Received: 31 May 2019 | Accepted: 8 July 2019

DOI: 10.1002/pros.23886

ORIGINAL ARTICLE

The Prostate WILEY

Trichomonas vaginalis infection and prostate-specific antigen concentration: Insights into prostate involvement and prostate disease risk

Marvin E. Langston[1] | Ankita Bhalla[1,2] | John F. Alderete[3] | Remington L. Nevin[4,5] | Ratna Pakpahan[1] | Johannah Hansen[1,6] | Debra Elliott[7] | Angelo M. De Marzo[7,8,9] | Charlotte A. Gaydos[10] | William B. Isaacs[8,9] | William G. Nelson[7,8,9,11] | Lori J. Sokoll[7,8,9] | Jonathan M. Zenilman[10] | Elizabeth A. Platz[8,9,12] | Siobhan Sutcliffe[1,13,14]

[1]Division of Public Health Sciences, Department of Surgery, Washington University School of Medicine, St. Louis, Missouri

[2]School of Dentistry, University of California, San Francisco, San Francisco, California

[3]School of Molecular Biosciences, College of Veterinary Medicine, Washington State University, Pullman, Washington

[4]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

[5]The Quinism Foundation, White River Junction, Vermont

[6]Los Angeles County Department of Public Health, Los Angeles, California

[7]Department of Pathology, Johns Hopkins University School of Medicine, Baltimore, Maryland

[8]Department of Urology, The James Buchanan Brady Urological Institute, Johns Hopkins University School of Medicine, Baltimore, Maryland

[9]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins, Baltimore, Maryland

[10]Division of Infectious Diseases, Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland

[11]Department of Pharmacology, Johns Hopkins University School of Medicine, Baltimore, Maryland

[12]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

[13]Alvin J. Siteman Cancer Center, Washington University School of Medicine, St. Louis, Missouri

[14]Department of Obstetrics and Gynecology, Washington University School of Medicine, St. Louis, Missouri

Correspondence
Marvin E. Langston, Division of Public Health Sciences, Washington University School of Medicine, 600 S. Taylor Ave, 2nd floor, Box 8100, St. Louis, MO 63110.
Email: langstonm@wustl.edu

Funding information
National Cancer Institute, Grant/Award Numbers: P30 CA006973, T32190194; Fund for Research and Progress in Urology, Johns Hopkins University School of Medicine; Barnes-Jewish Hospital Foundation; Alvin J. Siteman Cancer Center; Patrick C. Walsh Prostate Cancer Research Fund

Abstract

Background: The protist *Trichomonas vaginalis* causes a common, sexually transmitted infection and has been proposed to contribute to the development of chronic prostate conditions, including benign prostatic hyperplasia and prostate cancer. However, few studies have investigated the extent to which it involves the prostate in the current antimicrobial era. We addressed this question by investigating the relation between *T. vaginalis* antibody serostatus and serum prostate-specific antigen (PSA) concentration, a marker of prostate infection, inflammation, and/or cell damage, in young, male, US military members.

Methods: We measured *T. vaginalis* serum IgG antibodies and serum total PSA concentration in a random sample of 732 young, male US active duty military members. Associations between *T. vaginalis* serostatus and PSA were investigated by linear regression.

Marvin E. Langston and Ankita Bhalla are co-first authors.

Results: Of the 732 participants, 341 (46.6%) had a low *T. vaginalis* seropositive score and 198 (27.0%) had a high score, with the remainder seronegative. No significant differences were observed in the distribution of PSA by *T. vaginalis* serostatus. However, slightly greater, nonsignificant differences were observed when men with high *T. vaginalis* seropositive scores were compared with seronegative men, and when higher PSA concentrations were examined (≥0.70 ng/mL). Specifically, 42.5% of men with high seropositive scores had a PSA concentration greater than or equal to 0.70 ng/mL compared with 33.2% of seronegative men (adjusted $P = .125$).

