Published in final edited form as:

Prostate. 2018 September ; 78(13): 1024–1034. doi:10.1002/pros.23660.

SUSTAINED INFLUENCE OF INFECTIONS ON PROSTATE-SPECIFIC ANTIGEN CONCENTRATION: AN ANALYSIS OF CHANGES OVER 10 YEARS OF FOLLOW-UP

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Abstract

Background: To extend our previous observation of a short-term rise in prostate-specific antigen (PSA) concentration, a marker of prostate inflammation and cell damage, during and immediately following sexually transmitted and systemic infections, we examined the longer-term influence of these infections, both individually and cumulatively, on PSA over a mean of 10 years of follow-up in young active duty US servicemen.

Methods: We measured PSA in serum specimens collected in 1995–7 (baseline) and 2004–6 (follow-up) from 265 men diagnosed with chlamydia (CT), 72 with gonorrhea (GC), 37 with non-chlamydial, non-gonococcal urethritis (NCNGU), 58 with infectious mononucleosis (IM), 91 with other systemic or non-genitourinary infections such as varicella; and 125–258 men with no

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

infectious disease diagnoses in their medical record during follow-up (controls). We examined the influence of these infections on PSA change between baseline and follow-up.

Results: The proportion of men with any increase in PSA (>0 ng/mL) over the 10-year average follow-up was significantly higher in men with histories of sexually transmitted infections (CT, GC, and NCNGU; 67.7% versus 60.8%, $p=0.043$), systemic infections (66.7% versus 54.4%, $p=0.047$), or any infections (all cases combined; 68.5% versus 54.4%, $p=0.003$) in their military medical record compared to controls.

Conclusions: While PSA has been previously shown to rise during acute infection, these findings demonstrate that PSA remains elevated over a longer period. Additionally, the overall infection burden, rather than solely genitourinary-specific infection burden, contributed to these long-term changes, possibly implying a role for the cumulative burden of infections in prostate cancer risk.

Keywords

Sexually transmitted infection; infectious mononucleosis; prostate cancer; epidemiology

Introduction

Inflammation elicited by sexually transmitted infections (STIs) has long been considered to play a role in prostate cancer (PCa) development¹. Although symptomatic, STI-mediated prostate inflammation (i.e., acute and chronic bacterial prostatitis) is now rare and thus of possibly lesser relevance for PCa development, we have documented that asymptomatic, STI-mediated prostate inflammation still occurs, even in the current antibiotic era. Specifically, we observed that young infected men in two of our previous studies, one STI-clinic² and one US military-based³, were significantly more likely to have a large rise in their concentration of serum prostate-specific antigen (PSA), which we used as a marker of prostate inflammation and cell damage, at the time of their infection than controls. These findings suggest that as many as 25–30% of infected men had asymptomatic prostate infection^{2,3}. Interestingly, in the first of these studies, men's convalescent PSA concentrations remained elevated for at least several months after diagnosis and effective antibiotic therapy, raising the possibility of a longer-term influence of STIs on the prostate². These findings are consistent with those from cross-sectional studies of *Chlamydia trachomatis* (CT)⁴ and human herpesvirus type 8 serology^{5,6} that observed positive results with PSA, as well as those from longitudinal studies of men treated for febrile urinary tract infections (UTIs) that observed large PSA rises sustained over several months^{7,8}.

In addition to genitourinary infections, non-genitourinary and systemic infections have also been found to contribute to elevated serum PSA. In our previous study of young US military members, we found that serum PSA rose during episodes of adult-onset infectious mononucleosis (IM) and other systemic infections³, and remained higher than their baseline concentrations even after levels of high sensitivity C-reactive protein, a marker of systemic inflammation, fell⁹. Elevated PSA concentrations were also observed in a case report of a man with Chikungunya virus infection¹⁰. Together with findings for genitourinary tract infections, these results suggest that many types of infections may influence the prostate,

either directly through prostate infection or indirectly through possible mechanisms such as local genitourinary- or systemic inflammation-mediated cell damage, leading to chronic prostate inflammation. These findings also suggest that the influence of infections may be sustained over a period of at least a few months to one year¹¹.

To extend our previous findings and determine whether PSA changes are sustained over longer periods of time, we measured PSA concentration in specimens collected early in young US military men's careers and specimens collected an average of 10 years later from the same cases and controls as our previous US military-based study of infections and PSA^{3,11}. We used these concentrations to examine the influence of the individual and cumulative burden of STIs, IM, and other systemic infections on long-term PSA change. We focused on younger men because they are at higher risk of STIs and because they may be more susceptible to carcinogenic exposures¹², having completed prostate development and maturation more recently. PSA concentrations in young men in their thirties and forties have also been found to predict later PCa development^{13–16}, suggesting that our study may inform not only the long-term influence of infections on the prostate, but also their influence on PCa risk.

Materials and Methods

Study population and design

Department of Defense Serum Repository (DoDSR)—The DoDSR contains sera remaining from routine human immunodeficiency virus type 1 (HIV-1) antibody testing of all military personnel since 1990. Testing is performed before entering military service, during routine medical visits, for indication (i.e., during clinical work-up for STIs), before and after overseas assignments or deployment, and near the end of military service¹⁷. A standardized testing interval of at least every two years was implemented in 2004¹⁸. Sera collected from 1994 onwards can be linked to service members' medical information through their electronic medical record, which includes both reportable diagnoses (e.g., genital CT, gonorrhea (GC), and non-chlamydial, non-gonococcal urethritis (NCNGU)) and non-reportable diagnoses (e.g., UTIs)^{17,18}. The US military has stringent criteria for reporting CT, GC, and NCNGU, which includes laboratory confirmation of infection for CT and GC (e.g., culture or DNA/antigen detection), and the absence of laboratory evidence of these two organisms for NCNGU. Diagnoses are recorded using International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (see Supplementary Table 1 for corresponding ICD-10-CM codes). This study was performed with DoD collaboration, and was approved by the Walter Reed Army Institute of Research and Johns Hopkins Bloomberg School of Public Health Institutional Review Boards. All data and specimens were anonymized before release from the DoDSR.

