline and higher mean prostate volume (Table 1).

Median percentage of tissue area with inflammation increased from 2% to 5% to 9.5% across PSA tertiles (P-trend<0.0001; Table 2). Maximum percentage of tissue area with inflammation increased from 3% to 7% to 13% across PSA tertiles (P-trend<0.0001). For acute inflammation, mean and maximum extent and intensity scores were higher in the luminal and intraepithelial compartments and lowest in the stromal compartment. For chronic inflammation, mean and maximum extent and intensity scores were highest in the stromal followed by intraepithelial compartment, and were lowest in the luminal compartment. Scores for chronic inflammation in the stromal and epithelial compartments were substantially higher than for acute inflammation in any of the tissue compartments. The luminal compartment scores were comparable for acute and chronic inflammation. For acute inflammation, mean and maximum extent and intensity scores in the luminal and intraepithelial compartments increased across PSA tertiles (Table 2). For chronic inflammation, mean and maximum extent and intensity scores for the intraepithelial and stromal compartments significantly increased across PSA tertiles (Table 2).

After adjusting for biopsy age, for each 5% increase in mean and maximum percentage of tissue area with inflammation log PSA increased by 0.061 ng/mL (P-trend=0.0002) and 0.043 ng/mL (P-trend=0.0003; Table 3). When restricting to men who never had a prior biopsy (N=189), the results were unchanged (Table 3).

Prostate volume and percent tissue area of inflammation were only weakly correlated (Spearman correlation coefficient: r=0.12, P=0.07). After adjusting for prostate volume, the association in Table 3 remained in men (increase in log PSA at biopsy (ng/mL) per 5% increase in the mean percentage of tissue area with total inflammation: overall - 0.051, P-trend=0.001; men without a prior prostate biopsy - 0.065, P-trend=0.004). When stratifying by prostate volume (Table 3), the association between inflammation and PSA was present in men with a prostate volume below the median and in men with a prostate volume at or above the median, although the slope of the association appeared to be steeper for men with a prostate volume below the median; these associations were similar after further adjusting for prostate volume within the strata of prostate volume (data not shown).

Discussion

In men without clinical indication for biopsy and in whom the protocol-directed end-of-study biopsy was negative for prostate cancer, a greater extent and intensity of inflammation was associated with higher serum PSA in this cross-sectional analysis in the placebo arm of the PCPT. Extent and intensity of acute inflammation in the luminal and intraepithelial compartments and chronic inflammation in the stromal and intraepithelial compartments

increased across PSA tertiles. The association did not appear to be solely due to the link between inflammation and prostate volume or to the small number of men who during the trial previously had a prostate biopsy. Ours is the first study to evaluate the association of acute and chronic inflammation in each tissue compartment with concurrent PSA in a setting in which the opportunity for biopsy was unrelated to the link between intraprostatic inflammation and PSA.

Serum PSA is used for prostate cancer screening and for monitoring men after prostate cancer diagnosis. Any reason for PSA elevation other than prostate cancer compromises the utility of PSA for these purposes and could lead to inappropriate clinical decision-making (e.g., unnecessary biopsy for higher PSA due to inflammation rather than cancer). Some prior studies have investigated the association between intraprostatic inflammation and serum PSA in the setting of biopsies performed for prostate cancer suspicion or surgery for BPH; positive associations for various measures of inflammation have been found in many,[1,3–11] but not all studies.[2,18–21] Several[2,3,8,10,18,19,21] assessed inflammation aggressiveness (i.e., degree of epithelial disruption) using the method of Irani et al.,[11] and some concluded that extent or intensity of inflammation was not clearly associated with PSA, while grade of aggressiveness (e.g., presence of epithelial disruption) of inflammation was positively associated.[3,8,10,11] In our study, we used a different scoring system, based on a consensus document,[16] that evaluates aggressiveness by tissue area involved and inflammatory cell density in the intraepithelial compartment (i.e., inflammatory cells within the epithelial compartment and hence adjacent to epithelial cells), but also in luminal and stromal compartments, but does not directly examine degree of epithelial cell disruption. Nevertheless, our findings are somewhat consistent with those of Irani et al.[11] and others[2,3,8,10] in that extent of intraepithelial inflammation (both chronic and acute) correlated with PSA and it is quite likely, especially for acute inflammatory cells (e.g., neutrophils) that there is at least some accompanying epithelial disruption in many of those lesions. Our findings differ from those of Irani et al.[11] and some other studies,[3,8,10] in that we did find that extent of inflammation in the stromal compartment was associated with serum PSA. It is quite likely that part of the differences between findings could be explained by the relatively scant overall prostate sampling during needle biopsies.