Conclusions: Overall, our findings do not provide strong support for prostate involvement during *T. vaginalis* infection, although our suggestive positive findings for higher PSA concentrations do not rule out this possibility entirely. These suggestive findings may be relevant for prostate condition development because higher early- to mid-life PSA concentrations have been found to predict greater prostate cancer risk later in life.

KEYWORDS
inflammation, prostate cancer etiology, sexually transmitted infection, *T. vaginalis*

1 | INTRODUCTION

Trichomonas vaginalis causes the most common, nonviral sexually transmitted infection (STI) and has been proposed to contribute to the development of chronic prostate conditions, such as benign prostatic hyperplasia (BPH) and prostate cancer. Possible mechanisms by which it may contribute to these conditions include: (a) adherence to and lysis of prostate epithelial cells; (b) induction of intra-prostatic inflammation and cytokine production; (c) inhibition of prostate epithelial cell apoptosis; and (d) upregulation of proto-oncogenes.[1,2] More recently, *T. vaginalis* has also been observed to increase prostate cell line proliferation and invasiveness,[3,4] has been detected in prostate tissue from men with BPH,[2,5] and has been found to be associated with the presence of BPH,[6] as well as later prostate cancer risk and aggressiveness in some,[7,8] but not all,[9-14] sero-epidemiologic studies.

Many of the original observations of intra-prostatic *T. vaginalis* infection were made in men infected before the introduction of effective antitrichomonad therapies (ie, metronidazole)[15-17] or in men with trichomonal urethritis,[18] a less common manifestation of this frequently asymptomatic infection.[19] Therefore, an important question for prostate condition development is the extent to which trichomonal prostate infection occurs in the current antimicrobial era and in men with asymptomatic infection. We previously addressed this question for chlamydia and gonorrhea by measuring the proportion of young men whose concentration of serum prostate-specific antigen (PSA), a marker of prostate infection, inflammation, and/or cell damage, rose during documented infections.[20,21] However, we were not able to perform a similar type of analysis for *T. vaginalis* infection because this infection tends to be asymptomatic and is not typically investigated or diagnosed in STI clinics. Therefore, we addressed this question instead by measuring specific serum antibodies to a unique *T. vaginalis* immunogenic protein as a marker of current and past infection. We investigated the relation between the presence of these antibodies and serum PSA concentration in a study population at high risk for *T. vaginalis* (ie, young US military members with a high proportion (45%) of African American men[22]). In addition to informing prostate involvement during infection, our analysis may also inform a possible role for *T. vaginalis* in prostate carcinogenesis, because higher earlier-life PSA concentrations have been found to be associated with later prostate cancer risk in several studies.[23-26]

2 | MATERIALS AND METHODS

2.1 | Study population and design

Since 1985, the US Armed Forces has conducted routine human immunodeficiency virus (HIV) type-1 testing on all active duty members, as well as preservice testing and periodic pre- and post-deployment testing. Leftover sera are stored in the Department of Defense Serum Repository (DoDSR) for use in medical research and surveillance.[27] With Department of Defense collaboration and approval, sera from the DoDSR can be linked to service members' electronic military medical record, which includes inpatient and outpatient diagnoses previously coded using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

For the present study, we selected a random sample of 750 men with stored specimens in the DoDSR who met the following criteria: were less than 25 years old as of 1995, were HIV-1 negative, had

served on continuous active duty from 1995-2006, and had multiple serum specimens archived within the repository, including one from 2004-2006.[28] We used these criteria to ensure comparability with our broader parent study of STIs and PSA.[21,29,30] For each of these men, we selected the most recent serum specimen collected from 2004-2006. Of the original 750 men selected for this cross-sectional analysis, we excluded 18 with insufficient serum remaining after PSA testing or those whose specimens were left overnight at room temperature during PSA testing, leaving an analytic study sample of 732 men.