Analytic study population—For all our DoDSR analyses, we required participants to be: 1) <25 years of age as of 1995; 2) on continuous active duty from 1995 (near the start of the electronic medical record) through 2006; and 3) HIV-1 negative throughout follow-up. We also required men to have at least four available serum specimens, one collected in each of the following time windows: 1st 1995–7, 2nd 1998–2000, 3rd 2001–3, and 4th 2004–6. We

used specimens collected in the 2nd and 3rd windows for our previous analysis of the short-term influence of infections on PSA^{3,11}, and specimens collected in the 1st and 4th windows for our current analysis (Figure 1). Availability of specimens in all four windows ensured that participants could be included in both analyses.

Exudative STI and IM cases and controls—Exudative STI cases were defined as men with at least one laboratory-confirmed diagnosis of genital CT (ICD-9-CM 099.41), GC (098), or NCNGU (099.40) during the 3rd time window. To allow us to investigate the independent influence of each STI on PSA change, we limited individual STI cases to those diagnosed with only one type of STI during the 10-year follow-up period (CT only: n=265; GC only: n=72; and NCNGU only: n=37). Cases diagnosed with other types of exudative STIs were included in the analysis of any exudative STIs combined (n=479 total cases), but not in the individual STI analyses. We defined IM cases as men with one inpatient or two outpatient diagnoses of IM (ICD-9-CM 075) within 30 days of each other in either the 2nd or 3rd time window. A longer time frame was selected for the IM analyses (2nd and 3rd windows versus the 3rd window only) to achieve a larger sample size. IM cases were also required to be free of STI diagnoses for the entire follow-up period to examine the independent influence of IM (n=58). Finally, we defined controls as men with no STI or IM diagnoses (i.e., without ICD-9-CM 075, 090–099.9, and 131 diagnoses) in their military medical record, except for persistent viral infections (ICD-9-CM 054.1–0.54.9, 070.3, 070.51, and 078.1–078.19), throughout the entire follow-up period (1st–4th time windows). Controls were frequency-matched to the combined exudative STI and IM case group by race.

Other infection cases and controls—Although our study was originally designed to examine the short- and longer-term influence of exudative STIs and adult-onset IM on PSA change, we expanded our analysis to include additional infections based on our short-term findings for IM¹¹. These *post-hoc* analyses were limited to men in the original control group to avoid the influence of exudative STIs and IM on our findings. Specifically, we re-classified controls into the following additional case groups: **1) non-exudative viral STIs** (hepatitis (ICD-9-CM 070.3, 070.51), genital herpes (054.1–054.9), and viral warts (078.1–078.19)); **2) other genitourinary infections or conditions** that might contribute to prostate inflammation (orchitis and epididymitis (604.9), urethritis (597.8), UTIs (599.0), hydrocele (603.9), balanoposthitis (607.1), inflammatory disorders of the penis (607.2), prostatitis (601.0–601.9), and Peyronies disease (607.85)); **3) non-genitourinary, systemic infections** (diagnoses with cutaneous lesions such as varicella (022.0, 052.0–053.9, 057.9, 074.0, 085.4); staphylococcus infection (041.1); meningitis and encephalitis (047.9, 062.0); gastrointestinal tract infections such as colitis (003, 005.9, 008.4–009.2, 124.0); respiratory tract infections such as whooping cough (022.1, 033–038.9, 041.2–041.9, 079.0, 114.0); and other systemic diagnoses such as unspecified viral diseases (022.9, 078.89, 079.89, 079.99, 084.1, 100.0, 780.6)). We did not create additional case groups for non-infectious, inflammatory conditions at sites outside of the genitourinary tract because these conditions were not included in our original approved DoDSR ICD-9-CM request. Finally, we combined all previously described case types (*a priori* specified exudative STI and IM cases, and *post-hoc* derived non-exudative STI, genitourinary infection/inflammatory condition,

and systemic infection cases) into a **further case group (any infection/inflammatory condition)** to investigate the influence of any infection or inflammatory genitourinary condition on PSA change, as well as the number of these infections/conditions. Controls for these *post-hoc* analyses were defined as men who did not meet the definition for any of the case groups (n=125). We did not report findings for the non-exudative STI and genitourinary case groups separately because the sample sizes for these groups were too small for statistical model convergence; therefore, their contribution was limited to the combined any infection/inflammatory condition analysis.

PSA testing

For each case and control, we measured serum total PSA concentration in two specimens: 1) the earliest specimen collected in the 1st window (“baseline specimen”), and 2) the latest specimen collected in the 4th window (“follow-up specimen”) to maximize follow-up. PSA was measured rather than abstracted from participants’ military medical records because participants were too young (ages 18–27 at baseline specimen collection) for PSA-based prostate cancer screening and thus did not have PSA measurements in their medical record. Instead, we measured PSA at the Johns Hopkins Medical Hospital using the Access Hybritech PSA assay (Beckman Coulter). Concentrations below 0.01ng/mL, the lower limit of detection for the Hybritech assay were imputed to 0.01 ng/mL (n=8). PSA assay reproducibility was tested by including 25 blinded quality control pairs from the DoDSR in the testing sequence (coefficient of variation=12.4% and 6.9% after excluding one discrepant pair).

