Infectious mononucleosis, other infections and prostate-specific antigen concentration as a marker of prostate involvement during infection

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INFECTIONOUS MONONUCLEOSIS, OTHER INFECTIONS, AND PROSTATE-SPECIFIC ANTIGEN CONCENTRATION AS A MARKER OF PROSTATE INVOLVEMENT DURING INFECTION

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Short title: Infections and prostate-specific antigen

Key words: Infectious mononucleosis, infection, prostate-specific antigen, prostate cancer, epidemiology

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Abbreviations:

DoDSR=Department of Defense Serum Repository
EBV=Epstein-Barr virus
HIV=human immunodeficiency virus
ICD-9-CM=International Classification of Diseases, Ninth Revision, Clinical Modification
IM=infectious mononucleosis
NCNGU = non-chlamydial, non-gonococcal urethritis
PSA=prostate-specific antigen
STI=sexually transmitted infection

**Article category:** Infectious causes of cancer or epidemiology
NOVELTY AND IMPACT

Our study is the first, to our knowledge, to examine the influence of young-adult onset infectious mononucleosis (IM) and other systemic, inflammatory infectious diseases on prostate-specific antigen (PSA) levels. Our findings of a rise in PSA during or following IM and other systemic infectious diseases in young U.S. military members may have implications for PSA interpretation in middle- and older-aged men, among whom PSA is used as a screening test for prostate cancer.
ABSTRACT

Although Epstein-Barr virus has been detected in prostate tissue, no associations have been observed with prostate cancer in the few studies conducted to date. One possible reason for these null findings may be use of cumulative exposure measures that do not inform the timing of infection, i.e., childhood versus adolescence/early-adulthood when infection is more likely to manifest as infectious mononucleosis (IM). We sought to determine the influence of young adult-onset IM on the prostate by measuring prostate-specific antigen (PSA) as a marker of prostate inflammation/damage among U.S. military members. We defined IM cases as men diagnosed with IM from 1998-2003 (n=55) and controls as men without an IM diagnosis (n=255). We selected two archived serum specimens for each participant, the first collected after diagnosis for cases and one randomly-selected from 1998-2003 for controls (“index”), as well as the preceding specimen (“pre-index”). PSA was measured in each specimen. To explore the specificity of our findings for prostate as opposed to systemic inflammation, we performed a post-hoc comparison of other infectious disease cases without genitourinary involvement (n=90) and controls (n=220). We found that IM cases were more likely to have a large PSA rise than controls (≥20 ng/mL: 19.7% versus 8.8%, p=0.027; ≥40% rise: 25.7% versus 9.4%, p=0.0021), as were other infectious disease cases (25.7% versus 14.0%, p=0.020; 27.7% versus 18.0%, p=0.092). These findings suggest that, in addition to rising because of prostate infection, PSA may also rise because of systemic inflammation, which could have implications for PSA interpretation in older men.
INTRODUCTION

Infection with Epstein-Barr virus (EBV), a member of the gamma herpesvirus family, has been shown to contribute to the development of several cancers, including Burkitt’s lymphoma and nasopharyngeal carcinoma.1 Few studies have investigated EBV infection in relation to other cancers, such as prostate cancer. Evidence of EBV infection has been detected in at least five studies of benign and/or neoplastic prostate tissue,2-6 although it was not associated with prostate cancer risk in one of these studies.2 Two additional studies investigated EBV serology and prostate cancer with null or generally unstable results.7,8 However, it is possible these studies may have missed an association if the timing of EBV infection is important for carcinogenesis.9 For instance, whereas childhood EBV infections typically result in mild or no symptoms, infections acquired later in adolescence or early-adulthood are more likely to result in infectious mononucleosis (IM), a clinical syndrome characterized by symptoms of sore throat, malaise, and fatigue; and signs of pharyngitis, fever, and lymphadenopathy.10 These later-onset infections have been found to be important for risk of certain conditions, such as multiple sclerosis,11 and could also be important for other conditions, such as prostate cancer.

