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INSIGHT INTO INFECTION-MEDIATED PROSTATE DAMAGE: CONTRASTING PATTERNS OF C-REACTIVE PROTEIN AND PROSTATE-SPECIFIC ANTIGEN LEVELS DURING INFECTION

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Abstract

Background—To investigate mechanisms underlying our previous observation of a large rise in serum prostate-specific antigen, a marker of prostate pathology, during both sexually transmitted and systemic infections, we measured serum high-sensitivity C-reactive protein (hsCRP), a marker of systemic inflammation, in our previous case-control study of young, male U.S. military members and compared our findings to those for PSA.

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DISCLOSURE STATEMENT

The authors declare no conflicts of interest.

Methods—We measured hsCRP before and during infection for 299 chlamydia, 112 gonorrhea, and 59 non-chlamydial, non-gonococcal urethritis (NCNGU) cases; before and after infection for 55 infectious mononucleosis (IM) and 90 other systemic/non-genitourinary cases; and for 220–256 controls.

Results—Only gonorrhea cases were significantly more likely to have a large hsCRP rise (1.40 mg/L or 239%) during infection than controls ($p < 0.01$). However, gonorrhea, IM, and other systemic/non-genitourinary cases were more likely to have a rise of any magnitude up to one year post-diagnosis than controls ($p = 0.038$ – 0.077).

Conclusions—These findings, which differ from those for PSA, suggest distinct mechanisms of elevation for hsCRP and PSA, and support both direct (e.g., prostate infection) and indirect (e.g., systemic inflammation-mediated prostate cell damage) mechanisms for PSA elevation. Future studies should explore our PSA findings further for their relevance to both prostate cancer screening and risk.

Keywords

Sexually transmitted infection; infectious mononucleosis; infection; C-reactive protein; prostate-specific antigen; prostate cancer

INTRODUCTION

Sexually transmitted infections (STIs) have long been hypothesized to contribute to prostate carcinogenesis. Early proposed mechanisms focused around prostate epithelial cell transformation and induction of intraprostatic inflammation and prostate cell damage,^{1, 2} as a large proportion of STIs resulted in acute or chronic clinical prostatitis in the pre-antibiotic era.^{3–5} However, now that most STIs can be readily diagnosed and treated, and STI-associated clinical prostatitis is rare, the relevance of STIs for prostate cancer (PCa) risk warrants confirmation.

We previously investigated this question by using serum prostate-specific antigen (PSA) as a marker of prostate involvement during infection (i.e., prostate infection, inflammation, and/or cell damage) in two studies of young men.^{6, 7} Both of these studies observed that men with exudative STIs (chlamydia, gonorrhea, *Trichomonas vaginalis* infection, and non-gonococcal urethritis) were more likely to have a large PSA rise at the time of their infection than non-infected controls. We interpreted these findings to mean that some STIs had ascended to the prostate and contributed to a local inflammatory immune response and tissue injury, with subsequent release of PSA into the interstitial space and vasculature – i.e., a “direct” prostate-specific mechanism. However, as PSA also rose during infectious mononucleosis (IM) and other systemic or localized, non-genitourinary infections,⁸ the possibility of “indirect” mechanisms for PSA elevation (e.g., inflammation-mediated or pre-existing prostate damage together with increased vascular permeability)⁸ was raised.

Therefore, to help disentangle the relative contributions of direct versus indirect mechanisms for PSA elevation, we measured serum high-sensitivity C-reactive protein (hsCRP), a non-specific marker of systemic inflammation derived from the liver,⁹ in men from our previous study^{7, 8} and compared our findings to those for PSA.

MATERIALS AND METHODS

Study population

We performed our study among U.S. active-duty military members with stored sera in the Department of Defense Serum Repository (DoDSR). This repository contains sera remaining from routine human immunodeficiency virus type 1 (HIV-1) testing of all active-duty military personnel since the early 1990s, as well as sera collected for indicated HIV-1 testing (e.g., clinical work-up for STIs), pre-induction, major overseas deployments, and specialized physical examinations. These specimens are linked to information on demographics, service-related activity, and reportable (e.g., chlamydia, gonorrhea, and NCNGU) and non-reportable medical diagnoses (e.g., IM and other infectious diseases).^{10–12} These diagnoses are recorded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.¹⁰

Men eligible for our study were HIV-negative, <25 years of age as of 1995, on continuous active-duty from 1995–2006, and had 1 serum specimens collected in each of the following four time periods: 1995–1997, 1998–2000, 2001–2003, and 2004–2006. This last criterion was included to ensure generally similar availability and correlates of specimen availability across studies.

