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Smoking Is Associated with Acute and Chronic Prostatic Inflammation: Results from the REDUCE Study `FREE`

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Abstract

Both anti- and proinflammatory effects of cigarette smoking have been described. As prostate inflammation is common, we hypothesized smoking could contribute to prostate inflammation. Thus, we evaluated the association of smoking status with acute and chronic inflammation within the prostate of men undergoing prostate biopsy. We retrospectively analyzed 8,190 men ages 50 to 75 years with PSA levels between 2.5 and 10 ng/mL enrolled in the Reduction by Dutasteride of Prostate Cancer Events study. Smoking status was self-defined as never, former, or current. Prostate inflammation was assessed by systematic central review blinded to smoking status. The association of smoking with inflammation in the baseline, 2-year, and 4-year biopsies was evaluated with univariable and multivariable logistic regressions. At study enrollment, 1,233 (15%), 3,203 (39%), and 3,754 (46%) men were current, former, and never smokers, respectively. Current smokers were significantly younger and had smaller prostates than former and never smokers (all $P < 0.05$). Former smokers were significantly heavier than current and never smokers ($P < 0.001$). Acute and chronic prostate inflammations were identified in 1,261 (15%) and 6,352 (78%) baseline biopsies, respectively. In univariable analysis, current smokers were more likely to have acute inflammation than former (OR, 1.35; P, 0.001) and never smokers (OR, 1.36; P, 0.001). The results

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were unchanged at 2- and 4-year biopsies. In contrast, current smoking was linked with chronic inflammation in the baseline biopsy, but not at 2- and 4-year biopsies. In conclusion, among men undergoing prostate biopsy, current smoking was independently associated with acute and possibly chronic prostate inflammations. *Cancer Prev Res; 8(4); 312–7. ©2015 AACR*.

Introduction

Cigarette smoking has been associated with higher prostate cancer mortality in all comers and more disease recurrence, metastasis, and cancer-specific mortality after surgery and radiotherapy for prostate cancer (**1–5**). Although, the pathways by which smoking affects prostate carcinogenesis and prostate cancer progression are largely unknown, several potential mechanisms have been proposed, including genetic and epigenetic changes, enhanced angiogenesis, life style factors, and inflammation. Indeed, the effects of cigarette smoking on the immune system are far-reaching and may affect the prostate. For example, there is evidence suggesting cigarette smoking promotes an overall systemic inflammatory state by increasing levels of proinflammatory markers (**6**). Moreover, inflammatory changes in distant organs, such as eyes, arteries, and pancreas, have been described among active smokers (**7–9**). Conversely, active smoking has been linked to a decreased risk of ulcerative colitis, an inflammatory bowel disease (**10**), and rosacea, an inflammatory skin disorder (**11**). Thus, the direct inflammatory effects of cigarette smoking on several organs, including the prostate, remain to be determined.

Acute and chronic inflammatory infiltrates are frequently found in the prostate. Previous studies indicate that between 35% and 100% of prostate biopsies done for suspected prostate cancer had some histologic evidence of inflammation (**12–15**).

However, factors associated with inflammatory changes in the prostate of men undergoing biopsy are largely unknown. To date, no studies have evaluated the association of cigarette smoking with histologic prostatic inflammation. Therefore, we sought to evaluate the association of smoking status and histologic inflammation in the prostates of men undergoing prostate biopsy in the REduction by DUtasteride of Prostate Cancer Events (REDUCE) trial. The REDUCE trial was a 4-year, placebo-controlled study evaluating daily dutasteride to reduce the risk of biopsy detectable prostate cancer among patients with negative baseline prostate biopsy ([16]). Repeat prostate biopsies were performed at 2 and 4 years. Thus, REDUCE uniquely allows the examination of the relationship between baseline cigarette smoking and inflammatory changes on baseline-negative biopsies and subsequent repeat prostate biopsies. We hypothesize that smoking is associated with greater risk of inflammation in the prostate.

