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Original Contribution

Biomarkers of Systemic Inflammation and Risk of Incident, Symptomatic Benign Prostatic Hyperplasia: Results From the Prostate Cancer Prevention Trial

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The authors conducted a nested case-control study of serum inflammatory markers and risk of symptomatic benign prostatic hyperplasia (BPH), using data from the placebo arm of the Prostate Cancer Prevention Trial (1993–2003). Incident BPH ($n = 676$) was defined as treatment, report of 2 International Prostate Symptom Score (IPSS) values >14, or 2 increases of ≥ 5 from baseline values with at least one value ≥ 12. Controls ($n = 683$) were men who reported no BPH treatment or IPSS values >7 over the 7-year trial. Baseline serum was analyzed for C-reactive protein, tumor necrosis factor α (monomer), soluble tumor necrosis factor receptors I and II (sTNF-RI and sTNF-RII), interleukin 6, and interferon γ. Controlled for age and race, a high C-reactive protein concentration was associated with increased BPH risk (for quartile 4 vs. quartile 1, odds ratio (OR) = 1.40, 95% confidence interval (CI): 1.04, 1.88); this was attenuated after control for body mass index (OR = 1.30, 95% CI: 0.95, 1.75). Low sTNF-RII and high interleukin 6 concentrations were associated with increased BPH risk (for quartile 4 vs. quartile 1, sTNF-RII: OR = 0.61, 95% CI: 0.46, 0.82; interleukin 6: OR = 1.79, 95% CI: 1.32, 2.42); these associations were only in men aged <65 years. Results suggest that systemic inflammation or lower levels of soluble receptors that bind inflammatory cytokines increase BPH risk.

inflammation; obesity; prostatic hyperplasia

Abbreviations: BPH, benign prostatic hyperplasia; CI, confidence interval; IPSS, International Prostate Symptom Score; NSAID, nonsteroidal antiinflammatory drug; OR, odds ratio; sTNF-RI and sTNF-RII, soluble tumor necrosis factor receptors I and II, respectively.

Benign prostatic hyperplasia (BPH) is a common medical condition among middle-aged and older males, affecting 40%–50% of men by age 50 and nearly 80% of men by age 70 (1, 2). Histologically, BPH is characterized by hyperproliferation of the stromal and, to a lesser extent, epithelial regions of the prostate, which causes a constellation of lower urinary tract symptoms that affect quality of life and prompt many men to seek treatment (3–5). Medical and surgical treatment for BPH symptoms is expensive (6), and as the US population ages, both the number of men affected and the associated medical costs are expected to rise (7).

The pathogenesis of BPH remains poorly understood; however, it is likely that inflammation plays a role in its development or progression. Histologic evidence of acute and chronic inflammation is commonly found in prostate biopsy and BPH specimens (8, 9), and intraprostatic inflammation is associated with several characteristics of BPH (10–12). Furthermore, inflammatory cytokines, which function as potent mitogens capable of inducing the hyperplastic changes characteristic of BPH (13), are overexpressed in BPH tissue (14, 15).

The underlying causes of intraprostatic inflammation remain unclear, though several hypotheses have been proposed including the following: response to tissue damage caused by infection (16) or other causes (17, 18) or an autoimmune response (19). It is also plausible that systemic inflammation could contribute to the initiation or

progression within the prostate. Obesity and abdominal obesity, which are characterized by large deposits of adipose tissue that produce an excess of inflammatory cytokines (20), are well-established risk factors for BPH (21–23). Thus, it is reasonable to hypothesize that adipose-derived increases in circulating cytokine concentrations may influence BPH risk.

This report examines whether systemic concentrations of several inflammatory markers elevated in obesity, including tumor necrosis factor α (monomer), soluble tumor necrosis factor receptors I and II (sTNF-RI and sTNF-RII), interleukin 6, interferon γ, and C-reactive protein, affect the risk of symptomatic BPH and whether these factors mediate the relation between obesity and BPH risk.

MATERIALS AND METHODS

Data for this study have been described in detail previously. Briefly, data are from the Prostate Cancer Prevention Trial, a randomized, placebo-controlled trial testing whether finasteride reduced prostate cancer risk (24). Analyses are restricted to the 9,457 placebo-arm participants. Exclusion criteria for these analyses included self-reported history of BPH ($n = 1{,}904$), medical or surgical treatment for BPH ($n = 701$), an International Prostate Symptom Score (IPSS) >7 ($n = 1{,}820$) at baseline, and use of steroid hormones ($n = 61$), leaving 4,971 men eligible for this study.

Extensive medical data were collected at baseline, 6-month, and annual clinic visits and at every 3- and 9-month phone contact between visits. At recruitment (3 months prior to baseline), baseline, and annual clinic visits, participants completed the IPSS (25), a 7-item self-administered questionnaire assessing the frequency of lower urinary tract symptoms. At baseline, clinic staff measured height and weight. Age, race/ethnicity, physical activity, alcohol consumption, and history of smoking were collected by using self-administered questionnaires.

Definition of BPH cases and controls

Incident BPH was defined as either a report of treatment for or development of significant lower urinary tract symptoms. Treatments included use of α-blockers, finasteride, or surgical intervention. Development of significant symptoms was defined as either 1) 2 IPSS scores >14 or 2) substantial increase in lower urinary tract symptoms from baseline (2 IPSS scores at least 5 units higher than baseline plus at least 1 score ≥ 12). The latter is a more conservative version of the definition of BPH progression used in the Medical Therapy of Prostatic Symptoms Trial (26), in which a single increase of 4 defined significant, clinical progression. There were a total of 727 incident BPH cases that were further classified by type of BPH event (treatment or symptoms) and by predomiant type of BPH symptom (mostly obstructive, mostly irritative, or mixed obstructive/irritative). We defined the type of BPH symptom using the IPSS at or prior to (for treatment) the defining BPH event; obstructive (incomplete emptying, interrupted stream, weak stream, straining) and irritative (frequency, urgency, nocturia) IPSS items were weighted to contribute 50% to the total IPSS. If the obstructive or irritative score contributed $>55\%$ to the total IPSS, the BPH type was categorized by that symptom; otherwise, the BPH type was categorized as mixed obstructive/irritative.

