Association between trichomoniasis and prostate and bladder diseases: a population-based case–control study

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Trichomonas vaginalis infection is one of the most widespread sexually transmitted infections in the world. There are approximately 276 million cases worldwide. Most men remain undiagnosed and untreated because they are asymptomatic. The chronic inflammation induced by persistent infection may increase the risk of developing genitourinary cancers. In this study, we aimed to investigate the association between trichomoniasis and benign prostate hyperplasia (BPH), prostate cancer (PCa), and bladder cancer (BC) in Taiwan. We designed a case–control study by using the database of the National Health Insurance program in Taiwan. We used the International Classification of Diseases, 9th Revision classifications to classify all the medical conditions in the case and control groups. All odds ratios (ORs) and 95% confidence intervals (CIs) were analyzed using multivariable logistic regression to adjust for all comorbidities and variables. From 2000 to 2015, we enrolled a total of 62,544 individuals as the case group and 187,632 as the control group. Trichomoniasis exposure had a significant association with BPH and PCa (adjusted OR: BPH = 2.685, 95% CI = 1.233–4.286, \( P = 0.013 \); PCa = 5.801, 95% CI = 1.296–26.035, \( P = 0.016 \)). The relative risk was much higher if patients had both trichomoniasis and depression (adjusted OR = 7.682, 95% CI = 5.730–9.451, \( P < 0.001 \)). Men with trichomoniasis had a significantly higher risk of developing BPH and PCa than those without. Healthcare professionals should not only pay more attention to disease treatment, but also to public health education.

Abbreviations

AOR  Adjusted odds ratio
AR  Androgen receptor
BC  Bladder cancer
BMI  Body mass index
BPH  Benign prostate hyperplasia
CCL2  Chemokine ligand 2
CI  Confidence interval
COPD  Chronic obstructive pulmonary disease

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Benign prostate hyperplasia (BPH), prostate cancer (PCa), and bladder cancer (BC) are common diseases in the elderly male population. The pathological mechanism of these diseases is not yet fully understood. Inflammation of the prostate, which can cause proliferation of epithelium and stroma, is considered to be related to both BPH and PCa. In addition, urinary tract infection (UTI) is significantly associated with genitourinary cancers (GUC), including kidney, prostate, and bladder cancers. *Trichomonas vaginalis* infection is one of the most common sexually transmitted infections (STIs), accounting for approximately 276.4 million new cases annually. Because most male patients are asymptomatic and remain undiagnosed and untreated, persistent infection may cause chronic inflammation, which may increase the risk of GUC. There is a lack of research into the relationship between *T. vaginalis* infection and BC; however, some studies have mentioned that *T. vaginalis* infection may induce proliferation of prostatic epithelial cells and stromal cells. Some in vitro studies showed that PCa may be associated with the up-regulation of the expression of genes that can control cell apoptosis or be overexpressed as a proto-oncogene. The study from Vienna General Hospital discovered that 29/86 (33.7%) patients with BPH were positive for *T. vaginalis* on polymerase chain reaction (PCR) testing. The Health Professionals Follow-up Study (HPFS) demonstrated that *T. vaginalis* seropositivity had a positive correlation with PCa risk. However, conflicting results have also been reported. Miguelle et al. demonstrated that there was no significant association between *T. vaginalis* infection and PCa in Caucasian or African-American groups. Another multicenter study in the USA revealed that patients with a history of STIs and positive STI serologies demonstrated no association with BPH. In addition, there is still a lack of related literature regarding BC and Asian male populations. Thus, this study aimed to examine the association between *T. vaginalis* infection and BPH, BC, or PCa.

**Materials and methods**

**Data source.** We designed a population-based nationwide nested case–control study and obtained inpatient and outpatient files from Taiwan's National Health Insurance Research Database (NHIRD). The data were collected from the Longitudinal Health Insurance Database 2005 (LHID2005), a part of NHIRD. We randomly selected approximately 2,000,000 people among the total population. All personal information was encrypted by National Health Research Institutes before release.

