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IMMUNOLOGY AND HOST-PARASITE INTERACTIONS - ORIGINAL PAPER

Trichomonas vaginalis serostatus and prostate cancer risk in Egypt: a case-control study

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Abstract

Trichomonas vaginalis is one of the most common non-viral sexually transmitted infections (STIs) that has been associated with prostate cancer in some countries. This study aims to investigate if *T. vaginalis* infection can be a risk factor for prostate cancer in Egypt and its possible relationship with cancer prognostic factors and overall survival. Serum samples were collected from a total of 445 age-matched males; 126 with prostate cancer, 108 with bladder cancer, 91 with different types of cancers, and 120 healthy controls, and then analyzed by ELISA for detection of anti-*Trichomonas* IgG and prostate-specific antigen (PSA). The results revealed that only 8.3% of controls were seropositive for trichomoniasis, compared with 19% of prostate cancer patients ($P = 0.015$). There were positive associations between the levels of PSA and tumor stage with *T. vaginalis* IgG optical density scores among the seropositive cases ($P < 0.001$ and < 0.05, respectively). However, no significant correlations were detected between seropositivity of *T. vaginalis* and other prognostic factors or overall survival in those patients. In conclusion, chronic *T. vaginalis* infection may be associated with prostate cancer, but it does not seem that this STI aggravates the cancer status.

Keywords *Trichomonas vaginalis* · Prostate cancer · ELISA · Anti-*Trichomonas* IgG · Prostate specific antigen

Introduction

Trichomonas vaginalis is a sexually transmitted protozoan that colonizes the epithelium of human urogenital organs. Based on the World Health Organization (WHO) estimates from 2008 to 2016 (WHO 2012), trichomoniasis is considered the most prevalent non-viral sexually transmitted disease (STD) worldwide, affecting more than 276 million people every year (Leitsch 2016). In women, infection can persist for many years, with higher ratio of cases manifested by pruritus, vaginitis, and odorous vaginal discharge (Iqbal et al. 2016). In men, 50–75% of cases of trichomoniasis are asymptomatic and may not seek any treatment, while symptomatic subjects present with mild urethritis that is cleared by the host immune system within 3 weeks (Kissinger 2015; Leitsch 2016).

In long-term asymptomatic infections in men, *T. vaginalis* parasite can ascend the urethra to the prostate and infect prostatic epithelium (Seo et al. 2014). The parasite is generally an extracellular organism, but its presence in endo-epithelial cells and in sub-epithelial tissues suggests that it has the ability to invade cells and tissues (Gardner et al. 1986; Lopez et al. 2000; Iqbal et al. 2016). It is worth mentioning that *T. vaginalis* provokes an inflammatory response in prostate epithelial cells and secretes macrophage inhibitory factor that increases prostate cell proliferation. Thus, persistent infection in the prostate may result in a tumor promoting pro-inflammatory microenvironment (Twu et al. 2014).

Interestingly, *T. vaginalis* has been recognized as a major cause of chronic prostatitis and its sequelae as benign prostatic hyperplasia and prostate cancer (Iqbal et al. 2016; Kim et al. 2019). Despite that several researches reported a positive correlation between trichomoniasis and prostate cancer (Sutcliffe

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et al. 2006; Stark et al. 2009; Kim et al. 2019), others denied such association (Sutcliffe et al. 2009; Groom et al. 2012; Fowke et al. 2016). In Egypt, a former study detected *T. vaginalis* in 28.8% of male patients with urethral discharge and in 8.2% of those suffering from impotence and infertility (el Seoud et al. 1998). However, no previous study assessed the relationship between *T. vaginalis* infection and prostate cancer risk among Egyptians, which necessitates paying more efforts in exploring such link and filling the current gap induced by the conflicting results from other countries. Hence, this study is conducted to clarify whether there is an association between trichomoniasis vaginalis seropositivity and prostate cancer incidence in our locality. Also, this study aims to detect any correlation between different prognostic factors [tumor stage, nodal stage, metastasis status, Gleason score used for grading prostate cancer, and prostate specific antigen (PSA)] and overall survival (time from diagnosis to death or last follow-up) for prostate cancer patients in relationship to *T. vaginalis* seropositivity.

Subjects, materials, and methods

Ethical consideration

The current study was approved by the Institutional Review Board (IRB No. R.18.03.96) and performed following the ethical standards of the Helsinki declaration. An informed written consent was obtained from each participant after explaining the purpose and procedures of this study. The enrollment of human cases and use of their data and samples in the study were in compliance with the guidance of the Institutional Committee of Research Ethics, Faculty of Medicine, Mansoura University, Egypt.

Study population and design

A case-control study has been conducted on male patients referred to the Department of Clinical Oncology and Nuclear Medicine, Mansoura University Hospital, Egypt, between November 2017 and February 2019. A total of 325 patients aged 40–75 years; 126 with pathologically confirmed prostate cancer adenocarcinoma (all stages and grades whatever the treatment options, such as surgery, radiotherapy, hormonal or chemotherapy), 108 with bladder cancer, and 91 with different types of cancers other than urogenital neoplasms (head and neck cancer, $n = 35$; colorectal cancer, $n = 28$; pancreas cancer, $n = 14$; esophagus cancer, $n = 14$) were recruited in the study. In addition, 120 age-matched males from the attendants of Mansoura University Hospital outpatient clinics with no history of cancer were enrolled as a negative control group.

Cases with history of recent or past urinary tract or genital tract complaints or treatment for STDs were excluded from the study (considering the fact that trichomoniasis in male is usually asymptomatic, while genitourinary complaints are usually related to bacterial and viral infections).