Controls were drawn from the 1,497 men who, during the 7-year trial, had no more than 2 missing IPSS scores, had no single IPSS greater than 7, and reported no diagnosis of BPH or treatment for BPH. From this sample, we selected all men aged 70 years or more and all non-Caucasian men to maximize statistical power when examining these subgroups. The remaining controls were randomly selected to yield a total sample ($n = 727$) frequency matched to the age distribution (in 5-year age groups) of cases.

Blood collection, processing, and laboratory analysis

Blood samples were drawn at recruitment into a 7-mL ethylenediaminetetraacetic acid vacutainer tube and shipped overnight to a storage facility, where they were centrifuged, aliquoted, and stored at −70°C. These analyses used serum that had gone through one freeze-thaw cycle.

Serum concentrations of C-reactive protein and cytokines were quantified by using a SearchLight multiplex enzyme-linked immunosorbent assay (Pierce Biotechnology, Inc., Rockford, Illinois). Each array consisted of a 96-well plate prespotted with target antibodies for the specified analytes. Plates were imaged by using a SearchLight Black Ice imaging system and analyzed with SearchLight Array Analyst software (Pierce Biotechnology, Inc.).

Serum was not available from 39 men, and 56 men with evidence of active infection (C-reactive protein, ≥ 10 mg/L) were excluded, leaving data from 676 cases and 683 controls available for these analyses. The lower limits of detection and mean coefficients of variation (derived from samples run in triplicate at various dilutions) were as follows: C-reactive protein: 5.86 pg/mL, 8.0%; tumor necrosis factor α: 2.34 pg/mL, 15.3%; sTNF-RI: 0.78 pg/mL, 8.9%; sTNF-RII: 0.39 pg/mL, 8.3%; interleukin 6: 0.39 pg/mL, 11.2%; and interferon γ: 0.39 pg/mL, 15.2%, respectively. For observations with a detectable concentration below the lower limits of detection (tumor necrosis factor α: $n = 322$; interleukin 6: $n = 32$; and interferon γ: $n = 225$), the detected concentration was used. For observations with undetectable concentrations, a value halfway between zero and the lowest detectable concentration was assigned, which equaled 0.8 for tumor necrosis factor α ($n = 40$), 0.1/mL for interleukin 6 ($n = 26$), and 0.1 pg/mL for interferon γ ($n = 10$).

Statistical methods

Descriptive statistics were used to characterize the study sample and distribution of C-reactive protein and cytokine concentrations in cases and controls. Serum concentrations of analytes were categorized into quartiles using the distribution in controls, and unconditional logistic regression was used to calculate odds ratios and 95% confidence intervals for BPH risk. All models were adjusted for matching variables (age at baseline (continuous), race (white, other)), and additional models included body mass index (continuous)

and IPSS at baseline (continuous). Controlling for other factors associated with BPH risk in this sample, including the waist/hip ratio (21), insulin-like growth factors 1 and binding protein 3 (27), steroid hormones (testosterone, estradiol, and 3-α-diol glucaronide) (28), alcohol consumption, and diet (fat, protein, red meat, and vegetables) (29), as well as controlling for medical conditions strongly associated with either BPH risk and/or systemic inflammation (diabetes, arthritis, and cardiovascular disease), did not affect risk estimates. Tests for linear trend were performed by using an ordinal variable corresponding to rank (lowest to highest quartile) (30).

Additional analyses were completed stratified by age, body mass index, physical activity, and smoking status. Interaction tests were based on *P* values for the interaction term of C-reactive protein or cytokine concentration rank (lowest to highest tertile) multiplied by a dummy variable for age (<65 vs. ≥65 years), physical activity (sedentary/light vs. moderate/very active), smoking status (current vs. former/never), or body mass index (<25 vs. ≥25). Polytomous logistic regression models were used to calculate separate odds ratios for outcomes defined by time from baseline to BPH event (<4 or ≥4 years), type of BPH event (BPH treatment or symptoms), and type of BPH symptom (irritative, mixed obstructive/irritative, or obstructive). We also considered whether the previous finding of an increased BPH risk associated with obesity (21) was mediated by C-reactive protein or cytokines, by examining the association of obesity with BPH risk unadjusted and adjusted for analytes. All *P* values were 2-sided and considered statistically significant at $P < 0.05$. Statistical analyses were conducted by using SAS, version 9.1, software (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Distributions of participants' characteristics are given in Table 1. Participants were mostly white, overweight or obese, and nonsmokers. Compared with controls, men with BPH consumed less alcohol, were more likely to have cardiovascular disease, and had a higher IPSS at baseline. Table 2 gives the age- and race-adjusted geometric mean and median of C-reactive protein and cytokine concentrations in cases and controls. Differences in the geometric mean concentrations between cases and controls were statistically significant for sTNF-RI (5.5%), sTNF-RII (−8.8%), interleukin 6 (24.4%), and interferon γ (13.9%) and borderline significant for C-reactive protein (10.2%).