**Ethical approval.** Our study was approved by the Institutional Review Board of Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (TSGHIRB No.: B-109-31). All stages of the study were carried out in accordance with relevant guidelines and regulations. Because the patient identifiers were encrypted before their data were used for research purposes to protect confidentiality, the requirement for written informed consent from patients for data linkage was waived by Institutional Review Board of Tri-Service General Hospital, National Defense Medical Center, Taipei.

**Identification of the case and control groups.** We selected patients from 2000 to 2015 who had been diagnosed with BPH, PCa, or BC based on the International Classification of Diseases, 9th Revision. Clinical Modification (ICD-9-CM) codes as the case group (Table S1). We defined the date of the first disease diagnosis as the index date. We also used ICD-9-CM codes to identify patients with *T. vaginalis* infection (Table S1). In contrast, the control groups were patients without BPH, PCa, or BC. Among all patients in the case and control groups, we not only selected patients in a 1:3 case:control ratio, matching based on age and index date, but also excluded (1) women and patients of unknown sex, (2) patient’s aged less than 18 years, and (3) those last diagnosed with trichomoniasis within 1 year before the index date (Fig. 1). The matching method was taken propensity score matching, wherein match tolerance was set at 0.15. The propensity score matching was set as propensity score matching, wherein match tolerance was set at 0.15. The propensity score matching was set as
Covariates for analysis. The covariates in our study included age group (18–44, 45–64, ≥ 65 years), four seasons (spring, summer, autumn and winter), with or without diagnosis of depression, geographical area of residence (north, center, south, east and outlying islands of Taiwan), urbanization level of residence (levels 1 to 4), levels of hospitals as medical centers, regional and local hospitals, and monthly income (in New Taiwan Dollars [NT$]; < 18,000, 18,000–34,999, ≥ 35,000). The urbanization level of residence was defined according to the population, along with various indicators of the level of political, economic, cultural, and metropolitan development. Level 1 was defined as a population of > 1,250,000, and a specific designation as political, economic, cultural, and metropolitan development. Level 2 was defined as a population between 500,000 and 1,249,999, and as playing an important role in the political system, economy, and culture. Urbanization levels 3 and 4 were defined as a population between 149,999 and 499,999, respectively.

Statistical analysis. The statistical analyses were performed using SPSS version 22.0 (IBM Corp, Armonk, NY, USA). A P-value < 0.05 was considered significant. The Chi-squared or Fisher exact test was used to evaluate distributions between the case and control groups. Continuous variables were evaluated using the t test. Unconditional multiple logistic regression analyses were performed to evaluate the risks of BPH, PCa, and BC associated with trichomoniasis after adjusting for age, insurance premium, comorbidities, season, urbanization, and level of care. Adjusted models with significant covariates were constructed using background selection with the likelihood ratio test.

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**Figure 1.** The flowchart of the study design (nested case–control study) from National Health Insurance Research Database in Taiwan.
Results

Demographic characteristics of the study population. Table 1 demonstrates the population distribution of different characteristics for 62,544 cases and 187,632 controls from 2000 to 2015. There were no significant differences in age between groups after matching. The proportion with trichomoniasis in the case group was 0.02% (14/62,544), while it was 0.01% (14/187,632) in the control group ($P<0.001$).

Variable evaluation in the multiple logistic regression. We present the results of the multivariable logistic regression analyses in Table 2. Patients with trichomoniasis had a significantly higher risk of BPH, PCa, or BC (adjusted odds ratio [AOR] = 2.999, 95% confidence interval [CI] = 1.426–5.301, $P=0.002$). There was also a significantly higher risk for patients with depression (AOR = 3.124, 95% CI = 1.808–4.838, $P<0.001$). The opposite result was noted in patients with middle or high insurance premiums (insurance premium NT$18,000–34,999: AOR = 0.745, 95% CI = 0.688–0.799, $P<0.001$; insurance premium > NT$35,000: AOR = 0.836, 95% CI = 0.701–0.979, $P=0.019$). Patients diagnosed in summer, autumn, or winter also had significantly lower risk than the control group (summer: AOR = 0.938, 95% CI = 0.902–0.953, $P<0.001$; autumn: AOR = 0.790, 95% CI = 0.758–0.805, $P<0.001$; winter: AOR = 0.862, 95% CI = 0.824–0.878, $P<0.001$). Patients who lived in areas with a higher urbanization level had a significantly higher risk of BPH, PCa, or BC (urbanization level