2.2 | Measurement of *T. vaginalis* serostatus

We assessed *T. vaginalis* infection by *T. vaginalis* serostatus rather than by obtaining diagnoses from the military medical record because *T. vaginalis* infection is frequently asymptomatic in men and is thus not frequently diagnosed. In addition, even when *T. vaginalis* infection does present with symptoms, it is not typically diagnosed as *T. vaginalis* infection, but rather as nongonococcal urethritis or nonchlamydial, nongonococcal urethritis (NCNGU). As *T. vaginalis* infection makes up only 1% to 20% of nongonococcal urethritis diagnoses,[31] we chose to ascertain *T. vaginalis* exposure by serology rather than by medical record diagnosis to reduce exposure misclassification.

Serum specimens were tested for *T. vaginalis* antibodies using an in-house enzyme-linked immunosorbent assay that detects IgG antibodies against a recombinant *T. vaginalis* α-actinin protein.[7,32] Specimens were tested in random order and in duplicate, with inferences determined by the average of the two values (coefficient of variation for the duplicate optical densities (ODs) = 6.6%). A control panel consisting of five quality control specimens of increasing seroreactivity from 0 (no reactivity) to 4+ (strong reactivity) was included in each run (n = 6 runs). The average of the control panel values across all runs was then used to determine cut-off points for seropositivity by dividing the average duplicate OD value of the seroreactive control specimens by the average of the 0 reactivity control specimens to create a positive to negative (P/N) ratio. Cut-off points were then derived by taking the mid-point between each P/N ratio—for instance, the cut-off point for the 2+ score was derived by taking the mid-point between the P/N ratios for the 2+ and 1+ control specimens. Scores were assigned to each DoDSR participant by comparing their P/N ratio (ie, their mean absorbance divided by the average of the 0 reactivity control specimens) to the above-described cut-off points. A score of 0 defined seronegativity, whereas the cut-off points of 1 and greater than or equal to 2 were used to assign low and high *T. vaginalis* seropositivity, similar to a contemporary analysis from the same laboratory.[9]

To determine the reproducibility of *T. vaginalis* serologic testing, we included 19 blinded, duplicate quality control pairs of serum from the DoDSR in the testing sequence (serostatus agreement =73.7% between duplicates).

2.3 | Measurement of PSA concentration

Serum specimens were stored in the DoDSR at −30°C for 0.7 to 3.7 years and then between −70 and −80°C for 3 to 15 months until PSA testing.[28] PSA remains relatively stable for up to 20 years at temperatures around −20°C.[33] Total PSA concentration was measured using the Beckman Coulter Access Hybritech assay (Beckman Coulter, Brea, CA) at the Johns Hopkins Hospital. PSA was measured rather than abstracted from participants' military medical records because these men were too young (ages 28–36 years at the time of blood draw) for routine PSA screening for prostate cancer based on contemporary guidelines. Specimens were tested in random order and assay reproducibility was determined by testing 25 blinded, quality control pairs from the DoDSR (coefficient of variation =12.4% and 6.9% after excluding one discrepant pair).[28]

2.4 | Statistical analysis

We compared participants' demographic, military, and infection history (STI, genitourinary, and any infection) characteristics by *T. vaginalis* serostatus, using the Student *t* test for continuous variables and χ^2 tests for proportions. Infection history was obtained from participants' military medical record and included the following diagnoses: *T. vaginalis* infection (ICD-9-CM code 131.02, 131.09, 131.9), NCNGU (099.4, 099.49), genital chlamydia (078.88, 099.3, 099.41, 099.50, 099.53, 099.54, 099.55), gonorrhea (098, 0980, 098.10, 098.11, 098.19, 098.2, 098.89), infectious mononucleosis (075), other STIs such as herpes viruses (054.10, 054.13, 054.19, and any other diagnoses between 090 to 099.9), other genitourinary infections and conditions such as urinary tract infections and BPH (ICD-9-CM codes from 580.0 to 609.0), and any infection or genitourinary condition (STIs [except for *T. vaginalis* and NCNGU]; infectious mononucleosis; genitourinary infections and conditions; and other nongenitourinary, systemic infections such as infections 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]). All diagnoses from the start of the electronic medical record (1995-1997) through to the date of participants' blood draw (2004-2006) were included.