Case definitions

Exudative STI cases were defined as men with a laboratory-confirmed¹² diagnosis of genital chlamydia (ICD-9-CM code=099.41; ICD-10-CM codes=A56.0, A56.1, A56.2), gonorrhea (ICD-9-CM=098 codes; ICD-10-CM=A54 codes), or NCNGU (ICD-9-CM code=099.40; ICD-10-CM code=N34.1) from 2001–2003 with an accompanying serum specimen collected within 7 days of diagnosis.⁷ IM cases were defined as men with one inpatient or two outpatient diagnoses of IM (ICD-9-CM code=075; ICD-10-CM code=B27) within 30 days of each other to increase the specificity of this non-reportable diagnosis. We extended the window of IM ascertainment to 1998–2003 to increase the number of cases. IM was diagnosed by the Monospot® test, Epstein-Barr virus antibody-specific tests, or symptoms, but the exact method of diagnosis was not recorded. We defined cases for our *post-hoc* analysis of other infectious diseases as men diagnosed with fever; a systemic infection; or a localized, inflammatory non-genitourinary infection from 1995–2006. Qualifying diagnoses identified in participants' medical records included streptococcal sore throat (ICD-9-CM code=034.0; ICD-10 codes=J02.0, J03.0), certain influenza diagnoses (ICD-9-CM codes=487.1, 487.8; ICD-10-CM codes=J10.1, J11.1, J11.2, J11.81, J11.89), *Haemophilus influenzae* infection (ICD-9-CM code=041.5, ICD-10-CM code=B96.3), intestinal infection due to specified or unspecified organisms (ICD-9-CM codes=008.43, 008.69, 008.8, 009.0; ICD-10-CM codes=A04.5, A08.39, A08.8, A09), unspecified viral infection (ICD-9-CM code=079.99; ICD-10-CM code=B97.89), other specified viral infection (ICD-9-CM code=079.89; ICD-10-CM code=B33.8, B34.1, B34.2, B34.4, B34.8, B97.19, B97.29, B97.89), unspecified infectious and parasitic diseases (ICD-9-CM code=136.9; ICD-10-CM code=B89, B99.9), fever not accompanied by another diagnosis (ICD-9-CM code=780.6; ICD-10-CM code=R50.9), varicella and herpes zoster infection (ICD-9-CM codes=052.9, 053.0; ICD-10-CM codes=B01.9, B02.1), and leptospirosis icterohemorrhagica (ICD-9-CM

code=100.0; ICD-10-CM code=A27.0). We selected other infectious disease cases from STI and IM cases (if their date of infectious disease diagnosis occurred before their STI/IM diagnosis) and from controls.⁸

Control definitions

We defined controls for the STI and IM analyses as men with no STI or IM diagnoses (ICD-9-CM codes=075, 090–099.9, and 131; ICD-10-CM codes=B27, A50-59, A64, N34.1), except persistent viral infections (ICD-9-CM codes=054 and 078.1; ICD-10-codes=A60, A63.0, B00, B07), in their medical record through 2006. Controls were frequency-matched to the entire case group by race (STI and IM analyses) and window of case ascertainment (1998–2000, 2001–2003; IM analysis). Other infectious disease controls were defined as any of the original STI or IM controls who did not meet the infectious disease case definition. Infectious disease controls were individually-matched to cases by race and window of case ascertainment (1995–1997, 1998–2000, 2001–2003, 2004–2006).^{7, 8}

Specimen selection

We selected two serum specimens for each participant. For STI cases, we selected one specimen within 7 days of their case diagnosis (“index” specimen), and the first specimen collected before their index specimen (“pre-index” specimen, range: 9 days–4 years before diagnosis).⁷ For IM cases, we selected the first specimens collected before (range: 3 days–4 years) and after (range: 1 day–3 years) their diagnosis. We did not require IM index specimens to have been collected within 7 days of diagnosis because HIV-1 testing is not indicated for IM, and thus few men would have had accompanying stored specimens. For other infectious disease cases, we selected the first specimens collected before (range: 172 days–7 years) and up to 359 days after their diagnosis. We limited index specimen collection to <1 year after diagnosis based on PSA findings in the IM analysis.⁸

Similar to cases, we selected two specimens for each control. For the STI analysis, we selected one randomly chosen specimen from 2001–2003 (“index”) and the first specimen collected before their index specimen (“pre-index”).⁷ We followed a similar approach for the IM and other infectious disease analysis except that we frequency- or individually-matched these specimens to the window of case ascertainment.⁸