To begin to explore this hypothesis, we investigated the extent of prostate pathogenesis during young adult-onset IM by measuring prostate-specific antigen (PSA) concentration as a marker of prostate inflammation and cell damage in young IM cases and controls with stored sera in the Department of Defense Serum Repository (DoDSR12). We used serum PSA as a marker of prostate inflammation/cell damage because PSA has been shown to be elevated in men with acute bacterial prostatitis and asymptomatic histologic prostate inflammation.13 In previous studies using this marker,14 including one using stored DoDSR specimens,15 we found that men with exudative sexually transmitted infections (STIs), such as chlamydia and gonorrhea, were
more likely to have a large rise in PSA (defined by a ≥40% increase in PSA) at the time of infection than men with no STI diagnoses, suggesting that prostate infection, inflammation, and/or cell damage occur in some men infected with sexually transmitted agents. In the present study, we sought to determine whether similar findings were observed for young adult-onset IM. In addition, because IM contributes to both organ-specific and systemic inflammation, we performed a post-hoc analysis of other infectious diseases and PSA to begin to explore the specificity of observed associations for prostate inflammation/cell damage as opposed to systemic or other non-prostate inflammation.

METHODS

Study population and design

The DoDSR contains sera remaining from routine human immunodeficiency virus type 1 (HIV-1) testing of all U.S. military personnel since the early 1990s. It also contains sera remaining from indicated HIV-1 testing (e.g., as part of standard clinical work-up for STIs), and sera collected for pre- and post-deployment sero-surveillance. Sera are linked to a relational database that contains information on demographics, service-related activity, and medical diagnoses for all active duty service members. Medical diagnoses are recorded as International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) coded records. IM is diagnosed in several ways in the military, including the Monospot® test, EBV antibody-specific tests, and symptoms; however, the method of diagnosis is not recorded.

For the present analysis, we required participants to be 18-25 years of age as of 1995, to be HIV-negative, and to have served on continuous active military duty from 1995-2006. As part of a broader parent study on infections and PSA, participants were also required to have at least
four serum specimens available in the DoDSR, one collected from each of the following four time periods: 1995-1997, 1998-2000, 2001-2003, and 2004-2006 (Supplemental Figure 1). This criterion was included to ensure generally similar availability of specimens and correlates of specimen availability across all studies. IM cases were defined as men with at least one inpatient diagnosis or two outpatient diagnoses of IM (ICD-9-CM code 075) within 30 days of each other from 1998-2003 (n=55). We selected these criteria to increase the specificity of the case definition for IM, as symptoms of IM can overlap with those of other infections, such as the common cold. We defined controls as men with no recorded IM diagnoses in their medical record as of 2006. We also required controls not to have any STI diagnoses (ICD-9-CM 090-099.9 and 131), except for persistent viral infections (ICD-9-CM 054 and 078.1), in their medical record to allow them to be used in multiple analyses, including a previous study of STIs. Although this restriction was not made for IM cases, no selection bias was introduced by this control criterion because none of the IM cases had STI diagnoses in their medical record. Finally, as part of the parent study, controls were frequency-matched to the entire case group (IM and STI cases) by race (n=255).

For each IM case, we selected two serum specimens from the DoDSR, a pre-IM specimen ("pre-index") and an acute or post-IM specimen ("index"). The pre-index specimen was defined as the first specimen collected at least 6 weeks before their diagnosis to account for the typical incubation period of IM (range: 46 days-4 years before diagnosis). The index specimen was defined as the first specimen collected seven days before to any time after their diagnosis (range: 1 day-3 years after diagnosis). Two specimens were also selected for each control, one randomly-selected from either 1998-2000 or 2001-2003 depending on the window of case diagnosis ("index" specimen), and the first specimen collected immediately before their
index specimen (“pre-index” specimen). Controls were additionally frequency-matched to cases by time of index specimen collection.

As IM contributes to systemic in addition to organ-specific inflammation, we also performed a post-hoc analysis of other infectious diseases and PSA to begin to explore the specificity of observed associations for prostate inflammation/cell damage as opposed to systemic or other non-prostate inflammation. Cases for this analysis were men with a confirmed or unconfirmed diagnosis of fever or an infection associated with systemic (e.g., influenza, ICD-9-CM 487) or localized non-genitourinary inflammation (e.g., streptococcal sore throat, ICD-9-CM 034) from 1995-2006. Infections associated with minimal inflammation were not included (e.g., dermatophytosis, ICD-9-CM 110). Other infectious disease cases were required to have an available serum specimen collected seven days before up to one year after their infectious disease diagnosis based on our findings for IM (described below). All original controls, as well as STI and IM cases, were eligible to serve as other infectious disease cases, as long as their other infectious disease diagnosis occurred before their index STI or IM diagnosis. Original controls who did not meet the definition for infectious disease cases were included as controls.