Statistical analysis

We followed the same analysis plan for each case type of interest. We first explored the influence of case diagnoses on long-term PSA change by calculating arithmetic and geometric mean baseline and follow-up PSA concentrations for cases and controls. We compared these values by linear regression with robust variance estimation to take repeated measures from the same participant into account (i.e., baseline and follow-up specimens). All models included adjustment for race to account for frequency matching. We also assessed any long-term shifts in the distribution of PSA change between the baseline and follow-up specimens for cases and controls by calculating proportions of race-adjusted categories of absolute and relative PSA change by linear regression, and then by comparing these distributions by logistic regression. Absolute PSA change was defined by 0.10 ng/mL categories ranging from 0.00 ng/mL–0.50 ng/mL, and relative percent change categories were defined by 20% increases in PSA ranging from 0% to 100%. Although large relative rises in PSA (40%) similar to those observed in our studies of the short-term influence of acute infections on PSA were not expected in this longer-term analysis, we explored large rises (40% increase in PSA from the baseline to follow-up specimens) in this analysis as well. Finally, we compared the percentage of cases and controls whose PSA rose to any degree (>0 ng/mL) between their baseline and follow-up specimens, also using linear and logistic regression.

We investigated potential confounding by entering covariates individually into the regression models and examining their influence on the difference in the change in PSA concentration

between cases and controls. Potential confounders included: age, marital status, military grade (officer vs. enlisted), baseline PSA concentration, calendar year of the baseline specimen, and time between the baseline and follow-up specimens. Inclusion of these potential confounders did not influence the results compared to the race-adjusted model; therefore they were excluded from the final models.

To examine the possible influence of additional diagnosed or undiagnosed STIs on our results, we performed several sensitivity analyses. We excluded: (1) higher rank officers, who may have had greater access to non-military health care, and thus possibly less complete military medical records; (2) men with clinical or other suspicion of HIV/STIs as their reason for blood draw for either their baseline or follow-up specimen; (3) men with small breaks (<60) days in their active duty status between specimens; (4) those deployed to a combat site (Afghanistan or Iraq) between specimens, as their medical record may have been less complete in war zones; and (5) men with any infectious disease/genitourinary diagnoses in their medical record in the: (a) 30 days, and (b) one year before their baseline or follow-up specimen collection. This last sensitivity analysis was performed to remove the possible transient influence of infections on PSA concentration. All sensitivity analyses yielded similar results as the main analysis.

Results

In our sample of active duty US military men, exudative STI cases (CT, GC, and NCNGU) were slightly younger and less likely to be married at the time of their baseline specimen collection than controls. They were also more likely to be enlisted, to have served in an active combat country (Afghanistan or Iraq) during follow-up, to have had their baseline specimen collected later in follow-up (1996–7) and to have a greater number of blood draws for HIV-1 testing during follow-up (Table 1). Although all exudative STI and IM cases were frequency-matched to controls by race as a group, distributions of individual STI types varied by race (i.e., GC cases were more likely to be African-American and IM cases were more likely to be White than controls). Baseline PSA concentrations ranged from <0.01 to 9.12 ng/mL, with median concentrations ranging from 0.46 to 0.59 ng/mL. Similar PSA concentrations were observed across all study groups (cases and controls) at baseline (Figure 2).

Exudative STIs

CT and NCNGU cases had a slightly greater increase in PSA over time than controls, as evidenced by greater mean and geometric mean changes in PSA, and greater proportions of those with large relative rises (>40%) and rises of any magnitude in PSA; however, none of these differences was statistically significant (Table 2). No differences were observed between GC cases and controls. When all exudative STI case groups were combined, similar findings were observed as in the individual CT and NCNGU analyses, except that the difference for a rise in PSA of any magnitude was significant with the larger combined sample size (67.7% vs. 60.8%, $p=0.043$).

We also investigated whether the number of exudative STI episodes influenced long-term PSA change (Supplementary Table 2), and found that the proportion of men with rises of

any magnitude in PSA increased as the number of STI episodes increased ($p_{\text{trend}}=0.014$). Null findings were observed when the number of exudative STIs was examined separately by type (e.g. multiple episodes of CT only, data not shown), although small sample sizes limited interpretation of these results.

IM and other systemic infections

IM and other systemic infection cases had a slightly greater increase in PSA over time than controls (Table 3). This change was evident both by non-significantly greater mean and geometric mean changes in PSA, as well as by a greater likelihood of a rise in PSA of any magnitude during follow-up (IM: 70.6% vs. 60.8%, $p=0.062$; other systemic infections: 66.7% vs. 54.4 %, $p=0.047$). Other systemic infection cases were also non-significantly more likely to have a large relative rise in PSA during follow-up than controls (32.4% vs. 23.0% $p=0.062$).

Any infection

Finally, we estimated the influence of the cumulative burden of infections on PSA (Table 4). This analysis included men with a history of exudative STIs, who formed the largest part of the case group, as well as smaller numbers of men with non-exudative STIs, IM, genitourinary infections and inflammatory conditions, and systemic infections. Overall, men with any of these infections had significant positive shifts in their absolute ($p=0.010$) and relative ($p=0.0004$) distributions of serum PSA from baseline to follow-up compared to controls. Also, they were non-significantly more likely to have a large relative increase in PSA (30.9% vs. 23.0% $p=0.070$) and an increase of any magnitude (68.5% vs. 54.4%, $p=0.003$). This percentage rose with increasing number of infections up to 74.2% for 3–4 infections, compared to 65.4% for 1 infection and 54.4% for controls ($P_{\text{trend}}=0.002$).