| BPH/prostate cancer, bladder cancer Variables | Total | Without | With |
|---------------------------------------------|-------|---------|------|
| Total                                       | 250,176 | 62,544  | 187,632 |
| Trichomoniasis                              |       |         |       |
| Without                                    | 250,148 | 99.99   | 62,530 |
| With                                       | 28     | 0.01    | 14    |
| Age (years)                                 | 73.15 ± 11.41 | 73.21 ± 10.65 | 73.13 ± 11.65 | $P=0.129$ |
| Age group (years)                           |       |         |       |
| 18–44                                      | 2664   | 1.06    | 666   |
| 45–64                                      | 50,292 | 20.10   | 12,573 |
| ≥ 65                                       | 197,220 | 78.83  | 49,305 |
| Insurance premium (NT$)                    |       |         |       |
| < 18,000                                   | 245,698 | 98.21   | 61,654 |
| 18,000–34,999                              | 3654   | 1.46    | 712   |
| ≥ 35,000                                   | 824    | 0.33    | 178   |
| Depression                                 |       |         |       |
| Without                                    | 217,896 | 87.10   | 50,509 |
| With                                       | 32,280 | 12.90   | 12,035 |
| CCI_R                                      | 1.74 ± 2.96 | 1.71 ± 2.77 | 1.75 ± 3.03 | $P<0.001$ |
| Season                                     |       |         |       |
| Spring (Mar–May)                           | 56,893 | 22.74   | 15,495 |
| Summer (Jun–Aug)                           | 60,567 | 24.21   | 15,709 |
| Autumn (Sep–Nov)                           | 72,621 | 29.03   | 16,666 |
| Winter (Dec–Feb)                           | 60,095 | 24.02   | 14,674 |
| Location                                   |       |         |       |
| Northern Taiwan                            | 99,711 | 39.86   | 26,475 |
| Central Taiwan                             | 71,555 | 28.60   | 16,878 |
| Southern Taiwan                            | 63,001 | 25.42   | 14,985 |
| Eastern Taiwan                             | 14,366 | 5.74    | 3957   |
| Outlying islands                           | 943    | 0.38    | 249    |
| Urbanization level                         |       |         |       |
| 1 (Highest)                                | 75,256 | 30.08   | 18,936 |
| 2                                           | 113,122 | 45.22  | 29,293 |
| 3                                           | 17,865 | 7.14    | 4119   |
| 4 (Lowest)                                 | 43,933 | 17.56   | 10,196 |
| Level of care                              |       |         |       |
| Hospital center                            | 89,122 | 35.62   | 23,060 |
| Regional hospital                          | 115,596 | 46.21  | 26,602 |
| Local hospital                             | 45,458 | 18.17   | 12,882 |

Table 1. Characteristics of the study group. $P$: Chi-square/Fisher exact test on categorical variables and $t$ test on continue variables.


Risk of BPH/PCa and BC in the trichomoniasis group stratified by covariates. The risk of BPH, PCa, or BC stratified based on variables using multivariable logistic regression is shown in Table 3. Patients with trichomoniasis had a 2.999 times higher risk of BPH, PCa, or BC than the control group (AOR = 2.999, 95% CI = 1.426–5.301). In the case of trichomoniasis, there were significantly higher risks of BPH, PCa, or BC in patients aged > 65 years old, with lower insurance premiums, with/without depression, first diagnosed in winter, urbanization level 2, and first diagnosed in a local hospital (age > 65 years: AOR = 3.685, 95% CI = 1.704–8.015; insurance premium < NT$18,000: AOR = 2.999, 95% CI = 1.426–5.301; with depression: AOR = 3.104, 95% CI = 1.704–5.301; without depression: AOR = 2.545, 95% CI = 1.138–4.289; first diagnosed in winter: AOR = 4.806, 95% CI = 1.104–19.675; urbanization level 2: AOR = 3.284, 95% CI = 1.057–10.978; first diagnosed in local hospital: AOR = 15.121, 95% CI = 1.762–118.976).