For each other infectious disease case, we selected two specimens, the first collected seven days before up to one year after their infectious disease diagnosis (index specimen, range: 0-359 days after diagnosis), as well as the preceding specimen (pre-index specimen, range: 172 days-7 years before diagnosis). We also selected two specimens for each control. These specimens were collected in the same windows of time as the case specimens. Controls were individually-matched to cases by race and window of index specimen collection (1995-1997, 1998-2000, 2001-2003, and 2004-2006).

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

**Measurement of PSA concentration**

As participants were too young for routine prostate cancer screening and thus did not have PSA measurements in their military medical record, we measured total PSA concentration at Johns Hopkins using the Access Hybritech PSA assay (Beckman Coulter, Brea, CA). Specimens from the same individual were tested adjacent to one another in random within-person order. We determined assay reproducibility 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 largely discrepant pair).

**Statistical analysis**

We explored PSA change between the pre-index and index specimens by calculating geometric and arithmetic mean pre-index and index PSA for cases and controls by linear regression with robust variance estimation. Values were adjusted for race and window of specimen collection to account for frequency- and individual-matching. We compared mean values by linear regression with robust variance estimation for the IM analysis and by conditional logistic regression for the post-hoc other infectious disease analysis. We further explored PSA change between cases and controls by calculating race- and time-adjusted categories of absolute and relative change using linear regression, and we compared these values by logistic regression with adjustment for race and window of specimen collection for the IM analysis, and by conditional logistic regression for the other infectious disease analysis. As in our previous studies,\textsuperscript{14,15} we defined a large PSA rise as a $\geq 40\%$ increase in PSA between the pre-index and index specimens. However, we also explored a definition based on the upper end of
the absolute change distribution (≥0.2 ng/mL), which we selected to generate approximately equal proportions of controls defined as having a large absolute and relative rise, and thus approximately equal power to detect a difference between cases and controls in both analyses. Finally, we also adjusted the results for age and time between the pre-index and index specimens. We did not adjust for body mass index (BMI) as a marker of overweight and obesity, which is also known to influence PSA levels, because U.S. active duty military members are required to maintain their weight below age-specific percent body fat cut-off points and, if they exceed these limits, are enrolled in mandatory weight-control programs; therefore, very few military members in our sample should have been overweight or obese.

To investigate possible differences in findings by time between diagnosis and index specimen collection, and by major infectious disease category (unspecified viral, gastrointestinal tract, and respiratory tract infection in the other infectious disease analysis), we included interaction terms in the model and evaluated their statistical significance by the likelihood ratio test. To investigate the susceptibility of our findings to additional diagnosed or possibly undiagnosed infections not taken into consideration in the analyses, we repeated the analyses excluding: 1) men with other infectious or genitourinary diagnoses (e.g., urinary tract infection, site not specified; ICD-9-CM 599) preceding their pre-index specimen or between their pre-index and index specimens for the IM analysis, and men with genitourinary diagnoses preceding their pre-index specimen or between their pre-index and index specimen for the other infectious diseases analysis; 2) men with “clinically-indicated” or “STI visit” reasons for blood draw for their pre-index or index specimens; 3) men with small breaks (<60 days) in active duty status between their pre-index and index specimens; 4) men deployed between these two specimens, as their medical records might be less complete during this time; and 5) higher rank officers who
may have greater access to non-military health care. Finally, to investigate the influence of control selection on our findings (i.e., chance assignment of particular controls to particular cases, as each control could, in theory, serve as a control for any case of the same race), we resampled controls nine additional times and compared the results to the main analysis.

RESULTS

Young adult-onset IM

We identified 55 IM cases who met study criteria and selected 255 controls for comparison. Compared to controls, cases were slightly younger and were more likely to be Caucasian because controls were frequency-matched to the entire group of STI and IM cases rather than only to IM cases (Table 1). Cases also had a greater length of time between their pre-index and index specimens than controls. Considering change in PSA between the pre-index and index specimens, although cases had a similar average change in PSA than controls, they were significantly more likely to have a large rise in PSA at the time of their index specimen than controls, as defined by both a large absolute and relative rise in PSA (≥0.2 ng/mL rise: 19.7% versus 8.8%, p=0.027; ≥40% rise: 25.7% versus 9.4%, p=0.0021, Table 2). When these results were investigated by time between IM diagnosis and index specimen collection, cases whose index specimen was collected within 3 months of diagnosis were no more likely to have a large rise in PSA than controls; those whose specimen was collected 4-12 months after diagnosis were significantly more likely to have a large PSA rise than controls; and those whose index specimen was collected >1 year after diagnosis were slightly, non-significantly more likely to have a large PSA rise than controls, at least for a large relative change (p-interaction=0.0002, 0.0003, Table 3).
Similar results were observed in sensitivity analyses designed to reduce the possible influence of additional diagnosed or undiagnosed infections on our findings (≥0.2 ng/mL rise: p=0.027-0.065; ≥40% rise: p=0.0028-0.019) and in repeated control sampling (p=0.030-0.12, 0.0026-0.016).