Discussion

In this large, longitudinal study of infections and PSA, we found that young, US military men with histories of any exudative STIs (CT, GC, and NCNGU), non-genitourinary systemic infections, and any infections in their military medical record were significantly more likely to have an increase in PSA of any amount over an average of 10 years of follow-up than controls. The magnitude of this percentage was generally similar across infections/infection groups (67–76%), as well as across the individual infections that made up these groups (i.e., CT, NCNGU, and young-onset IM), with statistical significance largely determined by sample size. Together, these findings suggest that overall infection burden (local or systemic), rather than solely genitourinary-specific infection or inflammatory burden, may have a long-lasting impact on the prostate, as evidenced by sustained and heightened PSA concentrations.

Our findings of long-term elevated PSA concentrations are generally in agreement with those from studies that examined PSA during acute infection. Specifically, although our findings differ from previous observations of a large rise in PSA during GC, but not NCNGU, in the same US military population as our present analysis³, they are similar to our previous observation of a large PSA rise during CT in the US military³, as well as to

observations of large PSA rises/high PSA concentrations during exudative STIs², febrile UTIs^{19,20}, and Chikungunya virus infection (one case report¹⁰). Our findings are also in agreement with several studies that observed sustained PSA concentrations over a period of three months to one year following infection in young and older men (e.g., exudative STIs², febrile UTIs^{19,20}, young-onset IM¹¹, and systemic, non-genitourinary infections¹¹), and with several, but not all^{21,22}, cross-sectional analyses that observed higher PSA concentrations in men seropositive for curable (CT⁴) and lifelong STIs (human herpesvirus infection type 8^{5,6}). Finally, although we saw less compelling evidence for large PSA rises in the present analysis than in previous studies of acute and recently-resolved infections, we still observed that PSA remained elevated in the long-term, demonstrating that PSA levels may not return completely to baseline values even many years after infection.

Despite the general consistency of higher PSA findings across studies of men with current and resolved infections, the mechanisms underlying these findings are not well understood. For acute genitourinary tract infections, such as STIs, we suspect that elevated PSA likely represents prostate infection and resulting inflammation and epithelial cell damage, or urethral inflammation with local, genitourinary tract inflammation and prostate epithelial cell damage. We previously hypothesized that PSA elevation may be more evident for some STIs than others (e.g., CT more than GC) because CT presents more often as an asymptomatic infection than GC²³, and thus may persist undiagnosed and untreated for a period of longer time, allowing for sustained damage to the prostate epithelium. This mechanism might also apply to sexually transmissible infections that have been detected in prostate tissue but have other dominant non-sexual modes of transmission (e.g., Epstein-Barr virus infection). In contrast to the above-described direct prostate-specific mechanism for PSA elevation, mechanisms for non-genitourinary, systemic infections, such as varicella, are likely less direct. We previously proposed that these infections may contribute to elevated PSA by several possible mechanisms, including systemic inflammation-mediated prostate cell damage and increased vascular permeability, or increased vascular permeability in the context of preexisting prostate epithelial cell damage/disruption from other sources¹¹. In addition, once infection has resolved, PSA could possibly remain elevated for months to years later for a number of reasons, including chronic inflammation against residual infectious antigens, continued healing, delayed or impaired ability to counteract future prostate insults, or broken tolerance to self-prostatic antigens², all of which could possibly amplify with repeated infections over time.

Irrespective of the mechanism by which infections raise PSA, a key question that remains to be addressed is the meaning of this elevation for prostate cancer risk. Although we did not observe many PSA values above recommended biopsy thresholds (2.5 or 4.0 ng/mL²⁴), we did still observe that infections were associated with a greater likelihood of an increase in PSA over the ten year period from men's twenties to thirties. This small increase may be important because higher than average PSA concentrations in young to mid-adulthood have been found to predict future prostate cancer risk and aggressiveness^{13–16}. For instance, in two previous studies of young men ages 40 to 49, those with PSA concentrations above the median (~0.6–0.7 ng/mL) had a 4–7 fold increase in future prostate cancer risk compared to those below the median^{16,25}. For comparison in our study, 15.5% of systemic infection cases had PSA concentrations higher than 0.7 ng/mL at the end of follow-up compared to 9.3% of

controls. Therefore, it is conceivable that this small difference in PSA could translate into a large difference in prostate cancer detection or risk, consistent with the hypothesis that persistent or repeated prostate epithelial cell damage and regeneration (the “injury and regeneration” hypothesis) increases the risk of cellular transformation and prostate carcinogenesis²⁶. As a further more troubling possibility, it is also conceivable that infections could contribute to an increase in the trajectory of PSA (i.e., a higher slope or rate of change), particularly if these insults occur during adolescence and young adulthood when the prostate is still growing and developing, and thus may be more susceptible to carcinogenic exposures¹². This type of increase might lead men to reach higher PSA concentrations than they would otherwise reach without infections, or to reach these concentrations at younger ages.