Risk of BPH/PCa and BC in subgroup with T. vaginalis exposure and the joint effect. Table 4 presents the T. vaginalis exposure ratio in each subgroup of BPH/PCa and BC. T. vaginalis exposure is significantly associated with a higher risk of BPH and PCa (BPH: AOR = 2.685, 95% CI = 1.233–4.286, P = 0.013;
AOR = 5.801, 95% CI = 1.296–26.035, \( P = 0.016 \), but has no significant association with BC (AOR = 4.012, 95% CI = 0.524–31.145, \( P = 0.151 \)). In addition, patients with both depression and \textit{T. vaginalis} exposure had a significantly higher risk of developing BPH, PCa, or BC in comparison with other groups with only one condition or without them (AOR = 7.682, 95% CI = 5.730–9.451, \( P < 0.001 \) (Table 5, Fig. 2).

### Discussion

We designed this case–control study based on nationwide data from Taiwan NHIRD. We found that \textit{T. vaginalis} infection was significantly associated with BPH and PCa in a male population. Therefore, \textit{T. vaginalis} could be a pathogen that induces BPH and PCa. However, there was no significant association between trichomoniasis and BC. Furthermore, patients with both trichomoniasis and depression had 7.682 times higher risk of developing BPH, PCa, or BC. This result suggests that the joint effect of trichomoniasis and depression could increase the risk of BPH, PCa, or BC.

### Table 3.

| BPH/prostate, bladder cancer Stratified | With Trichomoniasis exposure | Population | % | Without Trichomoniasis exposure | Population | % | Adjusted OR | 95%CI | 95%CI | \( P \) |
|----------------------------------------|-----------------------------|------------|---|---------------------------------|------------|---|-------------|-------|-------|-------|
| Total                                  | 14                          | 62,544     | 0.022 | 14                             | 187,632    | 0.007 | 2.999       | 1.426 | 5.301 | 0.002 |
| Age group (years)                      |                             |            |     |                                 |            |     |             |       |       |       |
| 18–44                                  | 0                           | 666        | 0.000 | 0                              | 1998       | 0.000 | -           | -     | -     | -     |
| 45–64                                  | 0                           | 12,573     | 0.000 | 2                              | 37,719     | 0.005 | 0.000       | -     | -     | 0.999 |
| ≥65                                    | 14                          | 49,305     | 0.028 | 12                             | 147,915    | 0.008 | 3.685       | 1.704 | 8.015 | 0.001 |
| Insurance premium (NT$)                |                             |            |     |                                 |            |     |             |       |       |       |
| <18,000                                | 14                          | 61,654     | 0.023 | 14                             | 184,044    | 0.008 | 2.999       | 1.426 | 5.301 | 0.002 |
| 18,000–34,999                          | 0                           | 712        | 0.000 | 0                              | 2942       | 0.000 | -           | -     | -     | -     |
| ≥35,000                                | 0                           | 178        | 0.000 | 0                              | 646        | 0.000 | -           | -     | -     | -     |
| Depression                             |                             |            |     |                                 |            |     |             |       |       |       |
| Without                                | 4                           | 50,509     | 0.008 | 7                              | 167,387    | 0.004 | 2.545       | 1.138 | 4.289 | <0.001 |
| With                                   | 10                          | 12,035     | 0.083 | 7                              | 20,245     | 0.035 | 3.104       | 1.704 | 5.972 | <0.001 |
| Season                                 |                             |            |     |                                 |            |     |             |       |       |       |
| Spring                                 | 3                           | 15,495     | 0.019 | 1                              | 41,398     | 0.002 | 7.745       | 0.671 | 70.986 | 0.175 |
| Summer                                 | 2                           | 15,709     | 0.013 | 4                              | 44,858     | 0.009 | 1.301       | 0.104 | 5.258 | 0.603 |
| Autumn                                 | 4                           | 16,666     | 0.024 | 6                              | 55,955     | 0.011 | 2.197       | 0.482 | 4.894 | 0.224 |
| Winter                                 | 5                           | 14,674     | 0.034 | 3                              | 45,421     | 0.007 | 4.806       | 1.104 | 19.675 | 0.033 |
| Urbanization level                     |                             |            |     |                                 |            |     |             |       |       |       |
| 1 (Highest)                            | 2                           | 18,936     | 0.011 | 2                              | 56,320     | 0.004 | 3.199       | 0.453 | 22.845 | 0.241 |
| 2                                      | 6                           | 29,293     | 0.020 | 6                              | 83,829     | 0.007 | 3.284       | 1.057 | 10.978 | 0.035 |
| 3                                      | 1                           | 4119       | 0.024 | 1                              | 13,746     | 0.007 | 3.351       | 0.210 | 53.777 | 0.382 |
| 4 (Lowest)                             | 5                           | 10,196     | 0.049 | 5                              | 33,737     | 0.015 | 3.086       | 0.889 | 10.801 | 0.077 |
| Level of care                          |                             |            |     |                                 |            |     |             |       |       |       |
| Hospital center                        | 1                           | 23,060     | 0.004 | 3                              | 66,062     | 0.005 | 0.965       | 0.094 | 9.301 | 0.886 |
| Regional hospital                      | 7                           | 26,602     | 0.026 | 10                             | 88,994     | 0.011 | 2.301       | 0.846 | 6.127 | 0.071 |
| Local hospital                         | 6                           | 12,882     | 0.047 | 1                              | 32,576     | 0.003 | 15.121      | 1.782 | 118.976 | 0.008 |