In a recent publication,[12] we reported that controls with ≥1 biopsy core with inflammation (of a mean of 3 assessed) had a higher PSA, and that as the number of cores with inflammation increased from none to some to all, PSA increased. These findings were also observed in controls without a clinical indication for biopsy. In the current analysis, we extended our work to men without an elevated PSA or abnormal DRE and a biopsy negative for prostate cancer to describe the percentage of tissue area with inflammation in relation to PSA. PSA increased with increasing percentage of tissue area with inflammation, again documenting that intraprostatic inflammation contributes to circulating PSA even in men with low PSA in a setting in which the opportunity for prostate biopsy was unrelated to the link between intraprostatic inflammation and PSA. We also adjusted for and stratified by prostate volume to address whether the association between inflammation and PSA is confounded by the weak correlation between prostate volume and inflammation and/or is the same on a background of differing PSA concentrations due to prostate volume. We observed that the positive inflammation-PSA association was present after adjusting for prostate

volume and in both men with higher and lower prostate volume, but the slope was steeper in men with lower prostate volume.

We also extended this work by investigating acute and chronic inflammation by tissue compartment and serum PSA. To do so, we used a slight modification of a standardized system described by Nickel et al.[16] Chronic inflammation was far more common than acute inflammation irrespective of PSA. We observed distinct and similar patterns of association for acute versus chronic inflammation with PSA by tissue compartment. For acute inflammation, the association with PSA was strongest for luminal inflammation, whereas for chronic inflammation, the association was stronger for stromal inflammation. However, both acute and chronic intraepithelial inflammation were associated with PSA even though both extent and intensity of intraepithelial was far greater for chronic. Acute stromal inflammation, which was not common, did not appear to be associated with PSA. Chronic luminal inflammation, which was also uncommon, was possibly, but not significantly associated with PSA. Biological explanations for these patterns are unknown. We speculate that acute inflammation in the lumen, and acute and chronic intraepithelial inflammation, may produce epithelial injury and thus release of PSA into the stroma, while chronic inflammation in the stroma (acute inflammation was uncommon in the stroma) results in vascular permeability allowing PSA to enter circulation.

Our study has several strengths including the unique study population, availability of tissue from men without clinical indication for biopsy, and use of data collected using a standardized method of assessment of inflammation by tissue compartment. We used the PSA concentration measured immediately before the end-of-study biopsy, as prostate biopsy transiently increases serum PSA. Our study also has some limitations. Acute and chronic inflammatory cells were visually determined based on H&E staining and morphology. We did not stain for immune cell surface markers and did not use image analysis. For feasibility, we assessed a mean of 3 biopsy cores of 6–10 taken per man. While neither the urologists' decisions about biopsy location nor the investigators' selection of the 3 cores was random, neither was done with respect to extent or intensity of intraprostatic inflammation. Thus, the accuracy in the evaluation of the extent or intensity of inflammation would not differ by PSA level and so we likely underestimated the association between inflammation and PSA. Also, we considered only total PSA, not free or its isoforms. While the men had low PSA and normal DRE, we cannot rule out that some had cancer that was not detected on biopsy (i.e., sampling error).

The implications of this study may be substantial. Most men undergoing prostate biopsy do so as a result of an elevated PSA; in the majority, the biopsy shows no cancer. While some indeed have a missed cancer, others do not and thus underwent an unnecessary biopsy leading to risks of bleeding and infection and cost. In the near term, it is possible that PSA could be adjusted for intraprostatic inflammation for decision-making about re-biopsy in men with elevated PSA but negative for cancer on a first biopsy. In the longer term, it is possible that biomarkers of prostate inflammation could be developed, and perhaps coupled with imaging technologies (e.g., multi-parametric MRI) and more specific tests (e.g., urinary PCA3, TMPRSS2-ERG), to aid in differentiating these causes of elevated PSA to eliminate unnecessary biopsies. While not investigated here, men on active surveillance may have

'false-elevations' in PSA that lead to unnecessary subsequent biopsies and/or treatment. If these false-positive PSA increases are due to inflammation, rather than change in cancer status, a similar approach could be used in them.