We explored the distribution of PSA concentration by *T. vaginalis* serostatus by calculating geometric mean, arithmetic mean and median values, and proportions of PSA categories (<0.29, 0.30-0.49, 0.50-0.69, 0.70-0.89, and ≥0.90 ng/mL). We also calculated the percentage of men with PSA values greater than or equal to 0.70 ng/mL, as this value has been found to be associated with future prostate cancer risk in previous studies of young to middle-aged men.[23,34] Linear regression was used to adjust for potential confounders, including age, race, marital status, military grade,

region of residence, reason for blood draw, history and frequency of STIs (excluding *T. vaginalis* infection and NCNGU), urogenital infections, and systemic infections. As only age, sex, and race influenced the point estimates for *T. vaginalis* serostatus, only these covariates were retained in the final models. Effect modification by race was investigated by including an interaction term in the regression model and evaluating the significance of this term using the likelihood ratio test.

To determine the possible transient influence of other infections on our findings, we performed sensitivity analyses excluding men diagnosed with any STIs, urogenital, or systemic infections other than *T. vaginalis* infection and NCNGU within the period of 1 year before to 7 days after specimen collection. We chose this timeframe because we previously observed that large rises in PSA concentration remained up to 1 year following infection[30] and to allow for delayed entry of infectious disease diagnoses into the military medical record (up to 7 days). We also performed sensitivity analyses varying the cut-off points for *T. vaginalis* seropositivity by using the P/N ratios rather than the midpoints of the P/N ratios as cut-off points. Statistical analyses were performed using SAS version 9.4 (SAS, Cary, NC).

This study was approved by the Institutional Review Boards at the Walter Reed Army Institute of Research and the John Hopkins Bloomberg School of Public Health. All data and specimens were anonymized before release from the DoDSR.

3 | RESULTS

Of the 732 study participants, 341 (46.6%) had a low *T. vaginalis* seropositive score (score = 1), and 198 (27.0%) had a high score (score ≥2); the remainder were seronegative. Seropositive men were more likely to be African American and married than seronegative men, but were similar with respect to all other demographic, military, and clinical characteristics (Table 1).

No statistically significant differences were observed in the geometric mean, arithmetic mean, median, or categories of PSA concentration between *T. vaginalis* seropositive and seronegative men in unadjusted or adjusted analyses (Table 2). However, slightly greater, nonsignificant differences were observed when men with high *T. vaginalis* seropositive scores were compared to seronegative men, and when PSA concentrations greater than or equal to 0.70 ng/mL were examined. Specifically, 42.5% of men with high seropositive scores had a PSA concentration greater than or equal to 0.70 ng/mL compared to 33.2% of seronegative men (adjusted $P = .13$). Generally similar results were observed in analyses stratified by race ($P_{int} = .12$), in sensitivity analyses excluding recent infections (41.5% of high seropositive scores with PSA ≥0.70 ng/mL vs 33.8% seronegative men, adjusted $P = .25$), and in sensitivity analyses using the P/N ratios instead of the midpoints as the cut-off points for seropositivity (41.2% of high seropositive scores with PSA ≥0.70 ng/mL vs 35.2% seronegative men, adjusted $P = .22$).

4 | DISCUSSION

Overall, no significant associations were observed between *T. vaginalis* serostatus and PSA concentration in our large cross-sectional sample of young US military members. However, our suggestive, nonsignificant association between high *T. vaginalis* serostatus and greater PSA concentrations (≥0.70 ng/mL) leaves open the possibility of an influence of *T. vaginalis* infection on the prostate.