**Other infectious diseases**

To begin to explore the specificity of observed associations for prostate inflammation/cell damage as opposed to systemic or other non-prostate inflammation, we performed a *post-hoc* analysis of other infectious diseases. We identified 90 infectious disease cases who met study criteria: 13 cases of streptococcal sore throat (ICD-9-CM 034.0), five influenza (ICD-9-CM 487.1, 487.8), one *Haemophilus influenzae* infection (ICD-9-CM 041.5), 14 intestinal infection due to specified or unspecified organisms (ICD-9-CM 008.43, 008.69, 008.8, 009.0), 46 unspecified viral infection (ICD-9-CM 079.99), two other specified viral infection (ICD-9-CM 079.89), two unspecified infectious and parasitic diseases (ICD-9-CM 136.9), four fever not accompanied by another diagnosis (ICD-9-CM 780.6), two chicken pox (ICD-9-CM 052.9, 053.0), and one leptospirosis icterohemorrhagica (ICD-9-CM 100.0). 220 of the original 255 controls met the eligibility criterion for comparison. In crude analyses, infectious disease cases had a significantly greater average change in PSA between their pre-index and index specimens than controls, and were more likely to have both a large absolute and relative rise in PSA. These findings attenuated, however, after adjustment for age and time between specimens, although they remained statistically significant for a large absolute rise in PSA (≥0.2 ng/mL rise: 25.7% versus 14.0%, p=0.020; ≥40% rise: 27.7% versus 18.0%, p=0.092, Table 4). After standardizing these values to the same distribution of time between specimens as for the IM analysis, these
proportions were 14.8% versus 3.1% for a ≥0.2 ng/mL rise, and 19.2% versus 9.5% for a ≥40% rise in PSA.

Generally similar results were observed for cases whose index specimen was collected within 3 or 4-12 months of diagnosis (p-interaction=0.13, 0.48), and for unspecified viral, gastrointestinal tract, and respiratory tract infection cases (p-interaction=0.90, 0.45, Table 5). Generally similar results were also observed in all sensitivity analyses (≥0.2 ng/mL rise: p=0.018-0.077; ≥40% rise: p=0.029-0.18), except for the analysis excluding officers (p=0.22, 0.76), and with repeated control sampling (p=0.0003-0.036, 0.032-0.23).

DISCUSSION

In our U.S. military-based study, we found that young men with adult-onset IM were more likely to have a large rise in PSA during or following infection than controls, as were young men with other infectious diseases not known to involve the prostate. To our knowledge, our study is the first to investigate the influence of these infections on PSA.

Given our positive findings for other infectious diseases, an important question to ask for both our IM and previous exudative STI results is the likelihood that these findings reflect prostate involvement during infection – our original interpretation of PSA elevation – versus other possible mechanisms of PSA elevation. Comparing the magnitude of associations across infections (Table 6), we observed the strongest association for chlamydia, an exudative STI with known potential to infect the prostate; and weaker associations of similar magnitude for gonorrhea, another STI with known potential to infect the prostate, as well as for IM and other infectious diseases not known to involve the prostate. Therefore, one potential interpretation of these findings could be that PSA may rise for multiple, possibly cumulative reasons, including:
1) prostate involvement (in the case of chlamydia and, to a lesser degree, possibly also gonorrhea and IM), and 2) other mechanisms related more generally to infection and inflammation (in the case of all infections studied). Based on this interpretation, prostate involvement may occur in a maximum of 25-27% of chlamydial infections\textsuperscript{15} (Table 6) to a minimum of 15% of chlamydial infections (minus 9.7-11.7% for the difference between other infectious disease cases and their respective controls). By the same logic, these numbers are 10-12% to 0-1% for gonococcal infections, and 11-16% to 0-6% for IM episodes. Why PSA did not raise for non-chlamydial, non-gonococcal urethritis cases who, by definition, have urethral inflammation is unclear.