Intervention

Full medical sheets were taken from all cases. The following data were reviewed: age, demographics, lifestyle, history of smoking, medical history, and diagnosis. For prostate cancer patients, data concerning the disease details (tumor stage, nodal stage, metastasis status, Gleason score, and PSA level) and overall survival were collected.

Blood samples were collected from all cancer patients and normal controls. Sera were separated and kept at − 80 °C in accordance with safety regulations until used (Campbell et al. 2008). *T. vaginalis* serostatus was examined by detection of anti-*Trichomonas* IgG antibody. Also, PSA was measured in all enrolled individuals. For prostate cancer patients, PSA levels were reported at time of initial diagnosis and follow-up, but we only considered its level before any therapeutic intervention. In all other enrolled participants, level of PSA was measured to exclude undiagnosed or secondary prostate malignancy and to confirm cancer-free status of the control subjects.

Assessment of *Trichomonas vaginalis* IgG antibody

Human *T. vaginalis* IgG antibody was detected in serum using ELISA kits (SinoGeneClon Biotech, HangZhou, China, Catalog number: SG-16001). The kits use purified antigen to coat microtiter plate wells to make solid phase antigen, then *T. vaginalis* antibody was added to wells. If antibody is present in sample, it will combine first with the coated antigen then with another antigen labeled with horseradish peroxidase (HRP) to make sandwich ELISA. Briefly, 10 μl of serum (brought to room temperature) was mixed with 40 μl of sample diluent, added to the designated wells and incubated for 30 min at 37 °C, then washed. A total of 50 μl of the supplied HRP-conjugate reagent was added to wells (except the blank) and incubated for 30 min at 37 °C. According to manufacturer's instructions, TMB substrate solution was then added after washing of ELISA plates to give blue color, then the reaction was terminated by addition of sulfuric acid solution, and the absorbance value of the obtained color was measured spectrophotometrically at a wavelength of 450 nm. All samples and controls were tested randomly and blindly in duplicate, then their mean optical density (OD) readings were calculated.

The calculated mean OD of negative control samples was 0.23. According to manufacturer's instructions, the cutoff value of the test was determined: 0.23 + 0.15 = 0.38, samples with OD < 0.38 were considered negative, and those with OD ≥ 0.38 were considered positive.

To ensure quality of the used kit, the OD of the included positive control sample was measured and serial dilutions (50%, 25%, 12.5%, and 6.3%) of this sample were prepared using the provided sample diluent.

The OD values of the positive and negative controls and the cutoff value of the test were all used to provide a scoring system for *Trichomonas* IgG serostatus. Score 0: samples with OD < negative control OD; score 1: samples with OD > negative control but < cutoff; score 2: samples with OD > cutoff and < 12.5% diluted positive sample; score 3: samples with OD between 12.5 and 25% diluted positive samples; score 4: samples with OD between 25 and 50% diluted positive samples; score 5: samples with OD > 50% diluted positive sample.

Assessment of prostate-specific antigen

The level of PSA in serum was assessed using enzyme immunoassay test kit (Chemux Bioscience, San Francisco, USA, Catalog number: 10109). The test used is a solid phase two-site immunoassay. Following manufacturer's instructions, rabbit anti-PSA was coated on the surface of the microtiter plate wells and the other anti-PSA monoclonal antibody labeled with HRP was used as the tracer. A total of 50 μl of the tested serum, standards, and controls were added to the designated wells and incubated with 100 μl of the zero buffer at room temperature for 60 min. Then, PSA molecules found in the standard solution or serum were sandwiched between the two used antibodies. After formation of the antibody-antigen-antibody-enzyme complex, the unbound tracers were removed by plate washing. The HRP activity bound in the wells was then assayed by a colorimetric reaction using a microtiter plate reader at 450 nm within 15 min, and the intensity of color formed was proportional to the concentration of PSA in the sample assayed. All samples, standards, and controls were tested blindly, in duplicate, then their mean ODs were calculated. By using the mean ODs of all reference standards, a standard curve was plotted and the PSA value (ng/ml) of each sample was determined using its mean OD.

Statistical analysis

Data were entered and statistically analyzed using the Statistical Package for Social Sciences (SPSS) version 16. Qualitative data were described as numbers and percentages. The Chi-square test and the Monte Carlo test were used for comparison between groups, as appropriate. Quantitative data were described as mean ± SD or median, as appropriate, and they were tested for normality by Kolmogorov-Smirnov test. In the normally distributed variables, one-way ANOVA with LSD post hoc multiple comparisons was used for comparison between groups. In the non-normally distributed variables, Kruskal-Wallis test was used for comparison between groups.

Overall survival of prostate cancer patients was studied using Kaplan-Meier survival analysis, and Log-rank test was used to compare survival distribution across groups. Correlation between two continuous variables was performed using Pearson's correlation, while non-parametric correlations were conducted using Spearman's rank correlation. Odds ratio and their 95% confidence interval (CI) were calculated. *P* values ≤ 0.05 were considered statistically significant.

Results

In a trial to clarify the relationship between *T. vaginalis* infection and prostate cancer among Egyptians, the current study included a total of 325 male cancer patients; 126 with prostate cancer (mean age = 64 ± 6.9 years), 108 with bladder cancer (mean age = 65.2 ± 8.1 years), and 91 with other types of cancers (mean age = 64.1 ± 6.1 years). Additionally, 120 age-matched normal males were included as a control group (mean age = 64 ± 3.2 years). All demographic and life-style data of the study participants are depicted in Table 1.