Comparing our findings to those from studies designed to examine the acute influence of infection on PSA, our nonsignificant findings are generally consistent with previous null findings for medical record–confirmed NCNGU in the US military,[21] as well as for those for confirmed gonorrhea and chlamydia when whole shifts in the PSA distribution were examined (ie, mean and median PSA).[7,21] Our findings differ, however, from previous positive findings for chlamydia and gonorrhea when greater changes in PSA concentrations were examined (≥40% increase above preinfection values), which we interpreted to mean that only a subset of participants with chlamydia and gonorrhea experienced prostate involvement.[7,21] Although we were not able to examine the distribution of PSA change during *T. vaginalis* infection in the present study, we did still observe a suggestion of a positive association between *T. vaginalis* serostatus and higher PSA concentrations, possibly implying prostate involvement during some *T. vaginalis* infections. Contrary to previous studies, though, this inference is more difficult to make in our analysis because we were not able to measure acute *T. vaginalis* infection directly but instead had to rely on a marker of cumulative *T. vaginalis* exposure (ie, both acute and resolved infections), thereby introducing a certain degree of exposure misclassification. This concern is further exacerbated by possible misclassification of *T. vaginalis* antibody measurement, although sensitivity analyses using alternative cut-off points yielded generally similar inferences and an expected positive association between *T. vaginalis* serostatus and African American race was observed.

Viewing our findings in the context of the longer-term or cumulative influences of current and/or resolved infections rather than the acute influences of infection, our nonsignificant findings are consistent with those from previous cross-sectional studies of nonlifelong infections (*T. vaginalis*[14] and syphilis) that observed null associations with PSA,[35] but differ from those from other cross-sectional and longitudinal studies that observed positive findings for *C. trachomatis* serostatus and histories of medical record–confirmed chlamydia and NCNGU diagnoses with PSA concentration and trajectories in younger men.[29,36] However, in the latter study, positive associations were observed only when PSA trajectories were examined and not when only one PSA measurement was used (% with PSA ≥0.7 ng/mL = 38.3 for chlamydia, 39.6 for gonorrhea, and 31.7 for NCNGU vs 37.1 for controls without these infections; $P = 0.772$, 0.639, and 0.659, respectively[29]). This latter finding is more in line with our findings and suggests that smaller long-term changes may require

TABLE 1 Demographic, military, and infection history characteristics of young male US military members by *Trichomonas Vaginalis* serostatus, 2004-2006

	Trichomonas vaginalis serostatus score				
	0 (n = 193)	1 (n = 341)	≥2 (n = 198)	*P* value[a]	*P* value[b]
Mean age, y	33.5	33.5	33.6	.81	.70
Race (%)					
African American	40.4	51.6	57.1	.003	.001
Caucasian	59.6	48.4	42.9		
Marital status (%)					
Married	77.2	84.5	86.4	.035	.019
Other	22.8	15.5	13.6		
Military grade (%)					
Enlisted	87.6	86.5	86.4	.93	.72
Officer	12.4	13.5	13.6		
Region of residence (%)					
Northeast	10.4	9.7	11.6	.89	.57
Midwest	16.6	15.0	16.2		
South	50.8	48.7	44.9		
West	9.3	9.7	8.6		
Unknown	12.9	17.0	18.7		
Reason for blood draw (%)					
General force	18.6	19.0	18.7	.27	.49
Physical exam	9.3	14.4	14.1		
Part of an STI visit	2.1	0.3	1.5		
Other/unknown	70.0	66.3	65.7		
History of (%)					
T. vaginalis infection[c]	1.0	0.6	1.0	.67	1.00
T. vaginalis infection or NCNGU[d]	3.1	4.1	3.0	.75	.96
Genital chlamydia[e]	5.2	5.6	6.6	.83	.56
Gonorrhea[f]	1.6	2.6	3.5	.45	.34
Infectious mononucleosis[g]	1.6	0.6	0.5	.50	.37
Urogenital infections and conditions[h]	34.7	27.3	30.8	.19	.41
Other STIs[i]	5.2	3.8	4.0	.75	.59
Any STI[j]	12.4	13.5	13.3	.94	.84
Any urogenital or systemic infection[k]	61.1	58.1	65.2	.27	.41