This study was approved by the institutional review boards at the Walter Reed Army Institute of Research and Johns Hopkins Bloomberg School of Public Health. All data and specimens were anonymized before release from the DoDSR.

hsCRP and PSA measurement

We measured serum hsCRP concentration using an automated latex-enhanced immunoturbidimetric assay (lower limit of detection=0.03 mg/L) performed on a Behring BN II nephelometer (Dade Behring, Deerfield, IL).¹³ Serum total PSA concentration was measured in the same specimens as part of our previous analysis using an Access Hybritech assay (Beckman Coulter, Brea, CA). Specimens from the same participant were tested adjacent to one another in random within- and across- participant order, and laboratory

members were blinded to the case-control status of all specimens. Assay reproducibility was assessed by including blinded, duplicate quality control pairs from the DoDSR in the testing sequence. The coefficient of variation was 3.5% for hsCRP (n=23 pairs) and 12.4% for PSA (n=25 pairs); it improved to 6.9% after excluding one largely discrepant pair.

Statistical analysis

We initially explored the change in hsCRP during infection by calculating geometric and arithmetic mean pre-index and index hsCRP concentrations for cases and controls. Values were standardized by race and window of specimen collection to account for frequency- and individual-matching, as appropriate. Values were compared by linear regression with robust variance estimation in the STI and IM analyses, and by conditional logistic regression in the other infectious disease analysis. We explored the full distribution of hsCRP change by calculating race- and time-standardized categories of absolute and relative change for cases and controls based on the distribution of change among STI controls. Specifically, we divided controls into those who did and did not have an increase in hsCRP, after which we sub-divided the distribution of positive change into quartiles. Finally, we performed *a priori*-specified analyses examining large absolute and relative rises (absolute: 1.40 mg/L; relative: 239%, the upper-most quartiles of change), as well as *post-hoc* analyses examining rises of any magnitude. We selected our large hsCRP cut-off points to give us similar power to detect these rises as to detect large PSA rises in our previous analyses.^{7, 8} Categories of change were compared by logistic regression for the STI and IM analyses, and by conditional logistic regression for the other infectious disease analysis. Crude models included frequency-matched variables, as appropriate, and adjusted models (IM and other infectious diseases only) included additional terms for age and time between specimens.

To investigate whether hsCRP is more likely to rise closer in time to diagnosis, we performed stratified analyses by time between diagnosis and index specimen collection for IM and other infectious diseases. Separate analyses were also performed by other infectious disease type. To investigate the possible influence of additional diagnosed and undiagnosed infections on our results, we conducted sensitivity analyses excluding: 1) participants with genitourinary or other infectious disease diagnoses, including persistent viral infections, up to one year before their pre-index specimen through to seven days before (cases) or after (controls) their index specimen; 2) participants with “clinically indicated” or “STI visit” reasons for blood draw for their pre-index (cases and controls) or index (controls only) specimens; 3) higher ranking officers who may have greater access to non-military healthcare; and 4) men with active-duty breaks or deployment one year before their pre-index specimen through to seven days after their index specimen. This last sensitivity analysis also excluded periods of time with potentially greater levels of acute stress, which have been hypothesized, but not found, to be associated with elevated hsCRP.^{14–16} Similar results were observed in all sensitivity analyses as in the main analyses. Finally, we examined the correlation between hsCRP and PSA in both pre-index and index specimens, and adjusted our original PSA findings for hsCRP.

RESULTS

We identified 299 chlamydia, 112 gonorrhea, 59 NCNGU, 55 IM, and 90 other infectious diseases cases, and selected 256 controls for comparison with STI and IM cases, and 220 for comparison with other infectious disease cases. Compared to controls, cases were slightly younger, gonorrhea cases were more likely to be African-American, and IM cases were more likely to be Caucasian. Men with chlamydia and gonorrhea were less likely to be married, STI cases were more likely to be enlisted, and all cases, except IM, were less likely to have had their index specimen drawn for routine purposes, and more likely to have a greater number of blood draws for HIV-1 testing than controls. STI cases also had a shorter mean time between specimens than controls, whereas IM cases had a greater mean time (Table 1).

Exudative STIs

Gonorrhea cases had a significantly greater increase in geometric mean hsCRP and a borderline significant increase in mean hsCRP between their pre-index and index specimens than controls. They were also significantly more likely to have large absolute and relative rises in hsCRP, and non-significantly more likely to have rises of any magnitude than controls, whereas no differences were observed for chlamydia or NCNGU (Table 2).