### Table 4.

| BPH/prostate, bladder cancer subgroup | Trichomoniasis exposure | Population | % | Adjusted OR | 95%CI | 95%CI | \( P \) |
|--------------------------------------|-------------------------|------------|---|-------------|-------|-------|-------|
| Without                              | 14                      | 187,632    | 0.007 | Reference   |        |       |       |
| With                                 | 14                      | 62,544     | 0.022 | 2.999       | 1.426 | 5.301 | 0.002 |
| BPH/prostate cancer                   | 15                      | 59,325     | 0.022 | 2.995       | 1.422 | 4.389 | 0.003 |
| PCa                                  | 11                      | 51,482     | 0.021 | 2.685       | 1.233 | 4.286 | 0.013 |
| Prostate cancer                       | 2                       | 6254       | 0.032 | 5.801       | 1.296 | 26.035 | 0.016 |
| Bladder cancer                        | 1                       | 3873       | 0.026 | 4.012       | 0.524 | 31.445 | 0.151 |

AOR = 5.801, 95% CI = 1.296–26.035, \( P = 0.016 \), but has no significant association with BC (AOR = 4.012, 95% CI = 0.524–31.145, \( P = 0.151 \)). In addition, patients with both depression and \textit{T. vaginalis} exposure had a significantly higher risk of developing BPH, PCa, or BC in comparison with other groups with only one condition or without them (AOR = 7.682, 95% CI = 5.730–9.451, \( P < 0.001 \) (Table 5, Fig. 2).
The mechanism of \textit{T. vaginalis} inducing BPH and PCa still remains unclear. Several studies have demonstrated different possible mechanisms. In women, \textit{T. vaginalis} induces pro-inflammatory cytokine production, including interleukin-6 (IL-6), interleukin-8 (IL-8), and chemokine ligand 2 (CCL2), while attaching to vaginal epithelial cells\textsuperscript{14}. A similar inflammatory reaction was also noted in \textit{T. vaginalis}-infected prostatic epithelial cells in some in vitro studies\textsuperscript{5,6}. Repeated cell damage and repair in chronic inflammation is likely to play an important role in inducing BPH\textsuperscript{15}. Furthermore, the alteration in cytokine expression during chronic inflammation may have effects on cell growth and proliferation of the prostate epithelium and stroma in BPH\textsuperscript{15}. The activated mast cells stimulated by \textit{T. vaginalis}-infected prostatic epithelial cells can initiate IL-8 and CCL2 expression\textsuperscript{5}. IL-8 could be a predictive marker for BPH\textsuperscript{16}. Some in vitro studies demonstrated that IL-8 can stimulate fibroblast growth factor 2 (FGF-2), which causes the mitosis of prostate stromal cells\textsuperscript{17}. IL-8 could also cause cyclin D1 expression to promote stromal cells proliferation\textsuperscript{18}. In addition, CCL2, secreted by the prostatic stroma fibroblast, could promote both BPH and PCa progression\textsuperscript{5}.

