Published in final edited form as:

Int J Cancer. 2019 May 15; 144(10): 2377–2380. doi:10.1002/ijc.31885.

Association between *Trichomonas vaginalis* and prostate cancer mortality

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Abstract

We previously observed a positive association between seropositivity for the parasite *Trichomonas vaginalis* and risk of clinically significant prostate cancer at diagnosis. Here, we examined whether *T. vaginalis* seropositivity was associated with increased prostate cancer-specific or all-cause mortality among prostate cancer patients.

We studied 749 men with prostate cancer from the Physicians' Health Study (PHS) and 736 men with prostate cancer from the Health Professionals Follow-Up Study (HPFS). We used Cox proportional hazard models to estimate multivariable hazard ratios (HRs) and 95% confidence intervals (CIs) of the association between *T. vaginalis* serostatus and progression to death from prostate cancer and from all causes.

In PHS, 423 men died of any cause during a median follow-up of 13.8 years from the date of cancer diagnosis, among whom 131 died of prostate cancer. In HPFS, there were 287 deaths, including 77 deaths from prostate cancer, during a median follow-up of 12.8 years. We found no association between *T. vaginalis* serostatus and either prostate cancer mortality or all-cause mortality in either the PHS or HPFS.

While previous studies suggest a possible role for *T. vaginalis* in the development of clinically significant prostate cancer, our findings do not support the hypothesis that *T. vaginalis* serostatus is associated with mortality among prostate cancer patients.

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Disclosure of Potential Conflicts of Interest:

No potential conflicts of interest were disclosed.

Keywords

Trichomonas vaginalis; sexually transmitted infections; prostate cancer; epidemiology

Introduction

Trichomonas vaginalis is a common parasitic sexually transmitted infection. Untreated *T. vaginalis* can ascend the urethra to the prostate, resulting in a chronic, persistent prostatic infection suggested to play a role in the development and progression of prostate cancer.^{1,2} Six epidemiological studies have investigated the association between *T. vaginalis* and prostate cancer risk.^{1–6} While results for localized stage disease have been largely null, several studies have observed a positive association with risk of clinically significant disease^{1,2} although more recent findings have been mixed.⁴ While previous studies have investigated the association between *T. vaginalis* and prostate cancer risk, no study has assessed how *T. vaginalis* influences prognosis. Here, we examined whether *T. vaginalis* seropositivity was associated with increased prostate cancer-specific or all-cause mortality among prostate cancer patients from the Physicians' Health Study (PHS) and Health Professionals Follow-Up Study (HPFS).

Materials and Methods

This study leveraged existing data on prediagnosis *T. vaginalis* seropositivity status measured in prior nested case-control studies in PHS² and HPFS¹. In both cohorts, men provided blood specimens prior to cancer diagnosis: in 1993–1994 (HPFS) and prior to randomization in 1982 (PHS). *T. vaginalis* serostatus was determined by the presence of IgG antibodies against purified, recombinant *T. vaginalis* α -actinin using ELISA.⁷ An absorbance value cut-off was used to identify samples positive for *T. vaginalis* antibody. For PHS, the cut point was determined based on a control panel consisting of pooled plasma from known seronegative and seropositive patients.² For HPFS, the cut point was based on expert opinion, and seropositive and seronegative samples were included in each experiment.¹ Of note, seroprevalences are not directly comparable between the two studies since they applied different cut-off methods. However, in a sensitivity analysis, applying the same absorbance cut point to both studies did not alter our conclusions (data not shown). *T. vaginalis* seropositivity status was available for 673 PHS participants selected as prostate cancer cases in Stark *et al.*² and for 691 HPFS participants selected as prostate cancer cases in Sutcliffe *et al.*¹ We included additional prostate cancer cases that were controls in the original case-control studies who went on to develop prostate cancer with additional follow-up after publication (58 in HPFS, 63 in PHS), resulting in a total of 736 prostate cancer cases in PHS and 749 prostate cancer cases in HPFS for the analysis. The studies were approved by institutional review boards at Harvard T.H. Chan School of Public Health and Partners Health Care.

Men were followed prospectively from date of cancer diagnosis to obtain information on their clinical course, including development of metastases. Deaths were ascertained through searches of the National Death Index. Cause of death was assigned by an Endpoints

Committee of physicians by review of medical records and death certificates. The primary outcomes were death from prostate cancer or any cause with follow-up through January 2012.

Multivariate-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using Cox proportional hazard regression models for PHS and HPFS separately. All models adjust for age at blood draw and time between blood draw and diagnosis. In multivariable models, we additionally adjusted for prostate-specific antigen (PSA) level at diagnosis, clinical Gleason grade, and clinical TNM stage. In additional models, we further adjusted for Caucasian race, family history, body mass index (BMI) at blood draw, and smoking status at blood draw. The proportional hazards assumption was met for all analyses. Data were analysed using R version 3.4.