Infectious mononucleosis

No differences were observed in the average or full distribution of hsCRP change between IM cases and controls (Table 3). In analyses stratified by time between diagnosis and index specimen collection, cases whose index specimen was collected <4 or 4–12 months after diagnosis were non-significantly more likely to have a rise of any magnitude than controls, whereas those whose index specimen was collected >1 year after diagnosis were significantly less likely to have a large hsCRP rise. Combining our findings for index specimens collected within the first year of diagnosis resulted in a marginally significant association between IM and any rise in hsCRP, indicating that our overall findings were attenuated by inclusion of cases whose index specimen was collected >1 year after diagnosis (Table 4).

Other systemic or localized, non-genitourinary infections

Infectious disease cases had a non-significantly greater change in geometric, but not arithmetic, mean hsCRP between their pre-index and index specimens than controls. Cases were also non-significantly more likely to have a large relative rise and significantly more likely to have a rise of any magnitude than controls (Table 3). In stratified analyses, cases whose index specimen was collected 4–12 months after diagnosis were non-significantly more likely to have a large relative rise and a rise of any magnitude than controls, as were cases with unspecified viral infections (Table 4).

hsCRP and PSA

Irrespective of infection type, the correlation between hsCRP and PSA was low when measured in the same specimen (pre-index specimens: Spearman $r=-0.0058$; index

specimens: $r=0.031$). In addition, adjustment for hsCRP did not change our previous PSA results (Table 5).

DISCUSSION

In this large, longitudinal study of infections and hsCRP, we found that only gonorrhea cases were significantly more likely to have a large hsCRP rise during infection than controls. However, gonorrhea, IM, and other systemic or localized, non-genitourinary cases were more likely to have a rise of any magnitude up to one year post-diagnosis than controls, possibly suggesting unresolved systemic inflammation in some infected men. Finally, compared to our findings for PSA (i.e., large rises for chlamydia, gonorrhea, IM, and other infectious diseases), our findings for hsCRP were generally distinct and adjustment for hsCRP did not alter our previous PSA results. These contrasting patterns of findings support both direct and indirect mechanisms for PSA elevation.

To our knowledge, only two studies have examined the influence of STIs on hsCRP or CRP.^{17, 18} The first of these studies observed higher levels of CRP in pregnant women with *Trichomonas vaginalis* infection than in those without infection,¹⁷ and the second observed higher levels in *C. trachomatis* positive women with mucopurulent cervicitis (i.e., symptomatic infection) or infertility than in asymptomatic, *C. trachomatis* positive women.¹⁸ While these findings are difficult to compare directly to our results because we do not have information on symptoms, we believe our results are consistent with these findings based on the typical presentation of chlamydia and gonorrhea in men. For instance, gonorrhea tends to cause symptomatic urethritis in men,¹⁹ which may explain its positive association with hsCRP, whereas chlamydia tends to be asymptomatic,¹⁹ which may explain its null association. Our results for gonorrhea and chlamydia are also in line with previous findings for acute clinical prostatitis (large hsCRP peak²⁰), symptomatic lower urinary tract infections (positive association with hsCRP/CRP^{21–23}), and asymptomatic bacteriuria (null association with CRP²⁴). Our findings for NCNGU are difficult to interpret because it is unclear to what extent this laboratory-based diagnosis is accompanied by symptoms in the U.S. military.

In contrast to the STI literature, a considerably larger number of studies have examined CRP levels during other infections. For instance, during respiratory tract infections, CRP peaks approximately 48 hours after the initial stimulus and then declines with a half-life of approximately 19 hours once the stimulus has resolved.^{9, 25–27} This rapid decline in CRP may explain our null findings for both IM and other infectious diseases with large hsCRP rises because participants' levels may have already declined by the time of index specimen collection. However, despite the strong likelihood that we missed infection-associated hsCRP peaks, we did observe positive associations for rises of any magnitude, possibly suggesting unresolved systemic inflammation in some infected men.

In addition to understanding the influence of infections on hsCRP, a major objective of our study was to help interpret our previous findings for infections and PSA. In the case of gonococcal infections that resulted in a large hsCRP but not PSA rise, we suspect these reflected symptomatic urethral infections that contributed to both a systemic immune

response and prompt antibiotic therapy, thereby preventing prostate infection. In contrast, for gonococcal and chlamydial infections that resulted in a large PSA but not hsCRP rise, we suspect these likely reflected asymptomatic urethral infections that were not treated promptly, thereby allowing establishment of a chronic, low-grade prostatic infection or damage to the prostate epithelium from persistent local urethral inflammation.⁸ Finally, in the case of systemic or localized non-genitourinary infections that resulted in large sustained rises in PSA but not hsCRP, we hypothesize these may be explained by at least two possible mechanisms: 1) “direct” prostate involvement by infectious agents previously detected in prostate specimens (e.g., Epstein-Barr virus,^{28–32} a lifelong virus that can cause IM); and 2) a sustained influence of systemic inflammation on the local prostate environment, even after resolution of infection. For instance, acute damage from circulating inflammatory cells could conceivably disrupt prostatic cellular repair or regeneration mechanisms, or possibly break self-tolerance to prostatic antigens, leading to a chronic, local inflammatory state and persistently elevated serum PSA.