\textit{T. vaginalis} possibly induces carcinogenesis of the prostate. The infected prostatic epithelial cells produce IL-6 in chronic inflammation\textsuperscript{19}. In early studies, an elevated serum IL-6 level was noted in patients with advanced PCa\textsuperscript{20}. The positive correlation between IL-6 receptor expression and cell proliferation has been reported\textsuperscript{21}. IL-6 also induces epithelial–mesenchymal transition (EMT) in breast cancer growth and metastasis\textsuperscript{22}, and the same reaction may also occur in prostatic epithelial cells\textsuperscript{23}. In addition, more than one study has demonstrated that IL-6 could enhance androgen receptor (AR) activity and AR gene expression\textsuperscript{24}, which is also related to prostate cancer growth. Twu et al. demonstrated that \textit{T. vaginalis} macrophage migration inhibitory factor (TvMIF) plays an important role in inducing PCa\textsuperscript{7}. There are already studies that have proven that higher human macrophage migration inhibitory factor (HuMIF) levels are present in several cancers, including PCa\textsuperscript{25}. The structure of TvMIF is similar to that of HuMIF, which might explain why TvMIF also has the ability to promote cell proliferation, sustain inflammation, and stimulate the growth of prostate cancer cells\textsuperscript{7}.

In previous studies, \textit{T. vaginalis} could play an important role as a carcinogen of female cervical cancer\textsuperscript{26,27}. However, there is no consensus regarding the relationship between trichomoniasis and cervical cancer\textsuperscript{28}. Likewise, the role of \textit{T. vaginalis} in the development of PCa is still controversial. Zhu et al. demonstrated that there was a negative association between PCa and trichomoniasis\textsuperscript{29}. Instead, they discovered culture supernatant of \textit{T. vaginalis} not only inhibited growth but also induced apoptosis of prostate cancer cell. \textit{T. vaginalis} could enhance anti-proliferative molecules and decrease the expression of anti-apoptotic molecule\textsuperscript{29}. The \textit{T. vaginalis} adhesion protein could induce T helper 2 cell cytokines reaction to stimulate the productions of specific antibody\textsuperscript{30}. This enhancement of the immune response might suppress the cancer cell activity\textsuperscript{31}. Moreover, another further study

| Trichomoniasis | Depression | n     | Adjusted OR | 95% CI      | 95% CI      | P       |
|----------------|------------|-------|-------------|-------------|-------------|---------|
| Without        | Without    | 167,387 | Reference   |             |             |         |
| With           | Without    | 50,509 | 2.975       | 1.429       | 3.608       | < 0.001 |
| Without        | With       | 20,245 | 3.014       | 1.586       | 4.297       | < 0.001 |
| With           | With       | 12,035 | 7.682       | 5.730       | 9.451       | < 0.001 |

Table 5. Risk of BPH/prostate cancer or bladder cancer stratified by trichomoniasis and depression status using logistic regression. \textit{Adjusted OR} adjusted odds ratio (adjusted for variables listed in Table 2), \textit{CI} confidence interval.
also showed that *T. vaginalis* seropositivity does not raise mortality risk in men with PCa. The inflammatory response caused by *T. vaginalis* might not have influence in the development and progression of PCa. However, the detail mechanism of immune response between *T. vaginalis* and prostate epithelial cell still remained unclear, further investigations are necessary.