Results

The study included 736 cases diagnosed between 1983–2012 in PHS and 749 cases diagnosed between 1994–2012 in HPFS. 179 (24%) and 94 (13%) cases were seropositive for *T. vaginalis* in PHS and HPFS respectively. Characteristics were similar comparing men positive and negative for *T. vaginalis* in both studies (Table 1). However, in PHS, seropositive cases had a higher percentage of clinical T4/N1/M1 stage disease compared to seronegative cases.

In PHS, 423 deaths occurred during a median follow-up of 13.8 years, including 131 deaths from prostate cancer. In HPFS, 287 deaths occurred during a median follow-up of 12.8 years, including 77 deaths from prostate cancer. Table 2 presents the age-adjusted and multivariate-adjusted HRs for prostate cancer-specific and all-cause mortality comparing men positive and negative for *T. vaginalis*. There was no association between *T. vaginalis* serostatus and prostate cancer mortality in either the PHS or HPFS cohorts. Similarly, we found no association with all-cause mortality.

Discussion

In this study of prostate cancer patients, we found no association between *T. vaginalis* serostatus and prostate cancer-specific or all-cause mortality. This is the first study to investigate the prognostic value of *T. vaginalis* among prostate cancer patients. The analysis leveraged two studies on incident prostate cancer, both of which supported positive associations with prostate cancer risk, especially for high-grade-prostate cancer (HPFS) and extraprostatic and metastatic/fatal prostate cancer (PHS).^{1–2} Other groups have investigated the association between *T. vaginalis* and prostate cancer incidence with mixed findings.^{3–6}

There are potential strengths and limitations to consider. Both cohorts have long and complete follow-up for cancer-specific and all-cause mortality. In addition, we could consider a range of demographic and clinical covariates as potential confounders. This study used serological detection to ascertain history of trichomonosis that better captures asymptomatic infection compared to self-reported measures. However, serology does not allow us to determine the timing, duration, or frequency of infection, which could potentially influence worse prostate cancer outcomes. This analysis does not distinguish between men

treated for infection and men not treated. It is possible that the influence of *T. vaginalis* on prostate cancer would differ across these groups. In addition, information on date of infection that led to seropositivity, presence and timing of antibody waning, and whether a man was infected after blood collection is unknown.

In summary, our data do not support the hypothesis that prostate cancer patients who are seropositive for *T. vaginalis* are at increased risk of overall or cancer-specific mortality.

Acknowledgements:

We are grateful to the participants of the Physicians' Health Study and Health Professionals Follow-up Study for their longstanding commitment and participation. We would also like to thank the research staff of the PHS and HPFS cohorts and Dr. John Alderete for help with *T. vaginalis* antibody testing.

Grant Support:

Harvard University Milton Fund (to L.A.M.), Dana-Farber/Harvard Cancer Center SPORE in Prostate Cancer (to L.A.M.), Prostate Cancer Foundation (to L.A.M.), and National Cancer Institute research grants CA055075, HL035464, U01CA167552 (Harvard), and P50CA58236 and P30CA006973 (Hopkins) from the NIH.

Abbreviations:

(PHS)	Physicians' Health Study
(HPFS)	Health Professionals Follow-Up Study
(HR)	hazard ratio
(CI)	confidence interval
(PSA)	prostate-specific antigen
(BMI)	body mass index

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Novelty and Impact:

Trichomonas vaginalis, a common parasitic sexually transmitted infection, can infect the prostate and elicit an inflammatory response that may play a role in the development and progression of prostate cancer. While previous studies have investigated the association between *T. vaginalis* and prostate cancer risk, no study has assessed how *T. vaginalis* influences prognosis. In this study of prostate cancer patients, we did not identify an association between *T. vaginalis* and prostate cancer-specific or all-cause mortality.

Clinical and descriptive characteristics of men with prostate cancer in the Physicians' Health Study and Health Professionals Follow-up Study by *T. vaginalis* serostatus.

Table 1.