Depending on *T. vaginalis*-IgG OD scores for case classification, 81% (102/120) of prostate cancer patients were seronegative (score 1), while the 19% (26/120) seropositive subjects were distributed among scores 2–5 (7.1%, 7.1%, 2.4%, and 2.4%, respectively). For bladder cancer group, 88.9% of patients (96/108) were seronegative and 11.1% (12/108) were seropositive; score 2. In the group of other types of cancer, 76.9% (70/91) were seronegative, while 23.1% (21/91) of patients were seropositive; designated to scores 2 and 3 (7.7% and 15.4%, respectively). Concerning the control group, 91.7% of cases (110/120) were seronegative and 8.3% (10/120) were seropositive (score 2), with statistically significant differences compared to prostate cancer group and other types of cancer group ($P = 0.001$, $P < 0.0001$, respectively), as described in Table 2.

Further in-depth analysis showed significant differences in the seroprevalence of trichomoniasis in prostate cancer group and the group of other types of cancer compared to the normal controls ($P = 0.015$ and 0.003, respectively). However, there was no significant difference in *T. vaginalis* seropositivity in prostate cancer group vs. bladder cancer group ($P = 0.09$) or other cancers group ($P = 0.47$), as shown in Table 3.

The characteristics of prostate cancer patients were detailed in Table 4. No significant relationships between *T. vaginalis* seropositivity rates and tumour stage, nodal status, presence of metastasis, or Gleason score were detected. However, *T. vaginalis*-IgG OD scores among trichomoniasis-seropositive prostate cancer patients ($n = 24$) showed significant associations with PSA level and tumour stage ($P < 0.0001$ and $P = 0.02$, respectively), as shown in Table 5.

Table 1 Characteristics of the study participants

Characteristics	Prostate cancer (n = 126)	Bladder cancer (n = 108)	Other cancers[a] (n = 91)	Normal (n = 120)	Test of significance
Age in years					
Mean ± SD	64.9 ± 6.9	65.2 ± 8.1	64.1 ± 6.1	64 ± 3.2	ANOVA; $F = 0.9$; $P = 0.5$
Range	47–79	52–82	57–78	58–69	
Residence					
Rural	56 (44.4)	75 (69.4)	28 (30.8)	35 (29.2)	$\chi^2 = 46.5$; $P < 0.0001$*
Urban	70 (55.6)	33 (30.6)	63 (69.2)	85 (70.8)	
Occupation					
Farmer	42 (33.3)	63 (58.3)	21 (23.1)	0 (0)	$\chi^2 = 156.4$; $P < 0.0001$*
Hand work	48 (38.1)	26 (24.1)	49 (53.8)	80 (66.7)	
Employer	15 (11.9)	6 (5.6)	21 (23.1)	40 (33.3)	
High official work	21 (16.7)	13 (12)	0 (0)	0 (0)	
Education					
Non-educated	67 (53.2)	58 (53.7)	35 (38.5)	80 (66.7)	$\chi^2 = 34.6$; $P < 0.0001$*
Low education	38 (30.2)	38 (35.2)	35 (38.5)	40 (33.3)	
High education	21 (16.7)	12 (11.1)	21 (23.1)	0 (0)	
Smoking					
Non-smoker	56 (44.4)	52 (48.1)	43 (47.3)	55 (45.8)	$\chi^2 = 7.86$; $P = 0.79$
Ex-smoker	46 (36.5)	36 (33.4)	29 (31.9)	38 (31.7)	
Current smoker	24 (19.1)	20 (18.5)	19 (20.9)	27 (22.5)	
Supplementary drugs					
No intake	58 (46.0)	66 (61.1)	63 (69.2)	55 (45.8)	Monte Carlo test; $P < 0.0001$*
Vitamins	26 (20.6)	18 (16.7)	21 (23.1)	45 (37.5)	
Calcium	42 (33.3)	18 (16.7)	7 (7.7)	20 (16.7)	
Vitamins + calcium	0 (0)	6 (5.6)	0 (0)	0 (0)	
Aspirin					
No intake	61 (48.4)	90 (83.3)	49 (53.8)	40 (33.3)	Monte Carlo test; $P < 0.0001$*
Infrequent	59 (46.8)	12 (11.1)	35 (38.5)	80 (66.7)	
Moderate	6 (4.8)	6 (5.6)	7 (7.7)	0 (0)	
Physical activity					
Light	19 (15.1)	18 (16.7)	14 (15.4)	40 (33.3)	$\chi^2 = 33.3$; $P < 0.0001$*
Moderate	74 (58.7)	54 (50.0)	35 (38.5)	35 (29.2)	
Very active	33 (26.2)	36 (33.3)	42 (46.2)	45 (37.5)	
No. of female partner	1 (0–3)	1 (0–2)	1 (0–1)	1 (0–1)	Kruskal-Wallis test; $P = 0.2$
No. of offspring	5 (0–9)	4 (1–7)	4 (0–6)	3 (2–4)	Kruskal-Wallis test; $P < 0.0001$*
Frequency of sexual activity/week	1 (0–3)	1 (0.5–2)	1 (0–2)	1 (0–1)	Kruskal-Wallis test; $P < 0.0001$*
Medical problems					
No	78 (61.9)	66 (61.1)	56 (61.5)	71 (59.2)	$\chi^2 = 3.36$; $P = 0.95$
Hypertension	25 (19.8)	22 (20.4)	14 (15.4)	24 (20)	
Diabetes	11 (8.7)	9 (8.3)	8 (8.8)	14 (11.7)	
Hypertension + diabetes	12 (9.5)	11 (10.2)	13 (14.3)	11 (9.2)	
Family history of cancers	9 (7.1)	12 (11.1)	0 (0)	0 (0)	Monte Carlo test; $P < 0.0001$*
Prostatic tests[b]					
Non	110 (87.3)	90 (83.3)	84 (92.3)	120 (100)	Monte Carlo test; $P < 0.0001$*
DRE	13 (10.3)	0 (0)	7 (7.7)	0 (0)	
Biopsy	3 (2.4)	18 (16.7)	0 (0)	0 (0)	