There were still a lack of studies to prove that trichomoniasis is associated with BC. We still included BC patients in our study because the inflammatory cytokines found in trichomoniasis, including IL-6 and IL-8, are also associated with a higher risk of developing BC and some parasites, such as *Schistosoma haematobium*, can induce BC. However, our study shows no significant association between *T. vaginalis* infection and BC probably because of limited sample.

We added depression as one of the comorbidities in our study due to another previous nationwide population-based cohort study in Taiwan which showed that patients with trichomoniasis had higher risks for developing an individual psychiatric disorder, including depression, anxiety, bipolar disorder, schizophrenia and substance abuse. Our study results demonstrate that except for depression, no comorbidities had a significant association with BPH, PCa, or BC. The joint effect of trichomoniasis and depression increased the risk by 7.682 times that of the control group. A recent study showed that depression is associated with decreased immunity. Moreover, depression can also cause cytokine dysregulation and increased serum IL-6 concentration, which might enhance carcinogenesis after *T. vaginalis* infection.

Although this study was a large-scale population-based nationwide design with long-term monitoring from 2000 to 2015, there are still several limitations. First, the NHIRD does not contain detailed information regarding the symptom severity of BPH, the histological and TNM classification of PCa and BC, serum sex hormone concentrations, Prostate-Specific Antigen (PSA) levels, *T. vaginalis* antibody test, family history, or personal history such as sexual exposure, physical activity, alcohol consumption or tobacco smoking. Second, we did not include body mass index (BMI) as one of our variables. Obesity is one of the risk factors for BPH and PCa, which might affect their association with trichomoniasis. Third, our study might underestimate the exact number of patients with trichomoniasis. Most male patients would not seek treatment due to being asymptomatic, and ineffective screening protocols because of the lack of public health awareness could also lead to possible *T. vaginalis* infection being neglected. Another reason that caused underestimation of our case group is that the antibody tests of *T. vaginalis* were not performed popularly during diagnosis and mostly were female patients. It is possible that *T. vaginalis* was substantially undercoded and underrepresented in the study population. Fourth, the number of cases of BC might be too small to be significant and the tracking time might not be sufficient for disease monitoring. Trichomoniasis can be a chronic infection. The outcomes in the study might present later in life, so in some men trichomonas exposure may happen a few years before these outcomes appear or many decades prior to diagnosis. Fifth, the outcome of each case was defined as the first code for BPH, PCa, or BC. This assumes that there is a common pathway between trichomoniasis and these 3 separate diseases. However, this approach method could also ignore these outcomes as comorbidities. For example, patients with PCa or BC could also have BPH or other urinary symptoms. It is possible that many PCa or BC outcomes were ignored if BPH was coded first. This might be another reason that our study samples were underestimated. Sixth, our study was designed as an observational case–control study, so the causation cannot be detected. We hope that in the future more research will support our thesis.

**Conclusion**

Male patients with *T. vaginalis* infection have an increased risk of developing BPH and PCa, especially in trichomoniasis patients with comorbid depression. Due to the lack of awareness of this pathogen, clinicians should not only treat patients who are already diagnosed but should also pay more attention to groups with higher trichomoniasis exposure risk.

**Data availability**

Data supporting the conclusions of this article are included within the article and its additional files. The datasets used and/or analyzed during the present study will be made available by the corresponding author upon reasonable request.

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**Author contributions**

H.C.L., H.Y.Y. and C.C.C. conceived the idea and wrote the first draft manuscript. R.Y.S. and K.Y.H. contributed to the manuscript. W.C.C., H.A.L., J.Y.W., and C.H.C. research data collection and statistical analyses. All authors read and approved the final manuscript.

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**Competing interests**

The authors declare no competing interests.
Additional information
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