Table 3 gives the adjusted odds ratios for risk of BPH associated with serum C-reactive protein and cytokine concentrations. In model 1 (adjusted for age and race), men in the highest quartile of C-reactive protein had a significantly increased risk of symptomatic BPH (odds ratio (OR) = 1.40, 95% confidence interval (CI): 1.04, 1.88; $P_{trend} = 0.03$); however, after adjustment for body mass index, the association was attenuated and no longer statistically significant. In model 2 (adjusted for matching variables and body mass index), men with sTNF-RII concentrations above the lowest quartile had a significantly reduced risk of BPH, with no

Table 1. Demographic and Lifestyle Characteristics of the Study Population, Prostate Cancer Prevention Trial, 1993–2003[a]

	Benign Prostatic Hyperplasia				*P* Value[b]
	Cases (*n* = 676)		Controls (*n* = 683)		
	No.	%	No.	%	
Age, years					
55–59	205	30.3	207	30.3	0.99
60–64	188	27.8	188	27.5	
65–69	179	26.5	179	26.2	
≥70	104	15.4	109	16.0	
Race/ethnicity					
White	626	92.6	638	93.4	0.56
Other	50	7.4	45	7.4	
Waist/hip ratio[c]					
<0.95	251	41.4	294	45.7	0.47
0.95–0.99	218	36.0	220	34.2	
1.00–1.04	119	19.6	111	17.2	
≥1.05	18	3.0	19	3.0	
Body mass index[c,d]					
Normal (<25)	161	24.2	194	28.5	0.17
Overweight (25–29.9)	350	52.6	346	50.9	
Obese (≥30)	154	23.2	140	20.6	
Alcohol consumption[c]					
<1 drink/month	191	28.3	151	22.1	0.04
1–3 drinks/month	93	13.8	121	17.7	
1–6 drinks/week	230	34.1	28	33.4	
7–13 drinks/week	97	14.4	107	15.7	
≥14 drinks/week	64	9.5	76	11.1	
Physical activity[c]					
Sedentary	108	16.1	96	14.1	0.23
Light activity	304	45.2	286	42.0	
Moderate activity	192	28.5	228	33.5	
Very active	69	10.3	71	10.4	
Current smoker[c]	50	7.4	41	6.0	0.57
Prevalent cardiovascular disease[e]	119	17.6	74	10.8	0.0004
Prevalent arthritis[e]	28	4.1	21	3.1	0.29
Prevalent diabetes[e]	5	0.7	1	0.2	0.10
Baseline IPSS					
0–3	296	43.8	531	77.8	<0.01
4–5	278	41.2	137	20.1	
6–7	102	15.1	15	2.2	

Abbreviation: IPSS, International Prostate Symptom Score.

[a] Excludes 23 cases and 16 controls with missing cytokine data and 28 cases and 28 controls with C-reactive protein >10 mg/L at baseline.

[b] From a chi-squared test.

[c] Number of participants missing data for waist/hip ratio, 109; body mass index, 11 cases and 3 controls; alcohol, 1; physical activity, 5; smoking status, 2.

[d] Weight (kg)/height (m)^2.

[e] Assessed at baseline.

Table 2. Serum Concentrations of Cytokines for Cases and Controls, Prostate Cancer Prevention Trial, 1993–2003[a]

	Benign Prostatic Hyperplasia		*P* Value
	Cases (*n* = 676)	Controls (*n* = 683)	
C-reactive protein, mg/L			
Median	1.49	1.32	0.04[b]
Geometric mean[c] (95% CI)	1.46 (1.31, 1.63)	133 (1.19, 1.49)	0.07[d]
5th–95th percentiles	0.26–6.20	0.27–5.55	
TNF-α monomer, pg/mL			
Median	10.6	10.6	0.67[b]
Geometric mean[c] (95% CI)	10.8 (9.2, 12.7)	11.2 (9.5, 13.1)	0.65[d]
5th–95th percentiles	0.8–107.2	0.3–100.4	
sTNF-R1, pg/mL			
Median	1,887	1,825	0.07[b]
Geometric mean[c] (95% CI)	1,841 (1,757, 1,929)	1,746 (1,665, 1,830)	0.01[d]
5th–95th percentiles	1,035–3,770	1,030–3,105	
sTNF-RII, pg/mL			
Median	850	960	<0.0001[b]
Geometric mean[c] (95% CI)	820 (780, 820)	899 (855, 945)	<0.0001[d]
5th–95th percentiles	475–1,620	390–1,770	
IL-6, pg/mL			
Median	3.30	2.80	<0.0001[b]
Geometric mean[c] (95% CI)	3.19 (2.86, 3.55)	2.56 (2.30, 2.86)	<0.0001[d]
5th–95th percentiles	0.6–11.0	0.4–7.8	
IFN-γ, pg/mL			
Median	2.40	2.20	0.02[b]
Geometric mean[c] (95% CI)	2.58 (2.26, 2.94)	2.27 (1.99, 2.59)	0.03[d]
5th–95th percentiles	0.4–14.4	0.4–12.4	

Abbreviations: CI, confidence interval; IFN-γ, interferon γ; IL-6, interleukin 6; sTNF-RI and sTNF-RII, soluble tumor necrosis factor receptors I and II, respectively; TNF-α, tumor necrosis factor α.

[a] Excludes 23 cases and 16 controls with missing cytokine data and 28 cases and 28 controls with C-reactive protein >10 mg/dL at baseline.

[b] Kruskal-Wallis test odds ratio (Wilcoxon rank-sum test).

[c] Adjusted for age and race.