To our knowledge, this study is the first to prospectively examine the influence of infections on long-term PSA change, as previous studies have looked either only cross-sectionally^{4,21,27} or directly following an acute infection^{2,3}. *A priori*, we recognized the potential of the following to impact our results: 1) undiagnosed infections among asymptomatic men (which may have been more pronounced in the case groups as one risk factor for future infection is past infection); 2) minor infections that did not warrant medical care and were thus not captured in the medical record (e.g., rhinovirus infections that cause the common cold); 3) undocumented infections among those seeking care outside the military or in a war zone; and 4) acute infections near the time of blood draw. However, we do not believe these impacted our results because our estimates were unchanged after excluding men with greater access to non-military care (military officers or those deployed to active combat countries), those with a suspected STI as their reason for blood draw, and those with any diagnoses up to one year before blood draw. Furthermore, if these factors had been present, they would likely only have attenuated our findings. As an additional possible limitation, we restricted case selection for exudative STIs and IM to the 3rd time window as previously mentioned to allow for our investigations of both the acute^{3,11} and long-term effects of infection. Therefore, men with exudative STI and IM diagnoses exclusively outside of the 3rd window did not meet our study inclusion criteria. If we relaxed this restriction, we would likely have seen similar results, as the effects of infection closer to baseline or follow-up blood draws would have been balanced throughout the study term. Finally, under optimal circumstances, we would have defined systemic infections in a more expansive manner for our *post-hoc* analyses, but were limited by the STI focus and design of our primary analysis. However, even with this narrower focus, our interesting findings for systemic infections provide the rationale to explore the impact of these infections further on prostate cancer risk.

Conclusions

In summary, we found that young men with histories of both genitourinary (CT, GC, and NCNGU) and non-genitourinary infections were more likely to have an increase in PSA of any magnitude over an average of 10 years of follow-up than controls. These findings raise the possibility that overall infection burden, rather than solely genitourinary-specific infection burden, may contribute to prostate cancer risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

We thank Dr. Angelia A. Eick-Cost and Zheng Hu at the Armed Forces Health Surveillance Center for help with participant selection, and Dr. Catherine G. Sutcliffe for help preparing serum specimens for testing and coordinating PSA testing.

Effort for the authors was funded by the Fund for Research and Progress in Urology, Johns Hopkins University School of Medicine (SS), the Barnes-Jewish Hospital Foundation and Alvin J. Siteman Cancer Center (MEL, RP, SS), and the National Cancer Institute of the National Institutes of Health under award numbers T32CA190194 (MEL) and P30CA006973 (AMD, WBI, WGN, EAP). This work was funded by the Patrick C. Walsh Prostate Cancer Research Fund.

The content of this work is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Citations

1. Caini S, Gandini S, Dudas M, Bremer V, Severi E, Gherasim A. Sexually transmitted infections and prostate cancer risk: a systematic review and meta-analysis. *Cancer Epidemiol.* 2014;38(4):329–338. [PubMed: 24986642]
2. Sutcliffe S, Zenilman JM, Ghanem KG, et al. Sexually transmitted infections and prostatic inflammation/cell damage as measured by serum prostate specific antigen concentration. *J Urol.* 2006;175(5):1937–1942. [PubMed: 16600802]
3. Sutcliffe S, Nevin RL, Pakpahan R, et al. Prostate involvement during sexually transmitted infections as measured by prostate-specific antigen concentration. *British journal of cancer.* 2011;105(5):602–605. [PubMed: 21792196]
4. Oliver JC, Oliver RT, Ballard RC. Influence of circumcision and sexual behaviour on PSA levels in patients attending a sexually transmitted disease (STD) clinic. *Prostate Cancer Prostatic Dis.* 2001;4(4):228–231. [PubMed: 12497023]
5. McDonald AC, Jenkins FJ, Bunker CH, Wilson JW, Patrick AL, Weissfeld JL. A case-cohort study of human herpesvirus 8 seropositivity and incident prostate cancer in Tobago. *Infect Agent Cancer.* 2011;6(1):25. [PubMed: 22151996]
6. Sutcliffe S, Till C, Jenkins FJ, et al. Prospective study of human herpesvirus type 8 serostatus and prostate cancer risk in the placebo arm of the Prostate Cancer Prevention Trial. *Cancer Causes Control.* 2015;26(1):35–44. [PubMed: 25359302]
7. Ulleryd P, Zackrisson B, Aus G, Bergdahl S, Hugosson J, Sandberg T. Prostatic involvement in men with febrile urinary tract infection as measured by serum prostate-specific antigen and transrectal ultrasonography. *BJU Int.* 1999;84(4):470–474. [PubMed: 10468764]
8. Zackrisson B, Ulleryd P, Aus G, Lilja H, Sandberg T, Hugosson J. Evolution of free, complexed, and total serum prostate-specific antigen and their ratios during 1 year of follow-up of men with febrile urinary tract infection. *Urology.* 2003;62(2):278–281. [PubMed: 12893335]
9. Milbrandt M, Winter AC, Nevin RL, et al. Insight into infection-mediated prostate damage: Contrasting patterns of C-reactive protein and prostate-specific antigen levels during infection. *Prostate.* 2017.
10. Aiken WD, Anzinger JJ. Chikungunya Virus Infection and Acute Elevation of Serum Prostate-Specific Antigen. *Case Rep Urol* 2015;2015:120535. [PubMed: 26167328]
11. Sutcliffe S, Nevin RL, Pakpahan R, et al. Infectious mononucleosis, other infections and prostate-specific antigen concentration as a marker of prostate involvement during infection. *Int J Cancer.* 2016.
12. Sutcliffe S, Colditz GA. Prostate cancer: is it time to expand the research focus to early-life exposures? *Nat Rev Cancer.* 2013;13(3):208–518. [PubMed: 23363989]