All values are presented as number (percentages), except for age; mean ± SD and range, and number of female partner and offspring as well as frequency of sexual activity; median (min-max)

n, number of examined cases; *DRE*, digital rectal examination

*$P \leq 0.05$

[a] Other cancers are head and neck cancer (n = 35), colorectal cancer (n = 28), pancreas cancer (n = 14), and esophagus cancer (n = 14)

[b] From history before diagnosis of prostate cancer

Analysis of the overall survival of prostate cancer patients showed a mean duration of 53.6 ± 2.0 months; about 54.6 ± 4.5 and 53.4 ± 2.3 months for seropositive and seronegative patients, respectively, with no statistically significant difference ($P = 0.86$) (Fig. 1).

Discussion

Despite the worldwide distribution of *T. vaginalis* infection, its prevalence is thought to be underestimated, mostly because of asymptomatic presentation in many populations. Some

Table 2 *Trichomonas vaginalis*-IgG optical density score distribution among the study participants

Trichomonas IgG OD scores	Prostate cancer No. (%)	Bladder cancer No. (%)	Other cancers No. (%)	Normal No. (%)	Test of significance
1	102 (81)	96 (88.9)	70 (76.9)	110 (91.7)	Monte Carlo test; $P < 0.0001$*;
2	9 (7.1)	12 (11.1)	7 (7.7)	10 (8.3)	$P_1 = 0.001$*; $P_2 = 0.48$; $P_3 < 0.0001$*
3	9 (7.1)	0 (0)	14 (15.4)	0 (0)	
4	3 (2.4)	0 (0)	0 (0)	0 (0)	
5	3 (2.4)	0 (0)	0 (0)	0 (0)	

Trichomonas-positive cases: scores ≥ 2. *Trichomonas*-negative cases: scores < 2

OD, optical density; P_1, significant difference between prostate cancer and normal control; P_2, non-significant difference between bladder cancer and normal control; P_3, significant difference between other cancers and normal control

*$P \leq 0.05$

previous studies have linked trichomoniasis with increased risk of human immunodeficiency virus (HIV) (McClelland et al. 2007), cervical cancer, and prostate cancer as well as advanced and metastatic prostate cancer (Zhang and Begg 1994; Stark et al. 2009). In fact, trichomoniasis is a curable disease; however, it may indirectly be a life-threatening malady.

Epidemiologic studies demonstrated conflicting results concerning association of *T. vaginalis* and prostate cancer risk among different populations (Table 6). In the current study, statistically higher *T. vaginalis* seropositivity rates were recorded in prostate cancer patients compared to normal controls (19% vs. 8.3%, $P < 0.05$), raising the possibility of an association between trichomoniasis and prostate cancer. Our findings corroborate with the Health Professionals Follow-up Study in America (Sutcliffe et al. 2006), the local cross-sectional study in Radiation and Nuclear Medicine Hospital, and Teaching Hospitals in Iraq (Al-Mayah et al. 2013), and the local study on males with prostate tumors in Korea (Kim et al. 2019), which recorded higher seropositivity for trichomoniasis among men with prostatic cancers. However, the current results differ from the Prostate Cancer Prevention Trial (PCPT) study conducted on Caucasian men (Sutcliffe et al. 2009), the Southern Community Cohort Study (SCCS) on African American men (Fowke et al. 2016), and the PLCO (prostate, lung, colorectal, and ovarian) Cancer Screening Trial on Caucasian and African American men (Marous et al. 2017), which did not support any association between *T. vaginalis* infection and prostate cancer. The discrepancy between results may be due to studying different population (varied races, ethnicities, and genetic characteristics) from various localities and in turn the possibility of different infecting *T. vaginalis* genotype strains and subsequent pathology. Moreover, differences in study design, number and demographics of the enrolled participants, methods evaluating *T. vaginalis* seropositive status as well as the diagnostic procedures for prostate cancer cannot be ruled out.

The association of *T. vaginalis* infection and prostatic cancer has been proposed for several reasons, including parasite's known prostatic tropism, its ability to elicit inflammation and damage in prostate epithelium, identification near foci of inflammation and hyperplastic prostate lesions, and its tendency to cause chronic and subclinical infections (Sutcliffe et al. 2009). *T. vaginalis* has also been shown to produce large

Table 3 *Trichomonas vaginalis* serostatus in the recruited cancer groups and normal controls

Groups	*Tv* positive cases (scores ≥ 2) No. (%)	*Tv* negative cases (scores < 2) No. (%)	Test of significance	OR (95% confidence interval)
Normal controls ($n = 120$)	10 (8.3)	110 (91.7)		
Prostate cancer ($n = 126$)	24 (19)	102 (81)	$P_1 = 0.015$*	2.6 (1.2–5.7)
Bladder cancer ($n = 108$)	12 (11.1)	96 (88.9)	$P_2 = 0.48$	1.4 (0.6–3.3)
Other cancers ($n = 91$)	21 (23.1)	70 (76.9)	$P_3 = 0.003$*	3.3 (1.5–7.4)
Test of significance	$\chi^2 = 11.7$, $P = 0.008$*			

Prostate cancer vs. bladder cancer: $\chi^2 = 2.8$, $P = 0.09$. Prostate cancer vs. other cancer: $\chi^2 = 0.5$, $P = 0.47$. Bladder cancer vs. other cancer: $\chi^2 = 5.1$, $P = 0.024$