Abbreviations: NCNGU, nonchlamydial, nongonococcal urethritis; STI, sexually transmitted infection.
[a]Global *P* value.
[b]*P* value comparing serostatus 0 and ≥2.
[c]Defined by ICD-9-CM codes: 131.02, 131.09, and 131.9.
[d]Defined by ICD-9-CM codes: 131.02, 131.09, 131.9, 099.4, and 099.49.
[e]Defined by ICD-9-CM codes: 078.88, 099.3, 099.41, 099.50, 099.53, 099.54, and 099.55.
[f]Defined by ICD-9-CM codes: 098, 0980, 098.10, 098.11, 098.19, 098.2, and 098.89.
[g]Defined by ICD-9-CM code: 075.
[h]Defined by ICD-9-CM codes: 580.0 to 609.0. Includes urogenital infections that might contribute to prostate inflammation such as benign prostatitic hyperplasia (600.0), 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 Peyronie's disease (607.85).
[i]All STIs (ICD-9-CM codes: 054.10, 054.13, 054.19, and 090 to 099.9), except for genital chlamydia, gonorrhea, *T. vaginalis*, and NCNGU.
[j]All STIs (ICD-9-CM codes: 078.88, 054.10, 054.13, 054.19, and 090 to 099.9), except for *T. vaginalis*, and NCNGU.
[k]Includes all STIs (except for *T. vaginalis* and NCNGU), infectious mononucleosis, urogenital infections and conditions, and nongenitourinary, systemic infections such as infections 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).

longitudinal measurements rather than one cross-sectional measurement to detect as statistically significant. Finally, although our findings differ from previous positive cross-sectional findings for human herpesvirus type 8 serostatus with PSA in older men,[37,38] human herpesvirus type 8 is a chronic, lifelong infection that reactivates periodically across the life course, as opposed to an infection, such as *T. vaginalis* infection, that can be cleared or cured, which may explain its stronger influence on PSA.

Lastly, if we view our findings in the context of prostate disease development rather than prostate involvement, our nonsignificant findings are in line with those from a growing body of studies that observed null associations between *T. vaginalis* serostatus and

TABLE 2 PSA distribution by *Trichomonas vaginalis* serostatus among young US male military members, 2004-2006

	T. vaginalis serostatus score				
	0 (n = 193)	1 (n = 341)	≥2 (n = 198)	*P* value[a]	*P* value[b]
Unadjusted PSA concentration (ng/mL)					
Geometric mean	0.58	0.59	0.62	.52	.25
Mean	0.70	0.75	0.73	.43	.20
Median	0.55	0.59	0.63	.38	.17
Interquartile range	0.41-0.84	0.39-0.84	0.44-0.88		
Full PSA distribution (%)					
<0.29	10.4	12.9	9.1	.43	.23
0.30-0.49	32.1	25.5	23.2		
0.50-0.69	22.8	21.7	23.7		
0.70-0.89	14.0	18.5	20.2		
≥0.90	20.7	21.4	23.7		
≥0.70	34.7	39.9	43.9	.17	.06
Adjusted PSA concentration (ng/mL)[c]					
Geometric mean	0.58	0.58	0.61	.63	.21
% ≥0.70 ng/mL	33.2	38.8	42.5	.17	.13

Abbreviation: PSA, Prostate-specific antigen.
[a]Global *P* value.
[b]*P* value comparing serostatus 0 and ≥2.
[c]Adjusted for age, race, and marital status.

prostate cancer risk and aggressiveness in older men,[9,11-14] as well as those from one,[5] but not the other,[6] previous study of *T. vaginalis* serology and BPH. However, our findings are not consistent with the high prevalence of *T. vaginalis* DNA and antigens observed in prostate tissue from older men with BPH.[2,5]

5 | CONCLUSIONS

In conclusion, we observed some suggestion of a positive association between *T. vaginalis* seropositivity and greater PSA concentration. However, this association was not statistically significant. Possible explanations for these nonsignificant findings include difficulties studying prostate involvement during infection using a cross-sectional study design and detection of antibodies, which does not distinguish between current and past infections, rather than diagnosis of acute infection directly. Future studies may need to address this question by studying changes in PSA during acute infections detected by genitourinary specimen testing in populations at high risk for *T. vaginalis* and other acute genitourinary infections.