[d] *t* test.

evidence of a linear dose-response association. In a post hoc analysis contrasting quartile 1 with quartiles 2–4, a high sTNF-RII concentration was associated with a 46% (95% CI: 32, 58; $P < 0.0001$) lower BPH risk. Men in the highest 2 quartiles of interleukin 6 had a 46% and 79% higher risk of BPH, respectively, with evidence of a dose-response association ($P_{trend} < 0.001$). There was a suggestion of increased BPH risk in the highest quartile for sTNF-RI and interferon γ, which is consistent with the significant difference in geometric means between cases and controls (Table 2); however, the trend test did not reach statistical significance. There was no association of tumor necrosis factor α with BPH risk. To control for preclinical disease, we also adjusted models for the IPSS at baseline (model 3); however, results were similar to the fully adjusted models (model 2). Results were similar when analyses excluded men diagnosed with prostate cancer ($n = 93$ cases, $n = 105$ controls) or who died during the Prostate Cancer Prevention Trial ($n = 22$ cases, $n = 12$ controls).

Associations of C-reactive protein and cytokines differed little across strata defined by body mass index (Tables 4–7), smoking status, and physical activity (data not shown), although there was an increased risk of BPH for the highest concentration of interferon γ among normal weight men only. However, for strata defined by age, there were strong associations between sTNF-RII and interleukin 6 and BPH risk among younger men only ($P_{interaction} = 0.02$ and $P_{interaction} = 0.03$, respectively; Tables 4–7), and there were no associations among older men. There were no substantial differences in associations of C-reactive protein, cytokines, and BPH risk when stratified by type of BPH event and time between blood collection and BPH event (Tables 4–7).

To further investigate the difference in associations among C-reactive protein, cytokines, and BPH risk between

Table 3. Main Effects of C-reactive Protein and Cytokines on Benign Prostatic Hyperplasia Risk, Prostate Cancer Prevention Trial, 1993–2003[a]

	Cases, no.	Controls, no.	Model 1[b]		Model 2[c]		Model 3[d]	
			Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval	Odds Ratio	95% Confidence Interval
C-reactive protein, mg/L								
Quartile 1	151	171	1.00		1.00		1.00	
Quartile 2	159	171	1.05	0.77, 1.43	1.04	0.76, 1.41	1.14	0.81, 1.60
Quartile 3	155	171	1.02	0.75, 1.39	0.98	0.72, 1.34	1.01	0.72, 1.43
Quartile 4	211	170	1.40	1.04, 1.88	1.30	0.95, 1.78	1.38	0.98, 1.94
P_{trend}				0.03		0.12		0.11
TNF-α (monomer), pg/mL								
Quartile 1	170	171	1.00		1.00		1.00	
Quartile 2	169	171	0.99	0.73, 1.34	0.99	0.73, 1.34	0.97	0.70, 1.35
Quartile 3	178	172	1.03	0.76, 1.38	1.03	0.76, 1.40	1.13	0.81, 1.57
Quartile 4	159	169	0.94	0.70, 1.28	0.96	0.71, 1.31	1.07	0.77, 1.50
P_{trend}				0.73		0.88		0.51
sTNF-RI, pg/mL								
Quartile 1	170	172	1.00		1.00		1.00	
Quartile 2	143	170	0.85	0.62, 1.15	0.84	0.62, 1.15	0.89	0.63, 1.24
Quartile 3	158	171	0.93	0.69, 1.26	0.92	0.68, 1.25	0.88	0.63, 1.23
Quartile 4	205	170	1.22	0.90, 1.63	1.21	0.90, 1.63	1.30	0.94, 1.80
P_{trend}				0.14		0.16		0.12
sTNF-RII, pg/mL								
Quartile 1	262	174	1.00		1.00		1.00	
Quartile 2	140	168	0.55	0.41, 0.74	0.55	0.41, 0.74	0.56	0.40, 0.77
Quartile 3	117	174	0.45	0.33, 0.61	0.45	0.33, 0.61	0.50	0.36, 0.69
Quartile 4	157	167	0.62	0.46, 0.83	0.61	0.46, 0.82	0.67	0.49, 0.92
P_{trend}				<0.001		<0.01		<0.01
IL-6, pg/mL								
Quartile 1	142	192	1.00		1.00		1.00	
Quartile 2	105	146	0.97	0.70, 1.36	0.96	0.69, 1.35	0.92	0.64, 1.33
Quartile 3	197	178	1.50	1.10, 2.02	1.46	1.08, 1.97	1.28	0.92, 1.78
Quartile 4	232	167	1.88	1.40, 2.53	1.79	1.32, 2.42	1.37	1.20, 2.32
P_{trend}				<0.001		<0.001		<0.001
IFN-γ, pg/mL								
Quartile 1	180	189	1.00		1.00		1.00	
Quartile 2	140	169	0.87	0.64, 1.18	0.87	0.64, 1.18	0.85	0.61, 1.19
Quartile 3	164	161	1.07	0.79, 1.44	1.06	0.79, 1.43	1.10	0.79, 1.53
Quartile 4	192	164	1.22	0.91, 1.64	1.24	0.92, 1.66	1.31	0.95, 1.81
P_{trend}				0.10		0.09		0.05

Abbreviations: IFN-γ, interferon γ; IL-6, interleukin 6; sTNF-RI and sTNF-RII, soluble tumor necrosis factor receptors I and II, respectively; TNF-α, tumor necrosis factor α.

[a] Quartile cutpoints—C-reactive protein: 0.67, 1.32, 2.48 μg/L; TNF-α: 4.5, 10.6, 24.4 pg/mL; sTNF-RI: 1,490, 1,825, 2,235 pg/mL; sTNF-RII: 740, 960, 1,185 pg/mL; IL-6: 1.6, 2.8, 4.2 pg/mL; IFN-γ: 1.2, 2.2, 4.0 pg/mL.

[b] Adjusted for matching covariates only (age at baseline and race).

[c] Adjusted for matching covariates and body mass index (linear).

[d] Adjusted for matching covariates, body mass index (linear), and International Prostate Symptom Score at baseline.