Materials and Methods

REDUCE design was published previously ([16]). In brief, eligible men were ages 50 to 75 years, had serum PSA ≥2.5 or 3.0 ng/mL according to age (50–60 and 60–75 years, respectively) but ≤10 ng/mL, one single negative prostate biopsy (6 to 12 cores) within 6 months of enrollment. Men were excluded if they had history of prostate cancer, high-grade intraepithelial neoplasia, atypical small acinar proliferation, prostate volume (PV) >80 mL, had undergone previous prostate surgery or had International Prostate Symptom Score ≥25 or ≥20 on alpha-blockers, or were previously on finasteride or dutasteride. Medical history was collected at baseline. All men were randomized in double-blind fashion to receive orally either dutasteride 0.5 mg or placebo daily and followed every 6 months for 4 years. To maintain the blinded nature of the study, PSA levels in the

dutasteride-treated men were doubled (given dutasteride reduces PSA levels by approximately half) and randomly adjusted by 0.1 ng/mL so that the final reported values were equally even and odd. PV was measured by ultrasonography at the time of randomization and 2 and 4 years later. Ten-core transrectal, ultrasound-guided biopsies were performed as part of the protocol at 2 and 4 years. Baseline biopsies had been performed before the start of the study (and independently of the study) and were reread centrally (at Bostwick Laboratories). Biopsies that were performed as part of the study were also read centrally. Central pathology laboratory had no access to the randomization codes or data on smoking status. Prostate cancer, acute and chronic prostate inflammation were coded as present or absent. Inflammation was also coded based on severity as mild, moderate and marked according to the average cell density and extent of tissue involvement in each biopsy core. Chronic inflammation consisted mainly of lymphocytes and variable number of plasma cells and macrophages. Acute inflammation consisted of neutrophils. Mild inflammation was defined as small scattered or patchy aggregates and presence of nests of inflammatory cells, usually no more than 10 to 15 cells per nest. Moderate inflammation was characterized by larger aggregates and nests, usually more than about 15 cells, invariably multifocal. Moderate inflammation was noticeable at low magnification. Sheets of inflammatory cells or extensive multifocal confluent masses of cells were noted in severe inflammation, which was obvious and noticeable at any magnification. Additional criterion for severe acute inflammation was tissue destruction of any size ([17]). Self-reported smoking status was determined at baseline and categorized in one of three groups: current, former, or never smoker. The protocol was approved by the Institutional

Review Board at each research site, and all participants provided written informed consent. Of the 8,231 patients enrolled in the REDUCE trial, we excluded 41 (<1%) due to missing data including smoking status or histologic inflammation. This resulted in a study sample of 8,190 (99%) men with centrally reviewed baseline biopsies and complete data. Positive baseline biopsies were not included in the study (i.e., negative baseline biopsy for prostate cancer was part of the inclusion criteria in REDUCE). Moreover, patients were selected for baseline biopsies based on PSA levels, whereas repeat biopsies were done regardless of PSA. To overcome this limitation, we analyzed the 2- and 4-year repeat biopsies given they include both positive and negative biopsies for prostate cancer. A total of 6,311 (77%) and 4,619 (56%) had 2- and 4-year per protocol repeat biopsies and were included in the repeat biopsy analyses. The details of men who underwent at least one on-study biopsy have been described previously ([18]).

Univariable comparisons of baseline characteristics between current, former, and never smokers were performed using χ^2 for categorical data and ANOVA for continuous variables. Given the low numbers of patients with moderate and marked acute and chronic inflammation, inflammation was analyzed as present or absent. The association of smoking status with acute and chronic inflammation in baseline, 2-, and 4-year repeat prostate biopsies was evaluated using logistic regression in univariable analysis. Multivariable logistic regression models were used to determine the association between smoking and prostate inflammation adjusting for baseline characteristics, such as age (continuous, in years), race (Caucasian, African American, Asian, American Hispanic, or other), body mass index (BMI, continuous and log-transformed, in kg/m^2),

digital rectal exam (DRE, coded as normal or abnormal), PV (continuous and log-transformed, in cm^3), PSA (continuous, in ng/mL) to test the association of smoking status and baseline prostate inflammation. The selection of covariates in multivariable models was based on their observed and/or previously established associations with baseline smoking status and/or inflammation ([19]). The analysis of smoking and inflammation at 2- and 4-year biopsies was adjusted for treatment arm as well. All statistical analyses were two-tailed and performed using Stata 11.2 (StataCorp). A $P < 0.05$ was considered statistically significant.