Other important questions raised by our analysis are possible non-prostate infection-related reasons for PSA elevation in young men. Although PSA has been detected in some extra-prostatic glands/organs (e.g., salivary glands/saliva,\textsuperscript{21-26} kidney,\textsuperscript{22,24} and pancreas\textsuperscript{22-24}), we believe that PSA secretion by these infected glands/organs is unlikely to explain our findings because these extra-prostatic sites produce considerably less PSA than the prostate (<1%\textsuperscript{22}). Instead, we believe that a systemic inflammatory contribution to PSA elevation is more likely. Under normal circumstances, PSA is produced by prostate epithelial cells and is secreted into the prostatic lumen to liquefy semen. However, when the prostate epithelial barrier is disrupted, such as by cell damage, PSA can leak into the extracellular space and, ultimately, into circulation. This leakage is facilitated by inflammation, which makes blood vessels more permeable to immune cells, as well as to small molecules, such as PSA.\textsuperscript{27} Our previous interpretation of PSA elevation focused on localized prostate inflammation and cell damage in the context of prostate infection,\textsuperscript{14,15} but it is conceivable that systemic inflammation might also contribute to PSA elevation, either through inflammation-mediated prostate cell damage and increased vascular permeability, or through increased vascular permeability in the context of pre-existing prostate
epithelial cell damage/disruption from other sources. Under this latter hypothesis, approximately 10% of young men might be expected to have prostate epithelial disruption at any single point in time based on our other infectious disease findings.

Our findings for IM, but not for other infectious diseases, varied by time since diagnosis. Results were null for men whose index specimen was collected most recently after diagnosis and strongly positive for men whose index specimen was collected later after diagnosis. While speculative, one possible explanation for this temporal association may be changes in the type and level of activity of convalescent men over time. Immediately following diagnosis or symptom onset, fatigued IM patients likely spend more time resting, which has been found to reduce PSA in hospitalized patients,\textsuperscript{28} and less time engaging in sexual and physical activity, which have been found to increase PSA in some studies.\textsuperscript{29-31} However, as men regain their energy later in their convalescence, it is possible they engage in these activities to a greater degree, leading to the stronger observed association from four months post-diagnosis onwards. Thus, the potential influence of IM-mediated systemic inflammation on PSA may be counter-balanced by immediate post-diagnosis rest and enhanced by later increases in activity, which likely eventually return to pre-IM levels.

Additional questions raised by our findings include the long-term persistence of infection-mediated PSA elevation, which is of interest given observed associations between PSA concentration at a younger age and later prostate cancer risk,\textsuperscript{32-34} and the generalizability of our findings to middle- and older-aged men undergoing PSA screening. Although routine PSA testing for early prostate cancer detection received a grade D recommendation from the U.S. Preventive Services Task Force,\textsuperscript{35} this question remains of interest for several reasons. First, informed and targeted PSA testing for early prostate cancer detection is still supported by several...
organizations,\textsuperscript{36-40} and is still frequently performed despite guideline changes.\textsuperscript{41} Second and more relevant to our findings, some organizations now support initiating PSA testing at a younger age than previously recommended (i.e., beginning at 40-45 rather than 50-55 years of age) to establish a baseline PSA value and to stratify men by their future prostate cancer risk and consequent prostate cancer screening regimen.\textsuperscript{39,40} Thus, whether a recent infection, such as a cold, influences PSA levels in middle- and older-aged men may be relevant for current and future PSA screening paradigms.