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 and coordinating PSA testing. Effort for the authors was funded by the National Cancer Institute (T32190194: MEL; P30 CA006973: AMD, WBI, WGN, and EAP), the Fund for Research and Progress in Urology, Johns Hopkins University School of Medicine (SS), and the Barnes-Jewish Hospital Foundation and Alvin J. Siteman Cancer Center (RP and SS). 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.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

ORCID

Marvin E. Langston http://orcid.org/0000-0002-4777-2425
John F. Alderete http://orcid.org/0000-0002-6741-9426
Remington L. Nevin http://orcid.org/0000-0002-0534-1889
Angelo M. De Marzo http://orcid.org/0000-0003-4847-5307
William B. Isaacs http://orcid.org/0000-0001-6599-6775
Elizabeth A. Platz http://orcid.org/0000-0003-3676-8954
Siobhan Sutcliffe http://orcid.org/0000-0002-4613-8107

REFERENCES

1. Sutcliffe SNC, Magnuson NS, Reeves R, Alderete JF. Trichomonosis, a common curable STI, and prostate carcinogenesis—a proposed molecular mechanism. *PLoS Pathog*. 2012;8(8):e1002801.
2. Mitteregger D, Aberle SW, Makristathis A, et al. High detection rate of *Trichomonas vaginalis* in benign hyperplastic prostatic tissue. *Med Microbiol Immunol*. 2012;201(1):113-116.
3. Kim JH, Kim SS, Han IH, Sim S, Ahn MH, Ryu JS. Proliferation of prostate stromal cell induced by benign prostatic hyperplasia epithelial cell stimulated with *Trichomonas vaginalis* via crosstalk with mast cell. *Prostate*. 2016;76(15):1431-1444.
4. Twu O, Dessi D, Vu A, et al. *Trichomonas vaginalis* homolog of macrophage migration inhibitory factor induces prostate cell growth,