13. Kuller LH, Thomas A, Grandits G, Neaton JD, Multiple Risk Factor Intervention Trial Research G. Elevated prostate-specific antigen levels up to 25 years prior to death from prostate cancer. *Cancer Epidemiol Biomarkers Prev.* 2004;13(3):373–377. [PubMed: 15006911]
14. Lilja H, Cronin AM, Dahlin A, et al. Prediction of significant prostate cancer diagnosed 20 to 30 years later with a single measure of prostate-specific antigen at or before age 50. *Cancer.* 2011;117(6):1210–1219. [PubMed: 20960520]
15. Whittemore AS, Cirillo PM, Feldman D, Cohn BA. Prostate specific antigen levels in young adulthood predict prostate cancer risk: results from a cohort of Black and White Americans. *J Urol.* 2005;174(3):872–876; discussion 876. [PubMed: 16093978]
16. Preston MA, Batista JL, Wilson KM, et al. Baseline Prostate-Specific Antigen Levels in Midlife Predict Lethal Prostate Cancer. *J Clin Oncol.* 2016;34(23):2705–2711. [PubMed: 27298404]
17. Rubertone MV, Brundage JF. The Defense Medical Surveillance System and the Department of Defense serum repository: glimpses of the future of public health surveillance. *Am J Public Health.* 2002;92(12):1900–1904. [PubMed: 12453804]
18. Armed Forces Health Surveillance Center. Updates: Routine screening for antibodies to human immunodeficiency virus, type 1 (HIV-1), civilian applicants for US military service and US Armed Forces, active and reserve components. *MSMR.* 2012;19(8):7.
19. Zackrisson B, Ulleryd P, Aus G, Lilja H, Sandberg T, Hugosson J. Evolution of free, complexed, and total serum prostate-specific antigen and their ratios during 1 year of follow-up of men with febrile urinary tract infection. *Urology.* 2003;62(2):278–281. [PubMed: 12893335]
20. Ulleryd P, Zackrisson B, Aus G, Bergdahl S, Hugosson J, Sandberg T. Prostatic involvement in men with febrile urinary tract infection as measured by serum prostate-specific antigen and transrectal ultrasonography. *BJU Int.* 1999;84:470–474. [PubMed: 10468764]
21. Werny DM, Saraiya M, Chen X, Platz EA. Prostate-specific antigen, sexual behavior, and sexually transmitted infections in US men 40–59 years old, 2001–2004: a cross-sectional study. *Infect Agent Cancer.* 2007;2(1):1. [PubMed: 17201927]
22. Marous M, Huang W-Y, Rabkin CS, et al. *Trichomonas vaginalis* infection and risk of prostate cancer: associations by disease aggressiveness and race/ethnicity in the PLCO Trial. *Cancer Causes & Control.* 2017;28(8):889–898. [PubMed: 28669054]
23. Zimmerman HL, Potterat JJ, Dukes RL, et al. Epidemiologic differences between chlamydia and gonorrhea. *Am J Public Health.* 1990;80(11):1338–1342. [PubMed: 2240301]
24. Smith RA, Andrews KS, Brooks D, et al. Cancer screening in the United States, 2017: A review of current American Cancer Society guidelines and current issues in cancer screening. *CA Cancer J Clin.* 2017;67(2):100–121. [PubMed: 28170086]
25. Fang J, Metter EJ, Landis P, Chan DW, Morrell CH, Carter HB. Low levels of prostate-specific antigen predict long-term risk of prostate cancer: results from the Baltimore Longitudinal Study of Aging. *Urology.* 2001;58(3):411–416. [PubMed: 11549490]
26. De Marzo AM, Platz EA, Sutcliffe S, et al. Inflammation in prostate carcinogenesis. *Nature Reviews Cancer.* 2007;7(4):256–269. [PubMed: 17384581]
27. Barykova YA, Logunov DY, Shmarov MM, et al. Association of *Mycoplasma hominis* infection with prostate cancer. *Oncotarget.* 2011;2(4):289–297. [PubMed: 21471611]

Figure 1.

All participants were required to have at least four serum specimens, one collected in each of the following time windows: 1st 1995–7, 2nd 1998–2000, 3rd 2001–3, and 4th 2004–6. Exudative sexually transmitted infection (STI) cases were defined as men with at least one laboratory-confirmed diagnosis of genital chlamydia, gonorrhea, or non-chlamydial, non-gonococcal urethritis during the 3rd time window. Infectious mononucleosis (IM) cases were defined as men with a diagnosis of IM in either the 2nd or 3rd time window to achieve a larger sample size for this less common diagnosis. Controls were required to be free of STI and IM diagnoses in all four time windows. Specimens collected in the 2nd and 3rd time windows were used to examine the acute influence of infections on PSA^{3,11}, whereas specimens collected in the 1st and 4th time windows were used to examine the longer-term influence of infections on PSA in the current analysis. Additional *post-hoc* case groups were also created to examine the longer-term influence of other infections (e.g., systemic infections) occurring in any of the four time windows on PSA. This figure is not drawn to scale on the y-axis and PSA concentration is solely depicted as a visual representation of study sampling methodology.

Figure 2.

For each box plot, the lowest line represents the smallest value; the lower end of the box represents the 25th percentile (P25); the line within the box represents the median (P50); the (X) represents the mean; the upper end of the box represents the 75th percentile (P75); the upper line at the top of the whisker represents the largest value below the upper fence (the sum of the 75th percentile and 1.5 times the interquartile range (the difference between the 25th and 75th percentile)); the circles represent values between the upper fence and the far upper fence (the sum of the 75th percentile and 3 times the interquartile range); and the asterisks represent values greater than the far upper fence. One observed outlier (9.12 ng/mL in the original control group, also classified in the systemic infection and any infection groups in post-hoc analyses) above the far upper fence was removed from the figure for scaling purposes.

Table 1.