Table 4. Associations of C-reactive Protein and Cytokines With Benign Prostatic Hyperplasia Risk, Stratified by Age, Prostate Cancer Prevention Trial, 1993–2003[a]

	Ages 55–64 Years				Ages ≥65 Years			
	Cases, no.	Controls, no.	Odds Ratio	95% Confidence Interval	Cases, no.	Controls, no.	Odds Ratio	95% Confidence Interval
C-reactive protein, mg/L								
Tertile 1	120	131	1.00		75	96	1.00	
Tertile 2	118	132	0.96	0.68, 1.37	91	93	1.18	0.77, 1.81
Tertile 3	151	130	1.23	0.86, 1.80	110	95	1.36	0.89, 2.07
$P_{interaction}$				0.53				
TNF-α, pg/mL								
Tertile 1	137	133	1.00		93	97	1.00	
Tertile 2	142	132	1.05	0.75, 1.18	94	96	1.05	0.70, 1.59
Tertile 3	114	130	0.84	0.59, 1.18	96	95	1.12	0.74, 1.68
$P_{interaction}$				0.30				
sTNF-RI, pg/mL								
Tertile 1	119	133	1.00		103	98	1.00	
Tertile 2	123	130	1.03	0.72, 1.46	78	95	0.78	0.51, 1.17
Tertile 3	151	132	1.26	0.90, 1.78	102	95	0.98	0.66, 1.47
$P_{interaction}$				0.41				
sTNF-RII, pg/mL								
Tertile 1	202	132	1.00		98	97	1.00	
Tertile 2	92	132	0.45	0.32, 0.64	81	95	0.85	0.56, 1.28
Tertile 3	95	129	0.48	0.34, 0.68	100	95	1.03	0.69, 1.54
$P_{interaction}$				0.02				
IL-6, pg/mL								
Tertile 1	91	134	1.00		82	97	1.00	
Tertile 2	102	131	1.15	0.80, 1.67	100	102	1.14	0.76, 1.70
Tertile 3	196	128	2.24	1.57, 3.18	94	88	1.17	0.77, 1.79
$P_{interaction}$				0.03				
IFN-γ, pg/mL								
Tertile 1	109	118	1.00		105	114	1.00	
Tertile 2	124	149	0.88	0.61, 1.25	73	81	1.03	0.68, 1.57
Tertile 3	160	128	1.34	0.94, 1.90	105	93	1.25	0.85, 1.86
$P_{interaction}$				0.71				

Abbreviations: IFN-γ, interferon γ; IL-6, interleukin 6; sTNF-RI and sTNF-RII, soluble tumor necrosis factor receptors I and II, respectively; TNF-α, tumor necrosis factor α.

[a] Adjusted for matching covariates and body mass index (linear).

younger and older men, we examined whether the type of lower urinary tract symptoms differed by age and whether the associations for C-reactive protein, sTNF-RII, and interleukin 6 and BPH risk among younger men differed by type of lower urinary tract symptoms. The distributions by type were similar by age group: The proportion of men reporting mostly irritative, mixed, or mostly obstructive symptoms, respectively, was 57.7%, 18.0%, or 24.3% for men aged 55–59 years; 48.5%, 28.4%, or 23.0% for those aged 60–64 years; 59.2%, 22.0%, or 18.9% for men aged 65–69 years; and 53.7%, 25.9%, and 20.4% for men aged over 70 years ($P = 0.31$). Furthermore, associations between C-reactive protein, sTNF-RII, and interleukin 6 and BPH, either in the total population or among men aged less than 65 years at baseline, did not differ by type of lower urinary tract symptoms (data not shown).

Obesity was associated with an increased risk of BPH in this cohort (21); therefore, additional analyses examined whether C-reactive protein or cytokines mediate the association between obesity and risk of BPH. Compared with men who were normal weight, overweight and obese men had a 26% (OR = 1.24, 95% CI: 0.97, 1.63) and 37% (OR = 1.37, 95% CI: 1.00, 1.87) increased risk of BPH, respectively ($P_{trend} = 0.05$). Control for interleukin 6 decreased the

Table 5. Associations of C-reactive Protein and Cytokines With Benign Prostatic Hyperplasia Risk, Stratified by Body Mass Index, Prostate Cancer Prevention Trial, 1993–2003[a]

	Body mass index, <25				Body mass index, ≥25			
	Cases, no.	Controls, no.	Odds Ratio	95% Confidence Interval	Cases, no.	Controls, no.	Odds Ratio	95% Confidence Interval
C-reactive protein, mg/L								
Tertile 1	70	92	1.00		135	135	1.00	
Tertile 2	48	61	0.84	0.43, 1.61	151	166	1.03	0.59, 1.81
Tertile 3	43	41	1.29	0.61, 2.72	218	185	1.18	0.67, 2.08
$P_{interaction}$				0.66				
TNF-α, pg/mL								
Tertile 1	57	65	1.00		173	166	1.00	
Tertile 2	61	65	1.07	0.64, 1.76	166	161	0.99	0.73, 1.34
Tertile 3	43	54	0.74	0.43, 1.26	165	159	1.00	0.73, 1.35
$P_{interaction}$				0.39				
sTNF-RI, pg/mL								
Tertile 1	52	65	1.00		161	162	1.00	
Tertile 2	42	65	0.79	0.46, 1.36	159	164	0.98	0.72, 1.34
Tertile 3	67	64	1.23	0.74, 2.10	184	160	1.16	0.85, 1.57
$P_{interaction}$				0.66				
sTNF-RII, pg/mL								
Tertile 1	79	67	1.00		230	165	1.00	
Tertile 2	33	64	0.41	0.24, 0.71	126	158	0.58	0.42, 0.79
Tertile 3	49	63	0.61	0.37, 1.02	148	164	0.64	0.47, 0.87
$P_{interaction}$				0.99				
IL-6, pg/mL								
Tertile 1	53	87	1.00		121	155	1.00	
Tertile 2	41	56	1.27	0.74, 2.17	167	150	1.43	1.03, 1.98
Tertile 3	67	51	2.34	1.38, 2.95	216	181	1.49	1.09, 2.04
$P_{interaction}$				0.22				
IFN-γ, pg/mL								
Tertile 1	39	56	1.00		155	162	1.00	
Tertile 2	49	77	0.89	0.51, 1.54	169	163	1.08	0.80, 1.48
Tertile 3	73	61	1.82	1.06, 3.13	180	161	1.15	0.85, 1.58
$P_{interaction}$				0.17				