Based on our findings in younger men, we would expect at least 10\% of middle- to older-aged men to have a rise in PSA of at least 0.2 ng/mL during or following an infection. Depending on their initial PSA value, this small magnitude of change might be sufficient to influence screening regimens in men in their 40s (recommended threshold of 1.0 ng/mL),\textsuperscript{39,40} but would be unlikely to influence the decision to biopsy unless men were close to the threshold (recommended threshold of 2.5-4 ng/mL).\textsuperscript{42,43} However, if the magnitude of PSA change is greater in middle- and older-aged men than in younger men, as might be expected based on their likely greater degree of pre-existing epithelial cell disruption and amount of PSA secreted, then these larger possible rises might be sufficient to influence both screening and biopsy decisions, and thus might be worth pursuing in future research. Additionally, whether or not non-infectious, inflammatory conditions, such as inflammatory bowel disease, influence serum PSA levels might also be of interest, but these have been examined in only a few small studies of hepatitis\textsuperscript{44-49} and periodontitis.\textsuperscript{50} We could not address this question in the present study because our original data request was limited to infectious disease and genitourinary ICD-9-CM codes consistent with our original hypothesis, and because our de-identified data can no longer be linked to the master DoDSR file.
In summary, we found that PSA rose during or following an episode of IM, a condition with possible prostate involvement, as well as during or following other inflammatory infectious diseases not known to involve the prostate, such as influenza. Taken together with our previous findings for chlamydia and gonorrhea, these findings suggest that PSA may rise for multiple possibly cumulative reasons, including prostate infection, inflammation and cell damage, as well as systemic inflammation. Additional questions raised by our findings are the long-term persistence of elevated PSA years to decades following resolution of infection and the generalizability of our findings to middle- and older-aged men undergoing PSA screening.
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<table>
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<tr>
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<th>IM cases (n=55)</th>
<th>Controls (n=255)</th>
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IM=infectious mononucleosis; HIV-1=human immunodeficiency virus type 1; STI=sexually transmitted infection

^a Values for cases and controls were calculated by linear regression adjusting for race (African-American, non-African-American) and window of specimen collection.

^b P-values were calculated by linear regression for continuous or 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.

^c At the time of blood draw of the index specimen.

^d Cases were frequency-matched to controls (also used for STI cases) by race/ethnicity.

^e Indicates 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).

^f Indicates blood drawn for self or clinical suspicion of HIV-1 or STIs, as well as from hospitalized patients or those visiting emergency rooms for certain clinical indications. Blood draws are coded as “clinically indicated/part of an STI visit” irrespective of the results of HIV-1 or STI testing.
Table 2: Pre-index and index serum total prostate-specific antigen concentration for 55 young, male infectious mononucleosis cases and 255 controls; U.S. military 1998-2003

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
<th>IM cases (n=55)</th>
<th>Controls (n=255)</th>
<th>p-value&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-index</td>
<td>Index</td>
<td>Pre-index</td>
</tr>
<tr>
<td>Geometric mean&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.58</td>
<td>0.61</td>
<td>0.55</td>
</tr>
<tr>
<td>Mean&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.67</td>
<td>0.70</td>
<td>0.65</td>
</tr>
<tr>
<td>Interquartile range&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.35-0.85</td>
<td>0.42-0.98</td>
<td>0.38-0.76</td>
</tr>
</tbody>
</table>

Absolute change in serum total PSA (%):<sup>b</sup>

| ≤0.00 ng/mL | 48.4 | 52.1 |
| 0.01-0.09 ng/mL | 17.0 | 23.8 |
| 0.10-0.19 ng/mL | 14.5 | 15.2 |
| 0.20-0.29 ng/mL | 8.8 | 3.4 | 0.26 |
| 0.30-0.39 ng/mL | 0.8 | 2.1 |
| 0.40-0.49 ng/mL | 4.6 | 1.3 |
| ≥0.50 ng/mL | 5.9 | 2.0 |

Large absolute rise in serum total PSA (%):<sup>b</sup>

| ≥0.2 ng/mL | 20.1 | 8.9 | 0.014 |
| ≥0.2 ng/mL<sup>d</sup> | 19.7 | 8.8 | 0.027 |

Relative percent change in serum total PSA (%):<sup>b</sup>

| ≤0 | 48.4 | 52.1 |
| 0.1-9 | 12.2 | 11.3 |
| 10-19 | 7.6 | 12.3 |
| 20-29 | 5.2 | 10.2 | 0.25 |
| 30-39 | 2.6 | 4.8 |
| 40-49 | 9.9 | 1.8 |
| ≥50 | 14.1 | 7.6 |

Large relative rise in serum total PSA (%):<sup>b</sup>

| ≥40 | 24.0 | 9.4 | 0.0025 |
| ≥40<sup>d</sup> | 25.7 | 9.4 | 0.0021 |

IM=infectious mononucleosis; PSA=prostate-specific antigen

<sup>a</sup> P-values were calculated by linear regression with robust variance estimation for continuous variables, linear regression for binary variables, and logistic regression for categorical variables. All models were adjusted for race (African-American, non-African-American) and window of specimen collection.

<sup>b</sup> 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.

<sup>c</sup> Not adjusted for race or window of specimen collection.