Conclusion

Greater overall inflammation, luminal and intraepithelial acute inflammation, and stromal and intraepithelial chronic inflammation in prostate biopsy tissue were associated with higher serum PSA in men with negative biopsies in the absence of a clinical indication for biopsy. This study supports the hypothesis that inflammation contributes to serum PSA and provides opportunities for improving this biomarker in screening and active surveillance.

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Abbreviations and Acronyms

DRE	Digital-rectal examination
MRI	Magnetic resonance imaging
PCPT	Prostate Cancer Prevention Trial
PSA	Prostate specific antigen
Log PSA	Natural logarithm of PSA

Table 1

Characteristics* of Men without Clinical Indication for Biopsy and Negative for Prostate Cancer by Tertile of Serum PSA at Biopsy, Placebo Arm, Prostate Cancer Prevention Trial

	Tertile of PSA Concentration at Biopsy (ng/mL)			
	1 (>0 to ≤0.8)	2 (>0.8 to ≤1.5)	3 (>1.5 to <4.0)	P-trend
N	77	71	76	
Mean Age at Baseline (years)	63	64	65	0.1
Mean Age at Biopsy (years)	70	71	72	0.1
Non-White (%)	16.4	15.4	16.3	1.0
Family History (%)	15.3	25.3	13.5	0.8
Cigarette Smoking History (%)				
Current	5.3	8.5	3.8	0.7
Former	61.4	67.6	60.1	0.9
Never	33.3	23.9	36.1	0.7
Mean Body Mass Index (kg/m^2)	27.9	27.6	27.5	0.5
History of Diabetes (%)	13.0	7.0	9.2	0.4
Mean Cholesterol Concentration (mg/dL)	207	200	204	0.6
Prior Prostate Biopsy (%)	15.1	15.6	16.2	0.9
Prior or Current Prostatitis (%)	7.7	1.4	9.3	0.7
Prior or Current Aspirin Use (%)	11.8	24.0	19.6	0.2
Prior or Current Non-steroidal Anti-inflammatory Drug Use (%)	40.0	19.7	29.2	0.1
Mean PSA Concentration (ng/mL)				
Baseline	0.61	1.04	1.67	<0.0001
Biopsy	0.56	1.18	2.46	<0.0001
Mean Prostate Volume (mL)	29.1	35.8	43.3	<0.0001

*Baseline characteristics except where otherwise noted. For all characteristics except age at baseline, from generalized models (linear for adjusted proportions and means and logistic for P-trends) adjusting for baseline age.

Table 2

Extent and Intensity of Intraprostatic Inflammation in Men without Clinical Indication for Biopsy and Negative for Prostate Cancer by Tertile of Serum PSA Concentration at Biopsy, Placebo Arm, Prostate Cancer Prevention Trial

	Tertile of Serum PSA Concentration at Biopsy (ng/mL)									P-Trend*
	1 (>0 to ≤0.8)			2 (>0.8 to ≤1.5)			3 (>1.5 to <4.0)			
	Mean	Median	IQR**	Mean	Median	IQR**	Mean	Median	IQR**	
N		77			71			76		
*Extent measured as the percentage of tissue area with total inflammation****										
Mean %	6.83	2(0–7.5)		9.19	5 (0.67–9.0)		15.09	9.5(2.5–24.5)		< 0.0001
Maximum %	9.99	3(0–10.0)		14.24	7(2.0–15.0)		20.80	13.0(5.0–32.5)		< 0.0001
*Extent measured using a consensus scoring system*****										
Mean score for acute inflammation										
Intraepithelial	0.01	0(0-0)		0.04	0(0-0)		0.11	0(0-0)		0.06
Luminal	0.03	0(0-0)		0.03	0(0-0)		0.13	0(0-0)		0.007
Stromal	0.00	0(0-0)		0.05	0(0-0)		0.05	0(0-0)		0.2
Maximum score for acute inflammation										
Intraepithelial	0.03	0(0-0)		0.07	0(0-0)		0.14	0(0-0)		0.06
Luminal	0.05	0(0-0)		0.04	0(0-0)		0.21	0(0-0)		0.007
Stromal	0.00	0(0-0)		0.10	0(0-0)		0.05	0(0-0)		0.2
Mean score for chronic inflammation										
Intraepithelial	0.55	0(0–1)		0.71	0.5(0–1)		1.00	1(0–1.5)		0.002
Luminal	0.04	0(0-0)		0.03	0(0-0)		0.08	0(0-0)		0.7
Stromal	1.24	1(0–2)		1.40	1(0.5–2)		1.93	2(0.5–3)		0.001
Maximum score for chronic inflammation										
Intraepithelial	0.84	0(0–1)		1.13	1(0–2)		1.38	1(0–2)		0.003
Luminal	0.08	0(0-0)		0.06	0(0-0)		0.11	0(0-0)		0.7
Stromal	1.70	1(0–3)		1.92	1(1–3)		2.50	2.5(1–4)		0.001
*Intensity measured using a consensus scoring system*****										
Mean score for acute inflammation										
Intraepithelial	0.01	0(0-0)		0.04	0(0-0)		0.13	0(0-0)		0.06