Results

Baseline patient characteristics

Mean baseline age, BMI, PSA, and PV of our cohort were 62.8 years, 27.4 kg/m^2, 6.1 ng/dL, and 45.7 cm^3, respectively. A total of 7,455 (91.0%) subjects were Caucasian. Abnormal DRE was identified in 284 (3.9%) patients. A total of 1,233 (15.1%), 3,203 (39.1%), and 3,754 (45.8%) men were current, former, and never smoker, respectively. Current smokers were significantly younger and had smaller prostates than former and never smokers (all $P < 0.05$) but had similar race, DRE, prebiopsy PSA, and treatment arm (all $P > 0.05$). Former smokers had significantly higher BMI than current and never smokers ($P < 0.001$; **Table 1**).

Table 1.

Baseline patient characteristics by smoking status

	Smoking status	
Characteristic	**Current**	**Former**
N (%)	1,233 (15.1)	3,203 (39.1)
Age (in years), mean (SD)	61.7 (6.0)	63.2 (6.0)
Race, *N* (%)		

White	1,118 (90.7)	2,923 (91.3)
Black	30 (2.4)	62 (1.9)
Asian	30 (2.4)	54 (1.7)
American Hispanic	44 (3.6)	129 (4.0)
Other	11 (0.9)	35 (1.1)
BMI (in kg/m^2), mean (SD)	27.0 (5.2)	27.7 (3.9)
DRE, N (%)		
Normal	1,055 (95.9)	2,807 (96.2)
Abnormal	45 (4.1)	112 (3.8)
PSA (in ng/mL), mean (SD)	6.0 (2.3)	6.1 (2.3)
PV (in cm^3), mean (SD)	44.2 (17.1)	45.9 (17.4)
Treatment arm, N (%)		
Placebo	630 (51.1)	1,627 (50.8)
Dutasteride	603 (48.9)	1,574 (49.2)

[a]χ^2 test for categorical variables and ANOVA for continuous variables.

Baseline biopsy

At baseline biopsy where all biopsies were negative for cancer, acute and chronic inflammation was detected in 1,261 (15.4%) and 6,352 (77.6%) cases, respectively. A total of 1,196 (14.6%) baseline biopsies showed both acute and chronic inflammation and 1,773 (21.7%) had no inflammation (Supplementary Table S1). Acute prostate inflammation was graded as mild, moderate, and marked in 1,235 (97.9%), 24 (1.9%), and 2 (0.2%), respectively. Chronic prostate inflammation was graded as mild, moderate, and marked in 5,653 (89.0%), 681 (10.7%), and 18 (0.3%), respectively. In univariable analysis, current smokers were more likely to have acute inflammation than former (OR, 1.35; P, 0.001) and never smokers (OR, 1.36; P, 0.001) at baseline biopsy. Similarly, in multivariable analysis, current smokers had

significantly more acute inflammation than former (OR, 1.29; *P*, 0.008) and never smokers (OR, 1.30; *P*, 0.005; **Table 2**) at baseline. Though there were trends for current smokers to be more likely to have chronic inflammation at baseline biopsy on univariable analysis, this did not reach statistical significance (**Table 2**). However, on multivariable analysis, current smokers were more likely to have chronic inflammation at baseline biopsy relative to former (OR, 1.23; *P*, 0.017) and never smokers (OR, 1.24; *P*, 0.014; **Table 2**). Most of the change in the OR of chronic inflammation occurred with the addition of PV to the multivariable models.

Table 2.

Association of smoking status with baseline acute and chronic prostate inflammations

	Acute inflammation (*N* = 1,261; 15.4%		
	Univariable		Multivari
Smoking status	OR (95% CI)	*P*	OR (95%
Former vs. never	0.99 (0.87–1.13)	0.901	1.01 (0.8
Current vs. never	1.35 (1.14–1.59)	0.001	1.30 (1.0

NOTE: Never smokers: 3,754 (45.8%); former smokers: 3,203 (39.1%); current smokers: 1,233 (15.1%).

Abbreviation: CI, confidence interval.

[a]Adjusted for age, race, BMI, DRE, PV, and PSA.