Demographic and military characteristics of young adult male infectious disease cases and controls at baseline blood specimen collection, US military 1995–2006^{1,2}

	Controls (n=258)	Chlamydia (n=265)	Gonorrhea (n=72)	NCNGU (n=37)	Cases		
					IM (n=58)	Systemic Infections (n=91) ³	Any Infection (n=636) ³
<i>Mean age (Years)</i>	23.4	23.0 *	23.0 *	22.9	23.3	23.1	23.1 *
<i>Race/ethnicity (%)⁴</i>							
African-American	54.3	49.8	76.4 *	46.0	13.8 *	56.0	55.7
White	36.8	39.3	18.1 *	48.7	81.0 *	36.3	35.9
Other	8.9	10.9	5.6 *	5.4	5.2 *	7.7	8.5
<i>Marital Status (%)</i>							
Married	81.7	66.9 *	74.2	73.2	79.7	85.3	71.8 *
Other	18.3	33.1 *	25.8	26.8	20.3	14.7	28.2
<i>Military Grade (%)</i>							
Enlisted	95.1	98.4 *	96.7	99.6	97.6	94.7	97.4
Officer	4.9	1.6 *	3.3	0.4	2.4	5.3	2.6
<i>Type of deployment during follow-up (%)</i>							
Active Combat Country	23.0	34.7 *	33.8 *	46.0 *	15.0	21.1	31.7 *
Non-Combat Country	77.0	65.3 *	62.2 *	54.0 *	85.0	78.9	68.3
<i>Year of baseline specimen collection (%)</i>							
1994	0.2	1.4 *	1.0	0.0	0.0	0.0	0.9
1995	55.0	41.4 *	46.5	48.8	56.8	60.0	48.6
1996	31.2	41.6 *	41.8	40.3	25.8	25.7	35.8
1997	13.6	15.7 *	10.7	11.0	17.2	14.4	14.7
<i>Mean time between the baseline and follow-up specimen collection (years)</i>	10.3	10.2	10.2	10.4	10.2	10.3	10.3
<i>Mean number of blood draws for HIV-1 testing from 1 January 1995 to 31 December 2006</i>	9.9	11.7 *	12.1 *	12.0 *	10.0	9.9	11.4 *

Abbreviations: HIV-1=human immunodeficiency virus type 1; IM=infectious mononucleosis; NCNGU=non-chlamydial, non-gonococcal urethritis.

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*
p<0.05.

¹ Values for cases and controls were calculated by linear regression adjusting for race (African-American and non-African-American), except for values for the race variable. All p-values refer to comparison of the respective case group to controls and were calculated by linear regression for continuous or binary variables and by logistic regression for categorical variables, and included adjustment for race. P-values for race were calculated by the chi-square test.

² Case types are mutually exclusive with the exception of the any infection case group.

³ Controls for this analysis had no history of infection during follow-up (N=125).

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

Table 2.

Long-term change in serum total PSA concentration following laboratory-confirmed exudative STIs in young adult male US military members, 1995–2006

	Controls (n=258)	Chlamydia (n=265)	Gonorrhea (n=72)	NCNGU (n=37)	Any Exudative STI (n=479) ¹	P-value ³
Change in serum total PSA from baseline to follow-up (ng/mL) ²	0.074	0.112	0.089	0.165	0.139	0.100
Geometric Mean Difference	0.042	0.106	0.066	0.087	0.109	0.127
Distribution of absolute change in serum total PSA (%) ²						
0.00 ng/mL	39.2	32.7	39.3	24.3	32.3	0.270
0.01–0.09 ng/mL	16.7	18.8	18.9	19.1	19.4	
0.10–0.19 ng/mL	18.3	17.4	22.9	22.2	18.6	
0.20–0.29 ng/mL	9.8	11.8	9.2	21.3	12.2	
0.30–0.39 ng/mL	5.6	5.8	0.8	5.4	4.4	
0.40–0.49 ng/mL	2.3	4.1	2.9	5.6	4.1	
0.50 ng/mL	8.1	9.4	6.0	2.2	9.1	
Distribution of relative percent change in serum total PSA (%) ²						
0%	39.6	33.1	39.1	24.2	32.5	0.204
0.1–19.9%	16.7	18.9	22.8	22.0	19.8	
20–39.9%	17.3	14.5	19.2	18.8	16.4	
40–59.9%	8.0	10.1	5.8	10.7	9.0	
60–79.9%	5.5	9.7	4.4	11.4	8.9	
80–100%	4.7	3.1	7.6	2.8	3.2	
>100%	8.2	10.6	1.1	10.1	10.1	
Large relative rise (40%) in serum total PSA (%) ²	26.5	33.9	18.9	35.0	31.5	0.138
Change >0 ng/mL (%) ²	60.8	67.3	60.7	75.7	67.7	0.043

Abbreviations: PSA, prostate-specific antigen; NCNGU, non-chlamydial, non-gonococcal urethritis; STI, sexually transmitted infection.

¹Includes any history of laboratory-confirmed chlamydia, gonorrhea, or non-chlamydial, non-gonococcal urethritis.

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Values were estimated 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 (African-American, non-African American) to account for frequency matching.

P-values were calculated by linear regression with robust variance estimation for continuous variables and by logistic regression for categorical variables. All models were adjusted for race to account for frequency matching.

Long-term change in serum total PSA concentration following IM and systemic infections in young adult male US military members, 1995–2006

Table 3.