Abbreviations: IFN-γ, interferon γ; IL-6, interleukin 6; sTNF-RI and sTNF-RII, soluble tumor necrosis factor receptors I and II, respectively; TNF-α, tumor necrosis factor α.

[a] Adjusted for matching covariates and body mass index (linear).

odds ratio between obesity and BPH risk by 35%, from 1.37 to 1.24 (95% CI: 0.90, 1.71; $P_{trend} = 0.17$), while control for sTNF-RII increased the odds ratio between obesity and BPH risk by 11%, from 1.37 to 1.41 (95% CI: 1.03, 1.92; $P_{trend} = 0.03$). In models with C-reactive protein or obesity alone, both were significantly and positively associated with BPH risk (C-reactive protein quartile 4 vs. quartile 1, OR = 1.40, 95% CI: 1.04, 1.88; $P_{trend} = 0.03$; obese vs. normal weight, OR = 1.37, 95% CI: 1.00, 1.87; $P_{trend} = 0.04$). However, in a model with both C-reactive protein and obesity, associations for both factors were attenuated, and neither reached statistical significance (C-reactive protein quartile 4 vs. quartile 1, OR = 1.30, 95% CI: 0.95, 1.77; $P_{trend} = 0.15$; obese vs. normal weight, OR = 1.28, 95% CI: 0.92, 1.77; $P_{trend} = 0.12$). In models controlled for one or more cytokines, once interleukin 6 was added to the model, control for C-reactive protein and/or sTNF-RII had no further effect on the association of obesity and BPH risk (data not shown).

DISCUSSION

In this prospective study, circulating levels of inflammatory markers were associated with risk of incident, symptomatic BPH. Specifically, high serum C-reactive protein concentrations (quartile 4) were associated with an

Table 6. Associations of C-reactive Protein and Cytokines With Benign Prostatic Hyperplasia Risk, Stratified by Type of Event, Prostate Cancer Prevention Trial, 1993–2003[a]

	Type of Benign Prostatic Hyperplasia-defining Event							
	Treatment[b]				Symptoms[b]			
	Cases, no.	Controls, no.	Odds Ratio	95% Confidence Interval	Cases, no.	Controls, no.	Odds Ratio	95% Confidence Interval
C-reactive protein, mg/L								
Tertile	111	227	1.00		97	227	1.00	
Tertile 2	109	229	0.93	0.66, 1.32	92	229	0.94	0.68, 1.31
Tertile 3	155	227	1.08	0.77, 1.53	112	227	1.29	0.94, 1.78
$P_{difference}$[c]				0.27				
TNF-α, pg/mL								
Tertile 1	101	231	1.00		133	231	1.00	
Tertile 2	102	225	0.98	0.72, 1.34	127	225	1.04	0.74, 1.45
Tertile 3	98	227	0.90	0.66, 1.23	115	227	0.99	0.71, 1.38
$P_{difference}$[c]				0.63				
sTNF-RI, pg/mL								
Tertile 1	95	230	1.00		123	230	1.00	
Tertile 2	89	225	0.86	0.62, 1.19	107	225	0.97	0.68, 1.36
Tertile 3	117	228	1.16	0.85, 1.58	145	228	1.24	0.89, 1.73
$P_{difference}$[c]				0.74				
sTNF-RII, pg/mL								
Tertile 1	175	232	1.00		140	232	1.00	
Tertile 2	91	223	0.53	0.38, 0.75	71	223	0.54	0.39, 0.74
Tertile 3	109	228	0.67	0.48, 0.92	90	228	0.62	0.46, 0.84
$P_{difference}$[c]				0.71				
IL-6, pg/mL								
Tertile 1	99	243	1.00		77	243	1.00	
Tertile 2	109	207	1.52	1.07, 2.16	100	207	1.27	0.91, 1.77
Tertile 3	167	233	1.60	1.13, 2.25	124	233	1.68	1.22, 2.31
$P_{difference}$[c]				0.67				
IFN-γ, pg/mL								
Tertile 1	89	190	1.00		93	190	1.00	
Tertile 2	102	273	1.04	0.75, 1.43	140	273	0.81	0.57, 1.14
Tertile 3	110	220	1.33	0.96, 1.85	142	220	1.06	0.75, 1.49
$P_{difference}$[c]				0.27				

Abbreviations: IFN-γ, interferon γ; IL-6, interleukin 6; sTNF-RI and sTNF-RII, soluble tumor necrosis factor receptors I and II, respectively; TNF-α, tumor necrosis factor α.

[a] Adjusted for matching covariates and body mass index (linear).

[b] Treatment includes men who received drug or surgical intervention ($n = 322$); benign prostatic hyperplasia symptoms include men with 2 International Prostate Symptom Scores of >14 or 2 scores at least 5 units higher than baseline plus at least 1 score ≥12 ($n = 405$).