2- and 4-year biopsies

At 2-year repeat prostate biopsy, the prevalence of acute and chronic inflammation was 1,405 (22.3%) and 5,084 (80.6%) cases, respectively. At 4-year repeat prostate biopsy, prevalence of acute and chronic inflammation was 1,067 (23.0%) and 3,690 (79.7%) cases, respectively (Supplementary Table S1). Supplementary Table S2 shows the prevalence inflammation by treatment arm. At both 2- and 4-year repeat prostate biopsies, baseline current smokers had significantly more acute inflammation than never smokers in both uni- and

multivariable analyses (all *P* < 0.05, **Tables 3** and **4**). Likewise, baseline current smokers had more acute inflammation than former smokers in both uni- and multivariable analyses at 2- (univariable: OR, 1.16; *P*, 0.105; multivariable: OR, 1.23; *P*, 0.022) and 4-year (univariable: OR, 1.35; *P*, 0.003; multivariable: OR, 1.35; *P*, 0.004) repeat prostate biopsies, although the associations did not reach statistical significance at 2-year repeat biopsy (**Tables 3** and **4**). Baseline smoking status was not associated with chronic prostate inflammation on either 2- or 4-year repeat biopsy on either univariable or multivariable analysis (**Tables 3** and **4**). Supplementary Table S3 shows the univariable ORs of inflammation by smoking status stratified by treatment arm. Supplementary Tables S4 and S5 show the association of smoking status with acute and chronic prostate inflammations at 2- and 4-year repeat biopsies by cancer status. Analysis of smoking status and inflammation severity (acute and chronic) was not possible due to limited number of patients with moderate and marked acute and chronic inflammations.

Table 3.

Association of smoking status with acute and chronic prostate inflammations at 2-year repeat biopsy

	Acute inflammation (*N* = 1,405; 22.3%		
	Univariable		Multivari
Smoking status	OR (95% CI)	*P*	OR (95%
Former vs. never	1.06 (0.93–1.21)	0.387	1.06 (0.9
Current vs. never	1.23 (1.03–1.46)	0.022	1.23 (1.0

NOTE: Never smokers: 2,908 (46.1%); former smokers: 2,490 (39.4%); current smokers: 913 (14.5%).

Abbreviation: CI, confidence interval.

[a]Adjusted for age, race, BMI, DRE, PV, PSA, and treatment arm.

Table 4.

Association of smoking status with acute and chronic prostate

inflammations at 4-year repeat biopsy

	Acute inflammation (N = 1,067; 23.0%		
	Univariable		Multivari
Smoking status	OR (95% CI)	P	OR (95%
Former vs. never	1.00 (0.86–1.16)	0.998	1.00 (0.8
Current vs. never	1.35 (1.10–1.66)	0.004	1.32 (1.0

NOTE: Never smokers: 2,178 (47.0%); former smokers: 1,823 (39.4%); current smokers: 631 (13.6%).

Abbreviation: CI, confidence interval.
[a]Adjusted for age, race, BMI, DRE, PV, PSA, and treatment arm.

Discussion

Cigarette smoking has a major impact on health issues worldwide. It is the leading cause of preventable morbidity and mortality in the United States ([20]). Several studies suggest many of the adverse consequences of smoking might be due to its effects on oxidative stress and immune–inflammatory system ([6]). Indeed, cigarette smoking has been linked to inflammation of specific organs, such as eyes, arteries, and pancreas ([7–9]). However, direct inflammatory effects of cigarette smoking on urologic organs including the prostate have not been described. Therefore, we retrospectively analyzed 8,190 men ages 50 to 75 years with PSA levels between 2.5 and 10 ng/mL enrolled in the REDUCE study. In both uni- and multivariable analyses, current smokers were more likely to have acute prostate inflammation than former and never smokers. Results were virtually unchanged in multivariable analysis and at 2- and 4-year repeat prostate biopsies. In addition, we found smokers were more likely to have chronic inflammation in their baseline biopsies.