invasiveness, and inflammatory responses. *Proc Natl Acad Sci USA*. 2014;111(22):8179-8184.
5. Iqbal J, Al-Rashed J, Kehinde EO. Detection of *Trichomonas vaginalis* in prostate tissue and serostatus in patients with asymptomatic benign prostatic hyperplasia. *BMC Infect Dis*. 2016;16(1):506.
6. Breyer BN, Huang WY, Rabkin CS, et al. Sexually transmitted infections, benign prostatic hyperplasia and lower urinary tract symptom-related outcomes: results from the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. *BJU Int*. 2016;117(1):145-154.
7. Sutcliffe S, Giovannucci E, Alderete JF, et al. Plasma antibodies against *Trichomonas vaginalis* and subsequent risk of prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2006;15(5):939-945.
8. Stark JR, Judson G, Alderete JF, et al. Prospective study of *Trichomonas vaginalis* infection and prostate cancer incidence and mortality: Physicians' Health Study. *J Natl Cancer Inst*. 2009;101(20):1406-1411.
9. Sutcliffe S, Alderete JF, Till C, et al. Trichomonosis and subsequent risk of prostate cancer in the Prostate Cancer Prevention Trial. *Int J Cancer*. 2009;124(9):2082-2087.
10. Shui IM, Kolb S, Hanson C, Sutcliffe S, Rider JR, Stanford JL. *Trichomonas vaginalis* infection and risk of advanced prostate cancer. *Prostate*. 2016;76(7):620-623.
11. Fowke JH, Han X, Alderete JF, Moses KA, Signorello LB, Blot WJ. A prospective study of *Trichomonas vaginalis* and prostate cancer risk among African American men. *BMC Res Notes*. 2016;9:224.
12. Vicier C, Werner L, Chipman J, et al. Elevated serum cytokines and *Trichomonas vaginalis* serology at diagnosis are not associated with higher Gleason grade or lethal prostate cancer. *Clin Genitourin Cancer*. 2019;17(1):32-37.
13. Tsang SH, Peisch SF, Rowan B, et al. Association between *Trichomonas vaginalis* and prostate cancer mortality. *Int J Cancer*. 2019;144(10):2377-2380.
14. Marous M, Huang WY, 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.
15. Weston T, Nicol C. Natural history of trichomonal infection in males. *Br J Vener Dis*. 1963;39(4):251-257.
16. Allison GG. Triehomoniasis in the male. A seventh venereal disease? *South Med J*. 1943;36(12):821-823.
17. Whittington MJ. The incidence of *Trichomonas vaginalis* in a sample of the general population: with some observations on its relation to the use of chemical contraceptives. *J Obstet Gynaecol Br Emp*. 1951;58(3):398-405.
18. Gardner WA Jr., Culberson DE, Bennett BD. *Trichomonas vaginalis* in the prostate gland. *Arch Pathol Lab Med*. 1986;110(5):430-432.
19. Sena AC, Miller WC, Hobbs MM, et al. *Trichomonas vaginalis* infection in male sexual partners: implications for diagnosis, treatment, and prevention. *Clin Infect Dis*. 2007;44(1):13-22.
20. 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.
21. Sutcliffe S, Nevin RL, Pakpahan R, et al. Prostate involvement during sexually transmitted infections as measured by prostate-specific antigen concentration. *Br J Cancer*. 2011;105(5):602-605.
22. Daugherty M, Glynn K, Byler T. Prevalence of *Trichomonas vaginalis* infection among US males, 2013-2016. *Clin Infect Dis*. 2019;68(3):460-465.
23. 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.
24. Kuller LH, Thomas A, Grandits G, Neaton JD. Multiple Risk Factor Intervention Trial Research Group. Elevated prostate-specific antigen levels up to 25 years prior to death from prostate cancer. *Cancer Epidemiol Biomarkers Prev*. 2004;13(3):373-377.
25. 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.
26. 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.
27. Silverberg MJ, Brundage JF, Rubertone MV. Timing and completeness of routine testing for antibodies to human immunodeficiency virus type 1 among active duty members of the U.S. Armed Forces. *Mil Med*. 2003;168(2):160-164.
28. Sutcliffe S, Pakpahan R, Sokoll LJ, et al. Prostate-specific antigen concentration in young men: new estimates and review of the literature. *BJU Int*. 2012;110(11):1627-1635.
29. Langston ME, Pakpahan R, Nevin RL, et al. Sustained influence of infections on prostate-specific antigen concentration: an analysis of changes over 10 years of follow-up. *Prostate*. 2018;78(13):1024-1034.
30. 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;138(9):2221-2230.
31. Horner PJ, Blee K, Falk L, van der Meijden W, Moi H. 2016 European guideline on the management of non-gonococcal urethritis. *Int J STD AIDS*. 2016;27(11):928-937.
32. Neace CJ, Alderete JF. Epitopes of the highly immunogenic *Trichomonas vaginalis* α-actinin are serodiagnostic targets for both women and men. *J Clin Microbiol*. 2013;51(8):2483-2490.
33. Ulmert D, Becker C, Nilsson JA, et al. Reproducibility and accuracy of measurements of free and total prostate-specific antigen in serum vs plasma after long-term storage at −20°C. *Clin Chem*. 2006;52(2):235-239.
34. 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.
35. 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;2:19.
36. Oliver JC, Oliver RTD, 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.
37. 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.
38. 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;6:25.

How to cite this article: Langston ME, Bhalla A, Alderete JF, et al. *Trichomonas vaginalis* infection and prostate-specific antigen concentration: Insights into prostate involvement and prostate disease risk. *The Prostate*. 2019;79:1622-1628. https://doi.org/10.1002/pros.23886