	Controls ¹ (n=258)	IM (n=58)	Controls ¹ (n=125)	Systemic Infections ² (n=91)
Change in serum total PSA from baseline to follow-up (ng/mL) ³				
			P-value ⁴	P-value ⁴
Geometric Mean Difference	0.058	0.153	0.153	0.100
Mean Difference	0.038	0.135	0.189	0.021
Distribution of absolute change in serum total PSA (%) ³				
0.00 ng/mL	39.2	29.4	0.258	33.3
0.01–0.09 ng/mL	16.7	24.6		21.5
0.10–0.19 ng/mL	18.3	15.0		20.6
0.20–0.29 ng/mL	9.8	7.2		8.8
0.30–0.39 ng/mL	5.6	5.3		4.1
0.40–0.49 ng/mL	2.3	5.1		3.4
0.50 ng/mL	8.1	11.7		8.4
Distribution of relative percent change in serum total PSA (%) ³				
0%	39.6	29.5	0.070	33.1
0.1–19.9%	16.7	27.8		21.6
20–39.9%	17.3	14.1		12.9
40–59.9%	8.0	7.2		13.0
60–79.9%	5.5	7.3		5.3
80–100%	4.7	1.2		3.7
>100%	8.2	12.8		10.5
Large relative rise (40%) in serum total PSA (%) ³	26.5	28.5	0.415	32.4
Change >0 ng/mL (%) ³	60.8	70.6	0.062	66.7

Abbreviations: PSA, prostate-specific antigen; IM, infectious mononucleosis.

¹ Controls with no history of systemic infections or any infection during follow-up.

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²Includes men with the following diagnoses during follow-up: diagnoses with cutaneous lesions (ICD-9-CM code=022.0, 052.0–053.9, 057.9, 074.0, 085.4); staphylococcus infection (041.1); meningitis and encephalitis (047.9, 062.0); gastro-intestinal tract infections (003, 005.9, 008.4–009.2, 124.0); respiratory tract infections (022.1, 033–038.9, 041.2–041.9, 079.0, 114.0); and other systemic infections (022.9, 078.89, 079.89, 079.99, 084.1, 100.0, 780.6).

³Values were estimated 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 (African-American, non-African American) to account for frequency matching.

⁴P-values were calculated by linear regression with robust variance estimation for continuous variables and by logistic regression for categorical variables. All models were adjusted for race to account for frequency matching.

Long-term change in serum total PSA concentration following infections in young adult male US military members, 1995–2006

Table 4.

	Controls (n=125)	Any Infection ¹ (n=636)	1 Infection ¹ (n=153)	2 Infections ¹ (n=162)	3–4 Infections ¹ (n=176)	5+ Infections ¹ (n=145)	P _{trend}
Change in serum total PSA from baseline to follow-up (ng/mL) ²							
Geometric Mean Difference	0.059	0.105	0.067	0.184	0.073	0.517	0.210
Mean Difference	0.038	0.098	0.317	0.107	0.297	0.064	0.166
Distribution of absolute change in serum total PSA (%) ²							
0.00 ng/mL	45.6	31.5	0.010	34.6	0.274	35.7	0.075
0.01–0.09 ng/mL	11.3	20.7	21.2	19.0	22.3	21.3	0.042
0.10–0.19 ng/mL	15.4	18.7	13.5	23.1	21.8	18.5	
0.20–0.29 ng/mL	10.5	11.1	11.7	9.9	10.0	11.1	
0.30–0.39 ng/mL	7.2	4.6	7.8	2.5	2.5	4.7	
0.40–0.49 ng/mL	1.0	4.0	2.7	2.8	5.5	5.1	
0.50 ng/mL	8.9	9.1	8.6	6.1	12.1	7.8	
Distribution of relative percent change in serum total PSA (%) ²							
0%	46.5	31.7	0.0004	34.5	0.037	35.5	0.043
0.1–19.9%	10.6	21.6	20.0	25.3	19.8	22.8	0.0003
20–39.9%	20.0	16.1	17.4	13.9	17.7	14.3	
40–59.9%	3.8	9.6	7.7	6.7	10.5	13.7	
60–79.9%	5.6	8.1	7.6	7.1	10.4	6.8	
80–100%	6.3	2.8	2.1	4.1	2.9	2.1	
>100%	7.2	10.2	10.7	7.3	13.0	7.9	
Large relative rise (40%) in serum total PSA (%) ²	23.0	30.9	0.070	28.1	0.275	25.2	0.827
Change >0 ng/mL (%)	54.4	68.5	0.003	65.4	0.076	64.3	0.097
							0.0004
							0.010
							0.002

Abbreviations: PSA, prostate-specific antigen;

¹Includes men with the following diagnoses during follow-up: 1) confirmed exudative STIs; 2) non-exudative viral STIs (ICD-9-CM code-hepatitis (070.3, 070.51), herpes (054.1–054.9), and viral warts (078.1–078.19)); 3) other genitourinary infections or conditions that might contribute to prostate inflammation (orchitis and epididymitis (604.9), urethritis (597.8), urinary tract infection (599.0), hydrocele (603.9), balanoposthitis (607.1), inflammatory disorders of the penis (607.2), prostatitis (601.0–601.9), and Peyronies disease (607.85); and 4) non-genitourinary, systemic infections (diagnoses with

cutaneous lesions (022.0, 052.0–053.9, 057.9, 074.0, 085.4); staphylococcus infection (041.1); meningitis and encephalitis (047.9, 062.0); gastro-intestinal tract infections (003, 005.9, 008.4–009.2, 124.0); respiratory tract infections (022.1, 033–038.9, 041.2–041.9, 079.0, 114.0); and other systemic infections (022.9, 078.89, 079.89, 079.99, 084.1, 100.0, 780.6).

² Values were estimated 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 (African-American, non-African American) to account for frequency matching.

³ P-values were calculated by linear regression with robust variance estimation for continuous variables and by logistic regression for categorical variables. All models were adjusted for race to account for frequency matching.