To date, no study has examined the link between cigarette smoking and objectively assessed

prostatic inflammation. In contrast, a few studies evaluated the association of cigarette smoking with prostatitis-related symptoms, but with mixed results. The largest study published by Liang and colleagues ([21]) evaluating 12,743 Chinese men found significant association between active smoking status and self-reported prostatitis-like symptoms. In addition, Bartoletti and colleagues ([22]) using data from 764 prostatitis cases and 152 controls found significant association between smoking and symptoms of chronic prostatitis/chronic pelvic pain syndrome. In opposition, Mi and colleagues ([23]) investigating 1,242 Chinese men failed to demonstrate any association between smoking and prostatitis-like symptoms. Moreover, Wallner and colleagues ([24]) studying 703 African American men did not find any association between self-reported smoking status and prostatitis. Similarly, Moon and colleagues ([25]) examining 184 self-answered questionnaires filled out by 20 to 49 years-old subjects failed to identify any correlation between smoking and urinary symptoms. Thus, it remains controversial whether smoking has any association with prostatitis-like symptoms. However, prostatitis symptoms may not be due to prostatic inflammation *per se* but could relate to bladder issues or even irritants in the urine from smoking. Indeed, symptoms compatible with prostatitis are not always accompanied by histologic inflammation and vice versa ([26]). As such, based on current literature, it is not possible to infer whether cigarette smoking is associated with histologic prostate inflammation or not. Thus, our study is the first to evaluate the association between smoking and prostatic inflammation, and, importantly, we found current smokers are more likely to have prostate inflammation than former and never smokers.

The effects of cigarette smoking on host immunity

including the innate and adaptive immune systems are far-reaching and occur at local and systemic levels. Many of the smoking-induced toxic effects, including the induction of carcinogenesis, result from direct genetic or epigenetic changes leading to abnormal gene function. In general, tissue damage associated with smoking is considered the main cause for increased numbers of neutrophils seen in acute inflammation. The oxidative stress causes elevated concentration of cytokines which in turn activates polymorphonuclear neutrophils and prolongs their survival. Smoking components (particularly reactive oxygen species) also activate intracellular signaling cascades generating inflammatory gene activation (such as production of interleukin-8 and tumor necrosis factor; ref. [27]). However, not all effects of smoking on host immunity are stimulatory. There is evidence showing smoking may impair the function of inflammatory cells. For example, smoking reduces the ability of neutrophils and macrophages to respond to stimuli, phagocytose, kill pathogens, and secrete cytokines. It also reduces proliferation of T cells and alters CD4 and CD8 cells ([6]). Unfortunately, there are no studies evaluating mechanisms linking smoking to inflammation specifically in the prostate. Our findings, however, provide objective evidence that smoking is linked to changes within the prostate, suggesting that chemicals within cigarette smoke may make it to the prostate and stimulate inflammatory changes. Thus, further study is required to understand the biology of how cigarette smoking promotes prostate inflammation.

The clinical implications of histologic prostate inflammation are not completely defined. However, there is increasing evidence linking histologic prostate inflammation with benign prostate hyperplasia (BPH) and degree of lower urinary tract symptoms ([28, 29]). For example, a previous

study using data from the REDUCE trial found significant correlation between chronic inflammation and urinary symptoms ([17]). Subgroup analysis of the Medical Therapies of Prostate Symptoms study found men with prostate inflammation were significantly more likely to experience worsening symptoms or acute urinary retention than those without inflammation ([30]). In our study, although smoking was significantly associated with prostate inflammation, smokers had smaller prostates compared with nonsmokers. Likewise, previous studies found an inverse correlation between smoking and BPH ([31, 32]). Thus, it seems the effects of smoking in PV and BPH may be mediated by other mechanisms than inflammation. Also, there is enough evidence to support that prostate inflammation is associated with elevated PSA levels ([33–35]). In our study, although smoking was significantly associated with prostate inflammation, no differences in PSA levels were seen between smokers and nonsmokers. In

Thus, it remains unclear whether smoking may affect PSA levels and if it does so by promoting prostate inflammation. Finally, the role of histologic prostate inflammation and smoking in prostate cancer is unknown. Multiple studies have suggested possible association between inflammation and clinical prostatitis with prostate cancer risk ([37–40]). For instance, several authors have demonstrated positive correlation between urogenital infection, prostatitis, and sexually transmitted disease with prostate cancer ([4, 38, 40]). Conversely, more recent data suggest histologic inflammation in the biopsy specimen may actually be associated with decreased risk of prostate cancer detection in subsequent biopsies ([19, 41–43]). Similarly, a meta-analysis of 24 cohort studies found an association between active smoking and prostate cancer risk ([44]). We have

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also linked smoking to high-grade prostate cancer in REDUCE (**45**). However, others found decreased risk of prostate cancer among smokers (**46**). Thus, the clinical implication of the association between smoking and prostate inflammation could not be ascertained by the current study and require further investigation.