While additional studies will be necessary to elucidate the mechanisms for our original PSA findings, we believe they are important for two reasons. First, they may have bearing on PCa screening if infections contribute to PSA rises in older men (>40–50 years of age) when some guidelines recommend PSA screening.^{33, 34} Second, our findings may also have bearing on PCa risk. Although previous etiologic studies have focused on infections known to involve the prostate,¹ it is possible that other systemic infections, particularly the cumulative burden of these infections, may also be important for PCa risk. This hypothesis merits investigation in future studies to identify possible modifiable sources of prostate inflammation and PCa risk.

CONCLUSIONS

In summary, we found that hsCRP rose during some gonococcal infections in young men, but not during chlamydia or NCNGU infections. hsCRP was also only minimally elevated months after IM or other systemic or local non-genitourinary infections, implying at least partial resolution of systemic inflammation by the time of blood draw. These results stand in contrast to previous findings for PSA,^{7, 8} suggesting distinct infection-mediated mechanisms for PSA and hsCRP elevation, and supporting both direct and indirect mechanisms for our previous PSA findings. Future studies should explore these findings further for their relevance to both PSA-based PCa screening and risk.

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TABLE 1

Demographic and military characteristics¹ of infectious disease cases and controls; U.S. military 1995–2006

	Controls ²	Cases				
		Chlamydia	Gonorrhea	NCNGU	IM	Other infectious diseases
N	256	299	112	59	55	90
Mean age (years) ³	29.9	29.2**	29.0**	29.1*	28.4**	28.8
Race/ethnicity (%) ⁴						
African-American	55.1	54.2	79.5**	52.5	16.4**	44.4
Caucasian	36.3	36.1	16.1	35.6	78.2	45.6
Other	8.6	9.7	4.4	11.9	5.4	10.0
Marital status (%) ³						
Married	79.3	60.7**	63.5*	73.4	73.7	76.6
Other	20.7	39.3	36.5	26.6	26.3	23.4
Military grade (%) ³						
Enlisted	91.1	96.2*	97.3*	99.0*	95.1	87.3
Officer	8.9	3.8	2.7	1.0	4.9	12.7
Reason for blood draw (%) ³						
Routine ⁵	69.6	22.3**	25.0**	17.6**	79.7	60.7*
Clinically indicated (part of an STI visit)	1.9	34.2	48.7	70.4	2.6	4.6
Other/unknown	28.5	43.5	26.3	12.0	17.7	34.7
Mean number of blood draws for HIV-1 testing from 1995–2006	9.9	12.0**	12.3**	13.4**	10.0	11.1*
Mean time between pre-index and index specimens (months)	16.8 ⁶	11.9**	11.9**	10.7**	23.4*	51.2

HIV-1=human immunodeficiency virus type 1; IM=infectious mononucleosis; NCNGU = non-chlamydial, non-gonococcal urethritis; STI=sexually transmitted infection.

* P-value: 0.0001 – 0.05

** P-value: <0.0001

¹Values for chlamydia, gonorrhea, and NCNGU cases and controls were calculated by linear regression adjusting for race (African-American, non-African-American), and values for IM and other infectious disease cases and controls were calculated by linear regression adjusting for race and window of specimen collection. P-values were calculated by linear regression for continuous or binary variables, and by logistic regression for categorical variables in the chlamydia, gonorrhea, NCNGU, and IM case-control comparisons. P-values for the other infectious disease case-control comparison were calculated by conditional logistic regression.

²Values presented are for controls in the chlamydia, gonorrhea, and NCNGU case-control comparisons. Values for the IM and other infectious disease case-control comparisons were similar except where noted.

³At the time of blood draw of the index specimen.

⁴Chlamydia, gonorrhea, NCNGU, and IM cases were frequency-matched as a group to controls by race/ethnicity.

⁵Indicates blood drawn for routine and pre- and post-deployment HIV-1 tests, as well as HIV-1 tests performed as part of specialized physical examinations (e.g., for flight school).

⁶The mean time between pre-index and index specimens for the other infectious disease controls was 53.1 months.