Tv: *Trichomonas vaginalis*; P_1, prostate cancer vs. normal control [$P = 0.015$; 95% CI, 2.6 (1.2–5.7)]; P_2, bladder cancer vs. normal control [$P = 0.48$; 95% CI, 1.4 (0.6–3.3)]; P_3, other cancers vs. normal control [$P = 0.003$, 95% CI, 3.3 (1.5–7.4)]; *OR*, odds ratio

*$P \leq 0.05$

Table 4 Disease characteristics of prostate cancer patients in relationship to *Trichomonas vaginalis* serostatus

Items	*Tv* positive cases (n = 24) No. (%)	*Tv* negative cases (n = 102) No. (%)	Test of significance
Tumor (T)			
T1–2	5 (11.4)	39 (88.6)	$\chi^2 = 2.6$, $P = 0.11$
T3–4	19 (23.2)	63 (76.8)	
Nodal status (N)			
No	17 (22.1)	60 (77.9)	$\chi^2 = 1.2$, $P = 0.3$
Yes	7 (14.3)	42 (85.7)	
Metastasis (M)			
No	10 (20.4)	39 (79.6)	$\chi^2 = 0.1$, $P = 0.6$
Yes	14 (18.2)	63 (81.8)	
Gleason score			
High risk (> 7)	6 (15.8)	32 (84.2)	$\chi^2 = 0.4$, $P = 0.5$
Low risk (≤ 7)	18 (20.5)	70 (79.5)	

n, number of examined cases; *Tv*, *Trichomonas vaginalis*

amounts of polyamines (Sutcliffe 2010) and up regulate expression of anti-apoptotic and other proto-oncogenes that have been linked to prostate cancer (Sutcliffe et al. 2012), and to increase the growth and invasiveness of benign and malignant prostate cells (Han et al. 2016; Zhu et al. 2016). A recent in vitro study declared that prostate epithelial cells stimulated by *T. vaginalis* produce cytokines such as IL-6, CCL2, and CXCL8, some of which stimulate the migration of THP-1 monocytes, and M2 polarization of macrophages which in turn promote proliferation of prostate cancer cells. Therefore, they suggested that *T. vaginalis* infection of prostate could create an inflammatory microenvironment by recruiting other immune cells and producing inflammatory cytokines (Han et al. 2020).

In our study, no significant relationship ($P > 0.1$ for all variables) was detected between *T. vaginalis* seropositivity rate and prognostic factors (i.e., tumor stage, lymph node affection, metastasis, and Gleason score) in prostate cancer patients. This is coping with results of Shui et al. (2016) that did not support the possibility of increased risk of advanced or metastatic prostate cancer in Americans with *T. vaginalis* seropositivity, and those of Marous et al. (2017) that did not link *T. vaginalis* serostatus with aggressive prostate cancer in Caucasian men. The current findings also corroborate those of Tsang et al. (2019) and Vicier et al. (2019), which declared no association between *T. vaginalis* seropositivity and likelihood of overall or prostate cancer mortality, or risk of intermediate, high grade, or fatal prostate cancer, respectively. However, our results differ from those of two previous studies, which revealed positive association between *T. vaginalis* seropositive status and risk of aggressive prostate cancer, including risk of advanced-stage prostate cancer (Sutcliffe et al. 2006), extra-prostatic extension, metastasis, and fatal disease (Stark et al. 2009).

Interestingly, positive correlations between high levels of PSA and high-grade cancer with increased *T. vaginalis*-IgG OD scores among prostate cancer patients were detected. Hence, we speculate that heavy burden of trichomoniasis may indicate a poor prognosis for prostate cancer. A recent study conducted on young American military members did not strongly support prostate involvement during *T. vaginalis* infection; however, authors declared non-significant association between high *T. vaginalis* serostatus and greater PSA concentrations (≥ 0.70 ng/ml). This may be relevant to chronic prostate involvement, as higher early life to midlife PSA concentrations have been found to predict greater prostate cancer risk later in life (Langston et al. 2019).

To the best of our knowledge, this is the first study testing *T. vaginalis* serostatus among Egyptian patients with prostate cancer compared to those with different types of cancer. It is worth mentioning that *T. vaginalis* seropositivity rate was 23.1% among patients with different types of neoplasms other than urogenital cancers, which could be linked to the general condition and immunosuppression status of cancer patients.

Conclusively, our findings support a role for *T. vaginalis* infection in the development of prostate cancer and suggest that prostate cancer might be a parasite-burden dependent.

Table 5 Correlation between some cancer prognostic factors and *Trichomonas vaginalis*-IgG optical density scores among trichomoniasis-positive prostate cancer cases (n = 24)

Measures	Correlation coefficient (r)	P value
Gleason score	0.1	0.5
PSA level (ng/ml)	0.7	< 0.0001*
Tumour stage	0.5	0.02*