The REDUCE study has many strengths, including its large international and multicentric population, per-protocol biopsies regardless of PSA levels, prospective data acquisition, and central pathology review. This is crucial in that prostatic inflammation can lead to PSA elevations resulting in prostate biopsy. As such, uniform biopsy protocol not driven by PSA fluctuations is crucial to prevent biases from inflammatory-driven biopsies. The main limitation of the present study is that only patients with PSA values between 2.5 and 10 ng/dL were

acinar proliferation, PV >80 mL, had undergone previous prostate surgery, or had an International Prostate Symptom Score ≥25 or ≥20 on alpha-blockers were excluded. Thus, all baseline biopsies were negative for cancer. Although these exclusions increase the homogeneity of the sample, they limit the generalizability of our results. Furthermore, the limited number of non-Caucasian men prevented us from exploring whether race influenced the association between smoking and prostatic inflammation. We did not consider off-protocol biopsies, including transrectal/transperineal needle biopsies, transurethral resections, and prostatectomies of any kind. In addition, patients were followed for 4 years, thus we were unable to study long-term consequences of smoking on prostate inflammation nor long-term clinical implications of prostate inflammation. We did not evaluate cumulative exposure, smoking duration, and time

since quitting smoking given the data were not available. Lastly, smoking status was determined at baseline only; therefore, we were not able to analyze changes in smoking status during the study interval.

In conclusion, among men undergoing prostate biopsy, current smoking status was independently associated with inflammatory changes in the prostate. Although the clinical implications of this finding were not determined by the present study, these findings provide an objective evidence that smoking is linked to changes within the prostate, suggesting that chemicals within cigarette smoke may make it to the prostate. This might be a mechanistic explanation for how smoking may influence prostatic conditions such as prostatitis or prostate cancer.

Disclosure of Potential Conflicts of Interest

J.C. Nickel reports receiving a commercial research grant and has provided expert testimony for Glaxo Smith Kline. G.L Andriole reports receiving other commercial research support from Johnson & Johnson, Medivation, and Trasxxson. He is also a consultant/advisory board member for Augmenix, Bayer, Genomic Health, GlaxoSmithKline, and Myriad Genetics. R. Castro-Santamaria has ownership interest (including patents) in GSK. S.J. Freedland reports receiving a commercial research grant from GSK. No potential conflicts of interest were disclosed by the other authors.

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Supplementary data

Data from Smoking Is Associated with Acute and Chronic Prostatic Inflammation: Results from the REDUCE Study

Supplemental Table 1: Inflammation by smoking status

| Inflammation | Smoking status | | | Overall |
	Never	Former	Current	
Baseline biopsy				
Acute inflammation				
Present	556 (15%)	471 (15%)	234 (19%)	1261 (15%)
Absent	3198 (85%)	2732 (85%)	999 (81%)	6929 (85%)
Chronic inflammation				
Present	854 (23%)	732 (23%)	252 (20%)	1838 (22%)
Absent	2900 (77%)	2471 (77%)	981 (80%)	6352 (78%)
2-year biopsy				
Acute inflammation				
Present	621 (21%)	556 (22%)	228 (25%)	1405 (22%)
Absent	2287 (79%)	1934 (78%)	685 (75%)	4906 (78%)
Chronic inflammation				
Present	2339 (80%)	2009 (81%)	736 (81%)	5084 (81%)
Absent	569 (20%)	481 (19%)	177 (19%)	1227 (19%)
4-year biopsy				
Acute inflammation				
Present	485 (22%)	406 (22%)	176 (28%)	1067 (23%)
Absent	1693 (78%)	1417 (78%)	455 (72%)	3565 (77%)

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Supplemental tables 1-5

Supplemental tables 1-5. Supplemental Table 1: Inflammation by smoking status. Supplemental Table 2: Inflammation by treatment arm. Supplemental Table 3: Univariable odds ratios of inflammation by smoking status stratified by treatment arm. Supplemental Table 4: Association of smoking status with acute and chronic prostate inflammations at 2-year repeat biopsy by cancer status. Supplemental Table 5: Association of smoking status with acute and chronic prostate inflammations at 4-year repeat biopsy by cancer status.

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