	Physicians' Health Study		Health Professionals Follow-Up Study	
	<i>T. vaginalis</i> serostatus		<i>T. vaginalis</i> serostatus	
	Negative (n = 557)	Positive (n = 179)	Negative (n = 655)	Positive (n = 94)
Age at blood draw, years, mean (SD)	59.1 (8.5)	59.6 (8.8)	65.6 (7.3)	66.7 (7.2)
Caucasian race, n (%)	525 (94.3)	169 (94.4)	625 (95.4)	85 (90.4)
Family history of prostate cancer ^J	-	-	143 (21.8)	21 (22.3)
Height, inches, mean (SD)	70.3 (2.6)	70.5 (2.4)	70.2 (2.6)	69.7 (2.5)
BMI at blood draw, kg/m ² , mean (SD) ²	24.7 (2.5)	24.4 (2.1)	25.7 (3.4)	25.5 (2.8)
Smoking status at blood draw, n (%)				
Never	258 (46.3)	88 (49.2)	291 (44.4)	40 (42.6)
Past	243 (43.6)	77 (43.0)	313 (47.8)	40 (42.6)
Current	56 (10.1)	14 (7.8)	30 (4.6)	9 (9.6)
Unknown			21 (3.2)	5 (5.3)
Aspirin use 2+/3+ times/week at blood draw, n (%)	234 (42.0)	78 (43.6)	277 (42.3)	30 (31.9)
Age at diagnosis, years, mean (SD)	69.4 (7.8)	69.4 (7.8)	69.4 (7.5)	70.1 (6.8)
Time from blood draw to diagnosis, years, mean (SD)	10.2 (4.7)	9.8 (4.9)	3.8 (2.8)	3.4 (3.0)
PSA level at diagnosis, ng/ml, mean (SD) ²	18.6 (53.4)	28.6 (93.7)	10.7 (13.9)	9.6 (9.7)
Clinical Gleason grade				
2–6	303 (54.4)	101 (56.4)	394 (60.2)	54 (57.4)
7	109 (19.6)	32 (17.9)	143 (21.8)	18 (19.1)
8–10	66 (11.8)	16 (8.9)	54 (8.2)	8 (8.5)
Unknown	79 (14.2)	30 (16.8)	64 (9.8)	14 (14.9)
Clinical TNM stage				
T1/T2	425 (76.3)	127 (70.9)	589 (89.9)	81 (86.2)
T3	33 (5.9)	11 (6.1)	13 (2.0)	4 (4.3)
T4/N1/M1	32 (5.7)	22 (12.3)	15 (2.3)	3 (3.2)
Unknown	67 (12.0)	19 (10.6)	38 (5.8)	6 (6.4)

	Physicians' Health Study		Health Professionals Follow-Up Study	
	<i>T. vaginalis</i> serostatus		<i>T. vaginalis</i> serostatus	
	Negative (n = 557)	Positive (n = 179)	Negative (n = 655)	Positive (n = 94)
Died of prostate cancer, n (%)	96 (17.2)	35 (19.6)	68 (10.4)	9 (9.6)
Died of any cause, n (%)	323 (58.0)	100 (55.9)	250 (38.2)	37 (39.4)

¹ Family history not available in PHS

² 104 missing BMI at blood draw (HPFS), 308 missing PSA level at diagnosis (52 HPFS, 256 PHS)

Table 2.

Hazard ratios (HRs) and 95% confidence intervals (CIs) of the association between *T. vaginalis* serostatus and prostate cancer-specific and all-cause mortality among men with prostate cancer.

	Physicians' Health Study		Health Professionals Follow-up Study	
	<i>T. vaginalis</i> serostatus		<i>T. vaginalis</i> serostatus	
	Negative (n = 557)	Positive (n = 179)	Negative (n = 655)	Positive (n = 94)
Prostate cancer mortality				
Number of events	96	35	68	9
Age-adjusted HR (95% CI) ¹	1.00 (ref)	1.01 (0.69, 1.49)	1.00 (ref)	0.86 (0.43, 1.73)
Multivariable 1 HR (95% CI) ²	1.00 (ref)	0.84 (0.56, 1.26)	1.00 (ref)	0.85 (0.41, 1.73)
Multivariable 2 HR (95% CI) ^{3,4}	1.00 (ref)	0.85 (0.57, 1.29)	1.00 (ref)	0.87 (0.42, 1.80)
All-cause mortality				
Number of events	323	100	250	37
Age-adjusted HR (95% CI) ¹	1.00 (ref)	0.88 (0.70, 1.10)	1.00 (ref)	0.99 (0.70, 1.40)
Multivariable 1 HR (95% CI) ²	1.00 (ref)	0.80 (0.64, 1.01)	1.00 (ref)	1.01 (0.71, 1.43)
Multivariable 2 HR (95% CI) ^{3,4}	1.00 (ref)	0.79 (0.63, 1.00)	1.00 (ref)	0.99 (0.69, 1.42)

¹The age-adjusted model adjusts for age at blood draw (continuous) and time between blood draw and diagnosis (continuous)

²The multivariable 1 model additionally adjusts for PSA level at diagnosis (categorical: <4, 4 to <10, 10 to <20, 20+, unknown), clinical Gleason grade (categorical: 2-6, 7, 8-10, unknown), and clinical TNM stage (categorical: T1/T2, T3, T4/N1/M1, unknown)

³The multivariable 2 model additionally adjusts for BMI at blood draw (categorical: <25, 25 to <27.5, 27.5+, unknown), smoking status (categorical: never, past, current, unknown), family history (categorical: yes, no), and Caucasian race (categorical: yes, no)

⁴Family history not included in PHS model