PSA, prostate-specific antigen

*$P \leq 0.05$

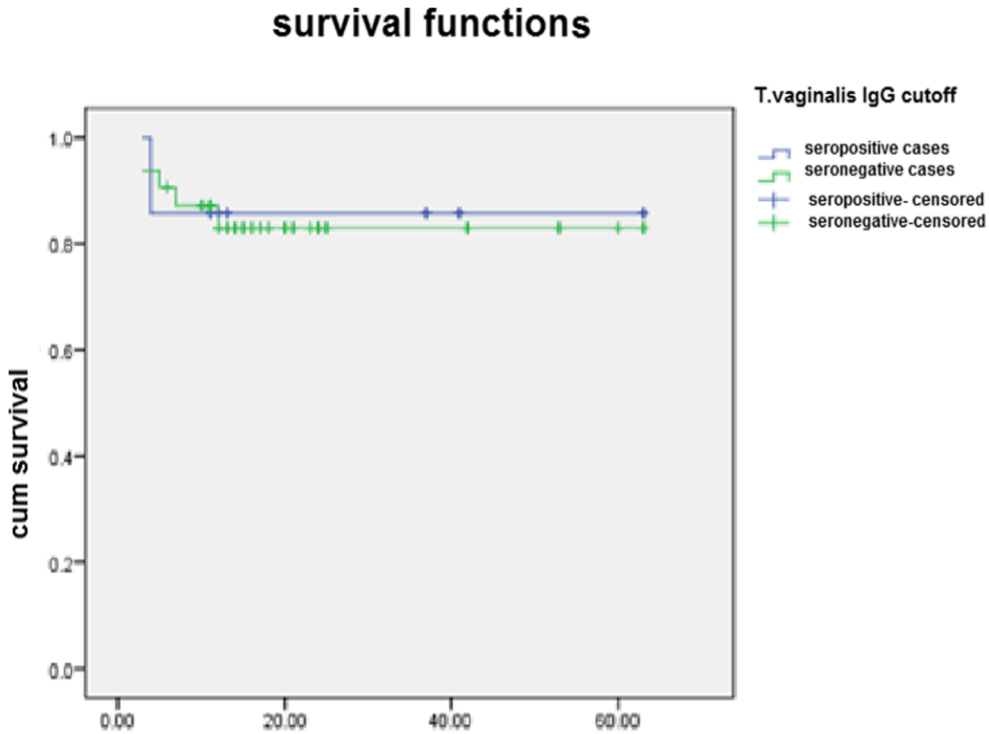

Fig. 1 Overall survival analysis by Kaplan-Meier survival analysis to compare between *Trichomonas vaginalis*-seropositive (blue line) and *Trichomonas vaginalis*-seronegative (green line) prostate cancer patients

Table 6 Summary of some previous studies on the association between trichomoniasis seropositivity and prostate cancer

Study participants	Study location	Trichomoniasis seropositivity	Conclusion	References
- A total of 691 prostate cancer patients. - A 691 controls with free prostate-specific antigen (PSA) test.	A nested case-control study within the Health Professionals Follow-up Study in America.	A 13% of patients and 9% of controls were seropositive.	Serological evidence of trichomoniasis is positively associated with incident prostate cancer and risk of advanced prostate cancer development.	Sutcliffe et al. (2006)
- A total of 673 patients with prostate cancer. - A 673 matched control subjects.	Physicians' Health Study (PHS) in America.	A 144 (21.4%) of controls and 165 (24.5%) of cases showed seropositivity to *T. vaginalis*.	Results supporting the association between trichomoniasis seropositive status and the risk of prostate cancer, as well as advanced and metastatic prostate cancer.	Stark et al. (2009)
- A total of 616 subjects diagnosed as prostate cancer. - A 616 control non-cancer cases.	Prostate Cancer Prevention Trial (PCPT) in American Men ≥ 55 years, screened annually for prostate cancer with a biopsy at end-of-study.	About 21.5% of patients and 24.8% of controls had low seropositivity level, while 15.2% and 15.0%, respectively, had high seropositivity level.	No association between *T. vaginalis* seropositivity and subsequent risk of prostate cancer among participants in the PCPT.	Sutcliffe et al. (2009)
- A total of 50 histopathological confirmed prostate cancer patients. - A 40 healthy controls.	Local cross-section study in Radiation and Nuclear Medicine Hospital, and Al-Kadhumyia Teaching Hospitals in Baghdad-Iraq.	A 24% of prostate cancer patients in comparison to only 7.5% of the normal individuals were seropositive.	*T. vaginalis* may increase the risk of prostate cancer when there is prolonged prostatic infection.	Al-Mayah et al. (2013)
- A total of 296 (253 African American) prostate cancer patients. - A 585 (497 African American) matched controls.	Southern Community Cohort Study (SCCS) in America.	A 69 (23.3%) of cases and 124 (21.2%) of controls were documented positive for trichomoniasis. For African American, 62 (24.5%) of patients and 111 (22.3%) of controls were *Trichomonas*-seropositive.	No evidence of association between baseline trichomoniasis infection and prostate cancer risk or diagnosis of aggressive prostate cancer in African American men.	Fowke et al. (2016)

Table 6 (continued)