Change in serum high-sensitivity C-reactive protein concentration during sexually transmitted infections in young U.S. military members, 2001–2003

TABLE 2

Cases										
Controls			Chlamydia		P-value ^I		Gonorrhea		P-value ^I	
	Pre-index	Index	Pre-index	Index			Pre-index	Index		
N	256		299		112		59			
Serum hsCRP concentration (mg/L) ²										
Geometric mean	0.78	0.94	0.67	0.73	0.30		0.75	1.22	0.028	0.96
Mean	1.82	2.10	1.57	1.59	0.48		1.51	2.74	0.067	0.56
Range	0.04–19.47	0.04–37.29	0.02–37.92	0.02–24.25	-----		0.05–12.84	0.05–27.18	-----	-----
Distribution of absolute change in serum hsCRP concentration (%) ²										
0.00 mg/L	44.6		47.1				34.6			45.3
0.00 – 0.20 mg/L	13.9		15.6				16.6			12.1
0.21 – 0.55 mg/L	13.4		13.5		0.72	0.043	12.2		15.4	1.00
0.56 – 1.39 mg/L	14.0		10.3				9.9		13.5	
1.40 mg/L	14.1		13.4				26.7		13.6	
Large absolute rise in serum hsCRP concentration (%) ²										
1.40 mg/L	14.1		13.4		0.82	0.0022	26.7		13.6	0.92
Distribution of relative change in serum hsCRP concentration (%) ²										
0%	44.6		47.1				34.6		45.3	
0 – 52%	14.1		16.2				16.1		15.9	
53 – 112%	14.3		15.0		0.45	0.12	12.1		12.2	0.90
113 – 238%	13.5		8.5				11.1		9.9	
239%	13.5		13.2				26.2		16.7	
Large relative rise in serum hsCRP concentration (%) ²										
239%	13.5		13.2		0.92	0.0022	26.2		16.7	0.54
Any rise in serum hsCRP concentration (%) ²										

Cases					
	Controls	Chlamydia	P-value ¹	Gonorrhea	P-value ¹
				NCNGU	P-value ¹
N	256	299		59	
> 0.00 mg/L or %	55.4	52.9	0.55	54.7	0.92

hsCRP=high-sensitivity C-reactive protein; NCNGU=non-chlamydial, non-gonococcal urethritis

¹P-values were calculated by linear regression with robust variance estimation for continuous variables, by linear regression for binary variables, and by logistic regression for categorical variables. All models were adjusted for race (African-American, non-African-American) to account for frequency-matching.

²Values were calculated by linear regression with robust variance estimation for continuous variables, and by linear regression for binary and categorical variables. All models were adjusted for race to account for frequency-matching.

Change in serum high-sensitivity C-reactive protein concentration during or following infectious mononucleosis and other infectious diseases in young U.S. military members, 1998–2003

TABLE 3

Controls			IM		P-value ¹	Controls		Other infectious diseases ²		P-value ¹
N	255		55			220		90		
Serum hsCRP concentration (mg/L) ³										
	Pre-index	Index	Pre-index	Index		Pre-index	Index	Pre-index	Index	
Geometric mean	0.78	0.92	0.75	1.00	0.52	0.70	0.79	0.47	0.76	0.06
Mean	1.83	2.07	1.83	2.44	0.64	2.54	1.78	1.23	1.88	0.17
Range	0.04–19.47	0.04–37.29	0.03–25.81	0.07–22.12	-----	0.02–184.48	0.05–19.47	0.02–18.51	0.02–29.93	
Distribution of absolute change in serum hsCRP concentration (%) ³										
0.00 mg/L	44.5		31.0		0.49	44.0		33.2		0.073
0.00 – 0.20 mg/L	13.3		15.9			15.1		19.0		
0.21 – 0.55 mg/L	14.2		17.4			10.0		19.8		
0.56 – 1.39 mg/L	14.6		20.7			16.5		11.5		
1.40 mg/L	13.4		15.0			14.5		16.5		
Large absolute rise in serum hsCRP concentration (%) ²										
1.40 mg/L	13.4		15.0		0.77	14.5		16.5		0.61
1.40 mg/L ⁴	13.6		15.9		0.69	14.2		17.2		0.65
Distribution of relative change in serum hsCRP concentration (%) ³										
0%	44.5		31.0		0.14	44.0		33.2		
0 – 52%	14.7		26.4			15.2		16.1		
53 – 112%	14.2		16.9			12.5		8.4		
113 – 238%	12.5		6.9			12.6		18.3		
239%	14.1		18.7			15.7		24.0		
Large relative rise in serum hsCRP concentration (%) ³										
239%	14.1		18.7		0.39	15.7		24.0		0.090
239% ⁴	16.3		10.1		0.34	16.3		23.6		0.084