<sup>d</sup> Additionally adjusted for age and time between pre- and index specimens.
| Time between diagnosis and index specimen collection: | Absolute change in serum total PSA<sup>a</sup> | | | Relative percent change in serum total PSA<sup>a</sup> |
|---|---|---|---|---|---|---|
| | Cases | Controls | Cases | Controls | Cases | Controls |
| N | ≥0.2 ng/mL (%) | N | ≥0.2 ng/mL (%) | p-value | N | ≥40% (%) | N | ≥40% (%) | p-value |
| <4 months | 19 | 10.7 | 255 | 8.8 | 0.77 | 19 | 10.1 | 255 | 9.6 | 0.94 |
| 4-12 months | 19 | 43.3 | 245 | 8.4 | <0.0001 | 19 | 49.0 | 245 | 8.9 | <0.0001 |
| ≥12 months | 17 | 15.7 | 150 | 13.6 | 0.80<sup>b</sup> | 17 | 25.5 | 150 | 13.1 | 0.13<sup>c</sup> |

PSA=prostate-specific antigen

<sup>a</sup> All values and p-values were calculated by linear regression adjusting for race, window of specimen collection, age, and time between pre- and index specimens.

<sup>b</sup> P-interaction=0.0002.

<sup>c</sup> P-interaction=0.0003.
Table 4: Pre-index and index serum total prostate-specific antigen concentration for 90 young male infectious disease cases and 220 individually-matched controls; U.S. military 1995-2006

<table>
<thead>
<tr>
<th>PSA (ng/mL)</th>
<th>Pre-index</th>
<th>Index</th>
<th>Pre-index</th>
<th>Index</th>
<th>p-value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric mean&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.54</td>
<td>0.57</td>
<td>0.51</td>
<td>0.70</td>
<td>0.0029</td>
</tr>
<tr>
<td>Mean&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.63</td>
<td>0.67</td>
<td>0.65</td>
<td>0.79</td>
<td>0.23</td>
</tr>
<tr>
<td>Interquartile range&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.37-0.76</td>
<td>0.39-0.78</td>
<td>0.36-0.79</td>
<td>0.41-0.93</td>
<td></td>
</tr>
</tbody>
</table>

Absolute change in serum total PSA (%):<sup>c</sup>
- ≤0.00 ng/mL: 37.4, 44.3
- 0.01-0.09 ng/mL: 21.5, 28.3
- 0.10-0.19 ng/mL: 13.6, 15.1
- 0.20-0.29 ng/mL: 10.4, 4.7
- 0.30-0.39 ng/mL: 5.4, 0.4
- 0.40-0.49 ng/mL: 2.8, 1.6
- ≥0.50 ng/mL: 8.9, 5.5

Large absolute rise in serum total PSA (%):<sup>c</sup>
- ≥0.2 ng/mL: 27.6, 12.2
- ≥0.2 ng/mL: 25.7, 14.0

Relative percent change in serum total PSA (%):<sup>c</sup>
- ≤0: 37.5, 44.8
- 0.1-9: 10.3, 15.0
- 10-19: 12.9, 12.1
- 20-29: 3.3, 6.4
- 30-39: 6.5, 5.3
- 40-49: 5.7, 5.1
- ≥50: 23.8, 11.2

Large relative rise in serum total PSA (%):<sup>c</sup>
- ≥40: 29.5, 16.3
- ≥40: 27.7, 18.0

PSA=prostate-specific antigen

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

<sup>b</sup> P-values were calculated by conditional logistic regression.

<sup>c</sup> Values were calculated by linear regression adjusting for race (African-American, non-African-American) and window of specimen collection.

<sup>d</sup> Not adjusted for race or window of specimen collection.

<sup>e</sup> Additionally adjusted for age and time between pre- and index specimens.
Table 5: Change in serum total prostate-specific antigen concentration (ng/mL) for young male infectious disease cases and individually-matched controls, stratified by time between diagnosis and index serum specimen collection, and infection type; U.S. military 1995-2006