Study participants	Study location	Trichomoniasis seropositivity	Conclusion	References
- A total of 146 men with advanced prostate cancer. - A 181 age-matched controls.	Data from 2 prior American population-based and case-control studies.	A 24/146 (16.4%) of patients and 42/181 (23.2%) of controls were seropositive.	No supportive data on increased risk of advanced or metastatic prostate cancer in *Trichomonas*-seropositive men.	Shui et al. (2016)
- A total of 1786 Caucasian men (861 controls + 438 Gleason 7 cases + 487 more advanced cases), and 556 African American men (355 controls + 201 cases).	The PLCO Cancer Screening Trial: a large randomized controlled trial to investigate the effects of prostate, lung, colorectal, and ovarian cancer screening on cancer-specific mortality.	No associations were observed for risk of Gleason 7 or more advanced prostate cancer in Caucasian men, or for risk of any prostate cancer in African American men.	Findings don't support any association between *T. vaginalis* infection and prostate cancer in either Caucasian or African American men.	Marous et al. (2017)
- A total of 139 with benign prostatic hyperplasia and 44 with prostate cancer. - A 58 healthy control males.	Local study on males with prostate tumors visiting Hanyang University Hospital in Korea.	A 19.7% of men with prostatic diseases (18.7% and 22.7%, respectively) and 1.7% of healthy controls were *Trichomonas*-seropositive.	Men with prostatic tumor revealed higher seropositivity against *T. vaginalis* than normal individuals.	Kim et al. (2019)
- A total of 732 young, military males were assessed for *Trichomonas* IgG and PSA level.	Study on US active-duty military males in America	A 341 (46.6%) had a low *T. vaginalis* seropositive score and 198 (27.0%) had a high score, and the remainder were seronegative.	Data do not support prostatic affection in trichomoniasis; however, positive findings for higher PSA levels do not exclude this possibility. These suggestive results may be attributed to prostate affection, as higher early- to mid-life PSA levels have been shown to speculate a higher risk of prostate cancer development later in life.	Langston et al. (2019)
- A total of 736 Caucasian men were diagnosed between 1983 and 2012 in the Physicians' Health Study (PHS) and 749 cases were diagnosed between 1994 and 2012 in Health Professionals Follow-Up Study (HPFS).	The Physicians' Health Study and the Health Professionals Follow-Up Study.	A 179 (24%) and 94 (13%) were seropositive in PHS and HPFS, respectively.	Data do not corroborate the assumption that people afflicted with prostate cancer and trichomoniasis are at high risk of all causes or prostate cancer specific-mortality.	Tsang et al. (2019)
- A 189 patients diagnosed from 1976–2007, and their details have been published (Oh et al. 2006; Penny et al. 2009). They involved 161 cases who did not suffer from metastatic relapse during follow-up and 28 cases who had morbid prostate cancer. - A 306 patients; comprised 86 intermediate- to high-risk prostate cancer, 49 low-risk patients, and 171 controls (low-risk or no prostate cancer).	The Dana-Farber Cancer Institute Gelb Center (DFCI) and the Early Detection Research Network (EDRN).	Trichomoniasis seroprevalence rates among men with localized prostate cancer and those with metastasis or lethal disease were 16% and 14%, respectively ($P = 0.94$). Upon classifying patients to cancer-free and those with low risk vs. intermediate or high risk, the seropositivity rates of *T. vaginalis* were 19.5% vs. 15.1%, respectively ($P = 0.36$).	Trichomoniasis is not associated with high-grade or morbid prostate cancer, thus we should not relay on *T. vaginalis* seropositivity as metric or biomarker for advanced or aggressive form of prostate cancer.	Vicier et al. (2019)

The reliance on measuring serum anti-*T. vaginalis* IgG cannot help differentiating recent from old infections, or determining duration or frequency of infection. Moreover, the inability to indicate time between infection and cancer incidence are other points of study limitations that need to be considered in further researches. Nonetheless, large-scale multicenter prospective studies with detailed trichomoniasis and cancer history presentations, and using different epidemiological and laboratory approaches are in demand to explore the causes of population differences in seropositivity to *T. vaginalis* and to clarify the possible mechanisms for the association between trichomoniasis and malignancies.

Authors' contributions Nora E. Saleh: methodology, data collection and interpretation, literature search, drafting the work, and approved the final form. Samar M. Alhusseiny: helped in laboratory investigations and statistical analysis and revised and approved the final version to be published. Wafaa M. El-Zayady: helped in literature search and data analysis and reviewed and approved the final version. Engy M. Aboelnaga, Wafaa N. El-beshbishi, and Yasser M. Saleh: clinical examination, data collection, and revised the work and approved the final version to be published. Hala S. Abou-ElWafa: statistical analysis, manuscript editing, reviewing, and approving the final form. Samar N. El-Beshbishi: conceptualization, visualization, data curation, drafted the work, edited, and revised it critically for important intellectual content.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict interest.

References

Al-Mayah QS, Al-Saadi MA, Jabbar RN (2013) *Trichomonas vaginalis* infection as a risk factor for prostate cancer. Int J Curr Microbiol App Sci 2(11):105–113

Campbell JD, Skubitz ABN, Somiari SB, Sexton KC, Pugh RS (2008) International society for biological and environmental repositories (ISBER). 2008 best practices for repositories collection, storage, retrieval, and distribution of biological materials for research. Cell Preserv Technol 6(1):3–58

el Seoud F, Abbas MM, Habib FS (1998) Study of trichomoniasis among Egyptian male patients. J Egypt Soc Parasitol 28(1):263–270

Fowke JH, Han X, Alderete JF, Moses KA, Signorello LB, Blot WJ (2016) A prospective study of *Trichomonas vaginalis* and prostate cancer risk among African American men. BMC Res Notes 9:224

Gardner WA, Culberson DE, Bennett BD (1986) *Trichomonas vaginalis* in the prostate gland. Arch Pathol Lab Med 110:430–432

Groom HCT, Warren AY, Neal DE, Bishop KN (2012) No evidence for infection of UK prostate cancer patients with XMRV, BK Virus, *Trichomonas vaginalis* or human papilloma viruses. PLoS ONE 7(3):e34221

Han IH, Kim JH, Kim SS, Ahn MH, Ryu JS (2016) Signaling pathways associated with IL-6production and epithelial-mesenchymal transition induction in prostate epithelial cells stimulated with *Trichomonas vaginalis*. Parasite Immunol 38(11):678–687

Han IH, Song HO, Ryu JS (2020) IL-6 produced by prostate epithelial cells stimulated with *Trichomonas vaginalis* promotes proliferation of prostate cancer cells by inducing M2 polarization of THP-1-derived macrophages. PLoS Negl Trop Dis 14:e0008126. https://doi.org/10.1371/journal.pntd.0008126