[c] The $P_{difference}$ is calculated as the difference in risk between benign prostatic hyperplasia treatment and symptoms as estimated from a polychotomous logistic model.

increased risk of BPH with no dose-response across lower quartiles (quartiles 1–3); low serum sTNF-RII concentrations (quartile 1) were associated with a significantly increased risk of BPH with no dose-response across higher quartiles (quartiles 2–4); and high serum interleukin 6 concentrations were associated with a dose-response increased risk of BPH. These associations did not differ by body mass index, smoking status, physical activity, type of BPH event, or time between blood draw and BPH event; however, associations of sTNF-RII and interleukin 6 with BPH risk were limited to men aged <65 years at baseline. There was also a suggestion of increased risk in the highest quartile for sTNF-RI and interferon γ; however, the associations were not statistically significant.

Table 7. Associations of C-reactive Protein and Cytokines With Benign Prostatic Hyperplasia Risk, Stratified by Time From Baseline to Event, Prostate Cancer Prevention Trial, 1993–2003[a]

	Time From Baseline to Benign Prostatic Hyperplasia Event							
	0–3 Years				4–7 Years			
	Cases, no.	Controls, no.	Odds Ratio	95% Confidence Interval	Cases, no.	Controls, no.	Odds Ratio	95% Confidence Interval
C-reactive protein, mg/L								
Tertile 1	34	227	1.00		174	227	1.00	
Tertile 2	38	229	1.11	0.67, 1.84	163	229	0.91	0.68, 1.21
Tertile 3	48	227	1.30	0.78, 2.14	219	227	1.18	0.89, 1.56
$P_{difference}$[b]				0.69				
TNF-α, pg/mL								
Tertile 1	37	231	1.00		197	231	1.00	
Tertile 2	41	225	1.20	0.74, 1.95	188	225	0.97	0.74, 1.28
Tertile 3	42	227	1.19	0.73, 1.94	171	227	0.89	0.68, 1.18
$P_{difference}$				0.25				
sTNF-RI, pg/mL								
Tertile 1	33	230	1.00		185	230	1.00	
Tertile 2	43	225	1.35	0.82, 2.22	153	225	0.83	0.62, 1.10
Tertile 3	44	228	1.30	0.79, 2.15	218	228	1.17	0.89, 1.54
$P_{difference}$				0.78				
sTNF-RII, pg/mL								
Tertile 1	57	232	1.00		258	232	1.00	
Tertile 2	26	223	0.47	0.29, 0.79	136	223	0.55	0.41, 0.73
Tertile 3	37	228	0.68	0.43, 1.07	162	228	0.63	0.48, 0.83
$P_{difference}$[b]				0.84				
IL-6, pg/mL								
Tertile 1	27	243	1.00		149	243	1.00	
Tertile 2	42	207	1.86	1.10, 2.16	167	207	1.29	0.97, 1.73
Tertile 3	51	233	1.89	1.12, 3.17	240	233	1.60	1.21, 2.12
$P_{difference}$[b]				0.68				
IFN-γ, pg/mL								
Tertile 1	30	190	1.00		152	190	1.00	
Tertile 2	47	273	1.11	0.67, 1.83	195	273	0.89	0.67, 1.18
Tertile 3	43	220	1.26	0.75, 2.10	209	220	1.18	0.89, 1.58
$P_{difference}$				0.89				

Abbreviations: IFN-γ, interferon γ; IL-6, interleukin 6; sTNF-RI and sTNF-RII, soluble tumor necrosis factor receptors I and II, respectively; TNF-α, tumor necrosis factor α.

[a] Adjusted for matching covariates and body mass index (linear).

[b] $P_{difference}$ is calculated as the difference in risk between benign prostatic hyperplasia treatment and symptoms as estimated from a polychotomous logistic model.

Our findings of an association between markers of systemic inflammation and BPH risk are supported by multiple lines of evidence suggesting that inflammation plays a role in the etiology of BPH. Histologic studies have found acute and/or chronic inflammation in up to 100% of BPH specimens (8–10, 31). In cross-sectional studies, the presence of inflammatory infiltrates in prostate tissue is associated with several measures of BPH including increased prostate volume (8, 10), more severe lower urinary tract symptoms (11), acute urinary retention (12, 32), and epithelial cell proliferation (33). Furthermore, in situ studies have found that expression of proinflammatory cytokines is increased in BPH tissue (14, 15, 34, 35), and in a rat prostate model, administration of immunostimulatory compounds induces epithelial proliferation and hyperplastic lesions similar to BPH nodules (13). In recent prospective studies, participants with acute inflammation in biopsy specimens had a greater risk of BPH progression (lower urinary tract symptoms) and acute

urinary retention (10). Furthermore, in a large population-based cohort of men, daily users of nonsteroidal antiinflammatory drugs (NSAIDs) had a lower risk of several clinical measures of BPH (low maximum flow rate, increased prostate volume, and elevated prostate-specific antigen) and a lower risk of developing moderate/severe lower urinary tract symptoms (36).

Only 3 previous studies have investigated the association between systemic inflammatory markers and BPH risk (37–39). Our findings are consistent with one small, hospital-based case-control study in which men with histologically confirmed BPH had higher concentrations of interleukin 6 than did controls (1.9 vs. 0.7 pg/mL, respectively) (37). Our results are also consistent with those from a cross-sectional study that found that men with elevated C-reactive protein concentrations had a nonsignificant increased risk of more severe lower urinary tract symptoms (38). In a small prospective study, high C-reactive protein concentrations were not associated with an absolute increase in lower urinary tract symptoms, although men with high C-reactive protein concentrations were more likely to have a rapid proportional increase in irritative lower urinary tract symptoms (39).