<table>
<thead>
<tr>
<th>Time between diagnosis and index specimen collection:</th>
<th>Absolute change in serum total PSA</th>
<th>Relative percent change in serum total PSA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>N ≥0.2 ng/mL (%)</td>
<td>N ≥0.2 ng/mL (%)</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>26.1</td>
</tr>
<tr>
<td></td>
<td>4-12 months</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>33</td>
<td>30.9</td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>26.0</td>
</tr>
<tr>
<td>Type of infection:</td>
<td>Cases</td>
<td>Controls</td>
</tr>
<tr>
<td></td>
<td>N ≥40% (%)</td>
<td>N ≥40% (%)</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>24.1</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>31.0</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>31.0</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>25.3</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>38.7</td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>32.0</td>
</tr>
</tbody>
</table>

PSA=prostate-specific antigen

<sup>a</sup> Values were calculated by linear regression adjusting for race, window of specimen collection, age, and time between pre- and index specimens.<br><sup>b</sup> P-values were calculated by conditional logistic regression adjusting for age and time between pre- and index specimens.<br><sup>c</sup> P-value for interaction=0.13.<br><sup>d</sup> P-value for interaction=0.48.<br><sup>e</sup> P-value for interaction=0.90.<br><sup>f</sup> P-value for interaction=0.45.
Table 6: Absolute and relative risks of large serum total prostate-specific antigen concentration (ng/mL) rises during or following infection among young male military members by infection type; U.S. military 1995-2006

<table>
<thead>
<tr>
<th>PSA rise ≥0.2 ng/mL</th>
<th>PSA rise ≥40%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Chlamydiaa</td>
</tr>
<tr>
<td>Absolute risk</td>
<td>26.9</td>
</tr>
<tr>
<td>difference</td>
<td>(20.4-33.4)</td>
</tr>
<tr>
<td>Relative risk</td>
<td>4.3</td>
</tr>
<tr>
<td></td>
<td>(2.8-6.7)</td>
</tr>
</tbody>
</table>

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

a Further details and complete results for these infectious diseases are presented in reference 15.
b Includes men with the following diagnoses: streptococcal sore throat (ICD-9-CM 034.0), influenza (487.1, 487.8), *Haemophilus influenzae* infection (041.5), intestinal infection due to specified or unspecified organisms (008.43, 008.69, 008.8, 009.0), unspecified viral infection (079.99), other specified viral infection (079.89), unspecified infectious and parasitic diseases (136.9), fever not accompanied by another diagnosis (780.6), chicken pox (052.9, 053.0), and leptospirosis icterohemorrhagica (100.0)
Supplemental Figure 1: IM and other infectious disease case and control selection, US military 1995-2001.

All participants were required to have at least four serum specimens available in the Department of Defense Serum Repository (DoDSR), one collected from each of the following four time periods: 1995-1997, 1998-2000, 2001-2003, and 2004-2006. IM cases were defined as men with at least one inpatient IM diagnosis or two outpatient diagnoses within 30 days of each other from either 1998-2000 or 2001-2003 (solid blue line). For each of these cases, we selected two serum specimens, one collected at least six weeks before their diagnosis and one collected after their diagnosis. Controls for IM cases were defined as men with no IM (or sexually transmitted infection (STI)) diagnoses in their medical record from 1995-2006. For each control, two specimens were selected, one randomly-selected from either 1998-2000 or 2001-2003, depending on the window of case diagnosis, as well as their previous specimen. These men were frequency-matched to cases by race and window of index specimen ascertainment, i.e., 1998-2000 or 2001-2003.

Other infectious disease cases were defined as men with a confirmed or unconfirmed diagnosis of fever or an infection associated with systemic or localized non-genitourinary inflammation from 1995-2006. All original controls, as well as IM cases and STI cases from a previous analysis, were eligible to serve as other infectious disease cases, as long as their other infectious disease diagnosis occurred before their index IM or STI diagnosis. Therefore, the window of other infectious disease case ascertainment for original IM and STI cases could be limited to 1995-1998 (solid blue line) or could extend almost up to the end of 2003, depending on the date of their original IM or STI diagnosis (striped blue line). The other infectious disease diagnosis
for original controls could occur at any time from 1995-2006 (solid blue line). Two specimens were selected for each case, one collected before their diagnosis and one collected within one year after their diagnosis. Original controls who did not meet the criteria for an other infectious disease case were considered to be other infectious disease controls. Two specimens were also selected for each of these men in the same windows of time as the case specimens. Controls were individually matched to other infectious disease cases by race and window of case ascertainment (1995-1997, 1998-2000, 2001-2003, and 2004-2006).
Supplemental Figure 1: IM and other infectious disease case and control selection, U.S. military 1995-2006

IM=infectious mononucleosis; STI=sexually transmitted infection