	Controls	IM	P-value ¹	Controls	Other infectious diseases ²	P-value ¹
N	255	55		220	90	
Any rise in serum hsCRP concentration (%) ³						
> 0.00 mg/L or %	55.5	69.0	0.084	56.0	66.8	0.086
> 0.0 mg/L or % ⁴	55.3	65.9	0.20	55.0	69.1	0.038

hsCRP=high-sensitivity C-reactive protein; IM=infectious mononucleosis

¹ P-values were calculated by linear regression with robust variance estimation for continuous variables, by linear regression for binary variables, and by logistic regression for categorical variables. All models were adjusted for race (African-American, non-African-American) and window of specimen collection to account for frequency-matching.

² Includes men with the following diagnoses: streptococcal sore throat (ICD-9-CM code=034.0), influenza (codes=487.1, 487.8), *Haemophilus influenzae* infection (code=041.5), intestinal infection due to specified or unspecified organisms (codes=008.43, 008.69, 008.8, 009.0), unspecified viral infection (code=079.99), other specified viral infection (code=079.89), unspecified infectious and parasitic diseases (code=136.9), fever not accompanied by another diagnosis (code=780.6), chicken pox (codes=052.9, 053.0), and leptospirosis icterohemorrhagica (code=100.0).

³ Values were calculated by linear regression with robust variance estimation for continuous variables, and by linear regression for binary and categorical variables. All models were adjusted for race and window of specimen collection to account for frequency-matching.

⁴ Additionally adjusted for age and time between pre- and index specimens.

Table 4

Change in serum high-sensitivity C-reactive protein concentration during or following infectious mononucleosis and other infectious diseases in young U.S. military members, stratified by time between diagnosis and index specimen collection, and infection type; 1995–2006

	N		Absolute change in serum hsCRP concentration (1.40 mg/L (%)) ¹		P-value ²		Relative change in serum hsCRP concentration (239 % (%)) ¹		P-value ²		Any rise in serum hsCRP concentration (>0.00 mg/L or % (%)) ¹		P-value ²	
	Controls	Cases	Controls	Cases	P-value ²		Controls	Cases	P-value ²		Controls	Cases	P-value ²	
Infectious mononucleosis														
<i>Time between diagnosis and index specimen collection:</i>														
< 4 months	255	19	13.8	19.5	0.52 ³		15.6	17.2	0.85 ³		54.5	77.5	0.06 ^{3,4}	
4 – 12 months	245	19	15.1	27.0	0.18 ³		16.5	15.5	0.91 ³		56.1	68.0	0.35 ^{3,4}	
12 months	150	17	11.9	0.0	0.044 ³		20.4	0.07	0.038 ³		61.8	57.6	0.75 ³	
					0.11 ⁵				0.21 ⁵				0.30 ⁵	
Other systemic or localized, non-genitourinary infections⁶														
<i>Time between diagnosis and index specimen collection:</i>														
< 4 months	83	33	16.6	21.3	0.95 ³		18.9	20.7	0.96 ³		59.2	71.8	0.20 ³	
4–12 months	136	57	12.7	14.9	0.56 ³		14.7	25.3	0.08 ³		52.4	67.8	0.05 ³	
					0.71 ⁵				0.26 ⁵				0.82 ⁵	
<i>Type of Infection:</i>														
Unspecified viral	115	48	15.0	20.8	0.33 ³		13.0	31.0	0.01 ³		58.1	74.4	0.01 ³	
Gastrointestinal tract	34	14	24.1	14.0	0.44 ³		26.9	15.7	0.34 ³		58.7	65.4	0.80 ³	
Respiratory tract	50	19	9.4	22.4	0.80 ³		21.9	17.8	0.53 ³		45.4	61.8	0.75 ³	
					0.51 ⁵				0.04 ⁵				0.48 ⁵	

hsCRP=high-sensitivity C-reactive protein

¹ All values were calculated by linear regression adjusting for race, window of specimen collection, age, and time between pre- and index specimens.

² P-values were calculated by linear regression adjusting for race, window of specimen collection, age, and time between pre- and index specimens for the infectious mononucleosis analysis; and by conditional logistic regression for the other infectious disease analysis.

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³ P-value for comparison between cases and controls.

⁴ Combining results for <4 months and 4–12 months, the percentages were 72.0% for cases and 54.0% for controls, $p=0.056$.