Iqbal J, Al-Rashed J, Kehinde EO (2016) Detection of *Trichomonas vaginalis* in prostate tissue and serostatus in patients with asymptomatic benign prostatic hyperplasia. BMC Infect Dis 16:506

Kim JH, Moon HS, Kim KS, Hwang HS, Ryu JS, Park SY (2019) Comparison of seropositivity to *Trichomonas vaginalis* between men with prostatic tumour and normal men. Korean J Parasitol 57(1):21–25

Kissinger P (2015) *Trichomonas vaginalis*: a review of epidemiologic, clinical and treatment issues. BMC Infect Dis 15:307

Langston M, Bhalla J, Alderete R, Nevin R, Pakpahan J, Hansen (2019) *Trichomonas vaginalis* infection and prostate-specific antigen concentration: Insights into prostate involvement and prostate disease risk. Prostate 79:1622–1628

Leitsch D (2016) Recent Advances in the Field. F1000Research 5:F1000 Faculty Rev-162

Lopez LB, De Melobraga MB, Lopez JO, Arroyo R, Filho FC (2000) Strategies by which some pathogenic trichomonads integrate diverse signals in the decision-making process. An Acad Bras Ci 72(2):173–186

Marous M, Huang WY, Rabkin CS (2017) *Trichomonas vaginalis* infection and risk of prostate cancer: associations by disease aggressiveness and race/ethnicity in the PLCO Trial. Cancer Causes Control. 28(8):889–898

McClelland RS, Sangare L, Hassan WM, Lavreys L, Mandaliya K, Kiarie J (2007) Infection with *Trichomonas vaginalis* increases the risk of HIV acquisition. J Infect Dis (2007 195:698–702

Oh WH, Hayes J, Evan C et al (2006) Development of an integrated prostate cancer research information system. Clin Genitourin Cancer 5:61–66

Penny KL, Salinas CA, Pomerantz M, Schumacher FR, Beckwith CA, Lee GS, Oh WK, Sartor O, Ostrander EA, Kurth T, Ma J, Mucci L, Stanford JL, Kantoff PW, Hunter DJ, Stampfer MJ, Freedman ML (2009) Evaluation of Bq24 and 17q risk loci and prostate cancer mortality. Clin Cancer Res 15:3223–3230

Seo MY, Im SJ, Gu NY, Kim JH, Chung YH, Ahn MH, Ryu JS (2014) Inflammatory response of prostate epithelial cells to stimulation by *Trichomonas vaginalis*. Prostate 74:441–449

Shui IM, Kolb S, Hanson C, Sutcliffe S, Rider JR, Stanford JL (2016) *Trichomonas vaginalis* infection and risk of advanced prostate cancer. Prostate 76:620–623

Stark JR, Judson G, Alderete JF, Mundodi V, Kucknoor AS, Giovannucci EL, Platz EA, Sutcliffe S, Fall K, Kurth T, Ma J, Stampfer MJ, Mucci LA (2009) Prospective study of *Trichomonas vaginalis* infection and prostate cancer incidence and mortality: physicians' health study. J Natl Cancer Inst 101(20):1406–1411

Sutcliffe S (2010) Sexually transmitted infections and risk of prostate cancer: review of historical and emerging hypotheses. Future Oncol 6(8):1289–1311

Sutcliffe S, Giovannucci E, Alderete JF, Chang TH, Gaydos CA, Zenilman JM, De Marzo AM, Willett WC, Platz EA (2006) Plasma antibodies against *Trichomonas vaginalis* and subsequent risk of prostate cancer. Cancer Epidemiol. Biomark Prev 15(5):939–945

Sutcliffe S, Alderate JF, Till C, Goodman PJ, Hsing AW, Zenilman JM, De-Marzo AM, Platz EA (2009) Trichomonosis and subsequent risk of prostate cancer in the prostate cancer prevention trail. Int J Cancer 124:2082–2087

Sutcliffe S, Naece C, Magnosum S, Reeves R, Alderate JF (2012) Trichomonosis, a common curable STI, and prostate carcinogenesis-a proposed molecular mechanism. PLoS Pathogens. 8:e1002801

Tsang SH, Peisch SF, Rowan B, Markt SC, Gonzalez-Feliciano AG, Sutcliffe S, Platz EA, Mucci LA, Ebot EM (2019) Association between *Trichomonas vaginalis* and prostate cancer mortality. Int J Cancer 144:2377–2380

Twu O, Dessi D, Vu A (2014) *Trichomonas vaginalis* homolog of macrophage migration inhibitory factor induces prostate cell growth, invasiveness, and inflammatory responses. Proc Nat Acad Sci USA 111:8179–8184

Vicier C, Werner L, Chipman J, Harshman LC, Patil DH, Fichorova RN, Rider JR, Sanda MG, Mucci LA, Sweeney CJ (2019) Elevated serum cytokines and *Trichomonas vaginalis* serology at diagnosis are not associated with higher Gleason grade or lethal prostate cancer. Clin Genitourin Cancer 17(1):32–37

World Health Organization (2012) Global incidence and prevalence of selected curable sexually transmitted infections-2008. Geneva, Switzerland. pp: 1-20

Zhang ZF, Begg CB (1994) Is *Trichomonas vaginalis* a cause of cervical neoplasia? Results from a combined analysis of 24 studies. Int J Epidemiol 23:682–690

Zhu Z, Davidson KT, Brittingham A, Wakefield MR, Bai Q, Xiao H, Fang Y (2016) *Trichomonas vaginalis*: a possible foe to prostate cancer. Med Oncol 33(10):115