Soluble tumor necrosis factor receptors reflect tumor necrosis factor α activity because they are shed from cellular tumor necrosis factor receptors in response to tumor necrosis factor α binding; therefore, we originally hypothesized that high soluble tumor necrosis factor receptor concentrations would be associated with increased risk of BPH. However, soluble tumor necrosis factor receptors also have direct antiinflammatory effects either by down-regulating the expression of cell membrane tumor necrosis factor receptors and decreasing the sensitivity of target cells to tumor necrosis factor α (40) or by binding to and thereby acting as a competitive antagonist for tumor necrosis factor α (41). Thus, the interpretation of low soluble tumor necrosis factor receptor concentrations is complex and, in this study, may reflect an inability to modulate responses to tumor necrosis factor α.

The associations between sTNF-RII and interleukin 6 and BPH risk in young men only are difficult to understand. Some studies are consistent with our findings: One reported a much stronger association between C-reactive protein and BPH risk among younger men (38), and another found an association between the serologic presence of sexually transmitted infections and symptomatic BPH among men aged 30–59 years but not among men aged ≥60 years (42). In secondary analyses, we found no age-related differences in the type of BPH symptoms reported, and associations between cytokines and BPH risk did not differ by symptom type. It is possible that BPH etiology differs in younger and older men; however, this needs confirmation in further studies.

In both this nested case-control sample and the Prostate Cancer Prevention Trial overall, there were significant associations of obesity with increased BPH risk (21). However, when examining whether this association was mediated by C-reactive protein concentrations, we found that both C-reactive protein and body mass index were attenuated to a similar degree and that neither reached statistical significance. This finding suggests that body mass index and C-reactive protein jointly contribute to BPH risk and that the effects of one cannot be separated from the other, although we cannot rule out the possibility that obesity and C-reactive protein are either markers of, or confounded by, another risk factor for BPH. Furthermore, when examining whether interleukin 6 concentrations mediate the association between obesity and BPH, we found that adjustment for interleukin 6 resulted in only a moderate attenuation (35%) of the association, suggesting that systemic inflammation is not the only mechanism through which obesity affects BPH risk. However, it is also possible that measurement error in interleukin 6 limited the ability to explain the association between obesity and BPH.

We found no associations between tumor necrosis factor α, sTNF-RI, and interferon γ and BPH risk. An increased risk of BPH was found for the highest concentration of interferon γ among normal weight men; however, this is inconsistent with the other cytokines and may be a chance finding. The lack of associations may be due to low cytokine concentrations, particularly for tumor necrosis factor α and interferon γ, where 27% and 17% of samples were below the limits of detection. sTNF-RI is derived from epithelial cells, whereas sTNF-RII originates primarily from activated T cells, B cells, and neutrophils (43). It is possible that activation of the tumor necrosis factor receptor results in distinct activities (44) and that TNF-RII plays a stronger role in the inflammatory response.

One important strength of this study is the prospective design. Men with a history of BPH or BPH symptoms at the time of blood draw were excluded, and all cases were incident. Cross-sectional and case-control studies of inflammation and BPH are problematic, because differences in serum cytokine concentrations could be due to BPH. In addition, this study used a rigorous definition of BPH, which captured all current medical treatments, as well as substantial lower urinary tract symptoms, and specifically excluded men who reported transient elevations in the IPSS or a physician diagnosis of BPH in the absence of symptoms or treatment. This is in contrast to previous studies that relied on a single incomplete assessment of lower urinary tract symptoms (38) or surgery alone as an endpoint (37).

There are several important limitations to this study. Our definition of BPH by lower urinary tract symptoms is not specific and cannot distinguish between lower urinary tract symptoms due to BPH and those due to other urologic, neurologic, or bladder conditions (45). However, there are 2 key arguments to suggest that our results are not substantially affected by lower urinary tract symptoms unrelated to BPH. First, we estimate that the prevalence of ''other conditions'' associated with lower urinary tract symptoms in the Prostate Cancer Prevention Trial study population is only 6.5% (based on the age-specific prevalences of these conditions (13.5%) within the Olmstead County cohort which also includes men with a history of prostate surgery) (46). Second, there were no differences in associations between cytokines and BPH by symptom type (mostly obstructive vs. mostly irritative), suggesting that the observed association was not due to prostate enlargement alone. We deliberately selected a control group free of significant lower urinary tract symptoms throughout the 7-year trial; thus, men who developed mild to moderate symptoms were excluded from

this study. It is unclear whether the development of mild/moderate symptoms is indicative of an intermediate form of BPH, but if so, inclusion of these men in the controls would have attenuated our results. We could not control for use of NSAIDs because it was not well captured in the Prostate Cancer Prevention Trial. One study reported modest inverse associations between NSAIDs and symptomatic BPH (36), and thus it is possible that NSAIDS somewhat confound our findings. Lastly, C-reactive protein and cytokine concentrations are subject to nondifferential measurement error. The C-reactive protein and cytokine concentration from a single baseline blood specimen may not accurately reflect the concentration at the physiologically relevant time point, and blood samples were nonfasting and drawn at all times during the day, which may have increased variability in concentrations.

This study supports the hypothesis that systemic inflammation plays a role in the development or progression of symptomatic BPH. High C-reactive protein concentrations were associated with a decreased risk of BPH, although the association was attenuated after adjustment for body mass index, suggesting that body mass index and C-reactive protein jointly contribute to BPH risk. Low sTNF-RII and high interleukin 6 concentrations were associated with an increased risk of BPH, however, only among men younger than 65 years, suggesting that the pathogenesis of BPH may differ between younger and older men. C-reactive protein and interleukin 6 explained only a moderate proportion (19%–35%) of the association between obesity and increased BPH risk; thus, elevations in these inflammatory markers may not be the only mechanism through which obesity affects risk of BPH. Several other factors including chronic infection or autoimmune inflammatory disorders could also contribute systemic inflammation and to the development of BPH. Future studies will be needed to confirm our findings and to assess the role of other sources of systemic inflammation.

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