	Tertile of Serum PSA Concentration at Biopsy (ng/mL)									P-Trend*
	1 (>0 to ≤0.8)			2 (>0.8 to ≤1.5)			3 (>1.5 to <4.0)			
	Mean	Median	IQR**	Mean	Median	IQR**	Mean	Median	IQR**	
Luminal	0.04	0(0-0)		0.03	0(0-0)		0.17	0(0-0)		0.007
Stromal	0.00	0(0-0)		0.07	0(0-0)		0.05	0(0-0)		0.2
Maximum score for acute inflammation										
Intraepithelial	0.03	0(0-0)		0.08	0(0-0)		0.18	0(0-0)		0.06
Luminal	0.08	0(0-0)		0.04	0(0-0)		0.30	0(0-0)		0.007
Stromal	0.00	0(0-0)		0.14	0(0-0)		0.07	0(0-0)		0.2
Mean score for chronic inflammation										
Intraepithelial	0.87	0(0–1)		1.03	0.5(0–1)		1.38	1(0–2)		0.006
Luminal	0.04	0(0-0)		0.04	0(0-0)		0.09	0(0-0)		0.6
Stromal	2.05	1(0–3.5)		2.18	1.5(0.5–3)		2.98	2.75(1–4.25)		0.002
Maximum score for chronic inflammation										
Intraepithelial	1.39	0(0–2)		1.65	1(0–2)		1.95	1(0–3)		0.009
Luminal	0.08	0(0-0)		0.07	0(0-0)		0.12	0(0-0)		0.7
Stromal	2.87	1(0–6)		3.11	2(1–5)		3.97	4(1–6)		0.003

* Cuzick test for trend

** 25 to 75th percentile

*** For each man, a mean of 3 biopsy cores was reviewed, one or more of which were mounted per slide. The mean or maximum of each man's slides was used in the analysis. Possible range is 0 to 100%.

**** Using a slight modification of the method described by Nickel et al.[16] Possible scores for extent: 0=none, 1=mild (<10% of tissue area involved by inflammatory cells), 2=multifocal (≥10% but <50%), 3=diffuse (≥50%). Possible range for extent is 0 to 3. Possible scores for grade: 1=mild, 2=moderate, and 3=severe. Possible range for intensity is 0 to 9.

Table 3

Association of the Mean and Maximum Percentage of Tissue Area of Inflammation with Log PSA Concentration at Biopsy in Men without Clinical Indication for Biopsy and Negative for Prostate Cancer, Placebo Arm, Prostate Cancer Prevention Trial

Per 5% increase in the percentage of tissue area with total inflammation**	Increase in log PSA at Biopsy (ng/mL)*	P-Trend
Overall		
Mean %	0.061	0.0002
Maximum %	0.043	0.0003
In men without prior prostate biopsy		
Mean %	0.057	0.001
Maximum %	0.041	0.001
In men with a prostate volume < median		
Mean %	0.067	0.007
Maximum %	0.043	0.01
In men with a prostate volume ≥ median		
Mean %	0.039	0.05
Maximum %	0.028	0.06

* Adjusted for age at biopsy.

** For each man, a mean of 3 biopsy cores was reviewed, one or more of which were mounted per slide. The mean or maximum of each man's slides was used in the analysis. Possible range is 0 to 100%.