⁵ P-interaction.

⁶ Includes men with the following diagnoses: streptococcal sore throat (ICD-9-CM code=034.0), influenza (codes=487.1, 487.8), *Haemophilus influenzae* infection (code=041.5), intestinal infection due to specified or unspecified organisms (codes=008.43, 008.69, 008.8, 009.0), unspecified viral infection (code=079.99), other specified viral infection (code=079.89), unspecified infectious and parasitic diseases (code=136.9), fever not accompanied by another diagnosis (code=780.6), chicken pox (codes=052.9, 053.0), and leptospirosis icterohemorrhagica (code=100.0).

TABLE 5

Absolute and relative risks of a large rise in serum total prostate-specific antigen (PSA) concentration during or following infection in young U.S. military members without and with adjustment for high-sensitivity C-reactive protein concentration, 1995–2006¹

Absolute PSA rise 0.20 ng/mL						Relative PSA rise 40%				
	Chlamydia	Gonorrhea	NCNGU	IM	Other infectious diseases ²	Chlamydia	Gonorrhea	NCNGU	IM	Other infectious diseases ²
N (cases)	299	112	59	55	90	299	112	59	55	90
Without adjustment for high-sensitivity C-reactive protein concentration										
Absolute risk difference ³	26.9 (20.4–33.4)	11.7 (3.0–20.5)	1.9 (–9.1–13.0)	10.9 (1.2–20.5)	11.7 (1.8–21.5)	24.8 (18.3–31.2)	10.3 (1.6–19.0)	0.0 (–11.6–10.4)	16.3 (5.9–26.7)	9.7 (0.0–19.6)
Relative risk ⁴	4.3 (2.8–6.7)	2.5 (1.4–4.3)	1.2 (0.5–2.9)	2.2 (1.0–4.9)	1.8 (1.1–3.0)	3.8 (2.5–5.8)	2.2 (1.2–3.8)	0.9 (0.4–2.4)	2.8 (1.5–5.2)	1.5 (0.9–2.3)
With adjustment for high-sensitivity C-reactive protein concentration										
Absolute risk difference ³	26.9 (20.4–33.4)	11.4 (2.6–20.2)	1.8 (–9.3–12.7)	11.2 (1.6–20.8)	10.3 (1.1–19.6)	24.9 (18.3–31.4)	9.8 (1.0–18.6)	0.0 (–11.6–10.4)	17.1 (6.6–27.5)	8.1 (–1.7–17.9)
Relative risk ⁴	4.3 (2.8–6.6)	2.4 (1.4–4.2)	1.2 (0.5–2.9)	2.2 (1.0–4.8)	1.6 (1.0–2.8)	3.8 (2.5–5.8)	2.1 (1.2–3.7)	0.9 (0.4–2.4)	2.8 (1.5–5.3)	1.4 (0.9–2.2)

IM=infectious mononucleosis; NCNGU=non-chlamydial, non-gonococcal urethritis; PSA=prostate-specific antigen

¹ Further details and complete results for these infectious diseases are presented in references 1,2.

² Includes men with the following diagnoses: streptococcal sore throat (ICD-9-CM code=034.0), influenza (codes=487.1, 487.8), *Haemophilus influenzae* infection (code=041.5), intestinal infection due to unspecified or unspecified organisms (codes=008.43, 008.69, 008.8, 009.0), unspecified viral infection (code=079.99), other specified viral infection (code=079.89), unspecified infectious and parasitic diseases (code=136.9), fever not accompanied by another diagnosis (code=780.6), chicken pox (codes=052.9, 053.0), and leptospirosis icterohemorrhagica (code=100.0).

³ Calculated by linear regression adjusting for race for chlamydia, gonorrhea, and NCNGU; and for race, window of specimen collection, age, and time between pre- and index specimens and other infectious diseases.

⁴ Calculated by Poisson regression with robust variance estimation adjusting for race for chlamydia, gonorrhea, and NCNGU; and adjusting for race, window of specimen collection, age, and time between pre- and index specimens and other infectious diseases.

⁵ Sutcliffe S, Nevin RL, Pakpahan R, Elliott DJ, Langston ME, De Marzo AM *et al*. Prostate involvement during sexually transmitted infections as measured by prostate-specific antigen concentration. *Br J Cancer* 2011; **105**(5): 602–605.

⁶ Sutcliffe S, Nevin RL, Pakpahan R, Elliott DJ, Langston ME, De Marzo AM *et al*. Infectious mononucleosis, other infections, and prostate-specific antigen concentration as a marker of prostate involvement during infection. *Int J Cancer* 2015.