The Association Between Trichomonas Vaginalis Infection and the Risk of Benign Prostate Hyperplasia, Prostate Cancer, and Bladder Cancer in Patients: a Nationwide Population-based Case-control Study

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Abstract

Background: 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.

Material and method: 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.

Result: 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).

Conclusion: 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.

Background

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 [1, 2]. In addition, urinary tract infection (UTI) is significantly associated with genitourinary cancers (GUC), including kidney, prostate, and bladder cancers [3]. Trichomonas vaginalis infection is one of the most common sexually transmitted infections (STIs), accounting for approximately 276.4 million new cases annually [4]. 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 [5, 6]. 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 [7, 8]. 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 [9]. The Health Professionals Follow-up Study (HPFS) demonstrated that T. vaginalis seropositivity had a positive correlation with PCa risk [10]. 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 [11]. Another multicenter study in the USA revealed that patients with a history of STIs and positive STI serologies demonstrated no association with BPH [12]. 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.

Material And Method

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 released.

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 comorbidities in our study included hypertension, myocardial infarction, congestive heart failure, cerebral or peripheral vascular disease, dementia, chronic obstructive pulmonary disease (COPD), type 2 diabetes, renal disease, and malignant disease except PCa and BC. We also evaluated depression as one of the comorbidities in our study because it may be associated with some cancers [13].

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.

Result
Demographic characteristics of the study population

Table 1 demonstrates the population distribution of different characteristics for 62,544 patients with BPH, PCa, or BC 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 ($P < 0.001$).
| Variables                        | Total     | With | Without | P   |
|---------------------------------|-----------|------|---------|-----|
| BPH/prostate cancer, bladder cancer | 250,176  | 62,544 | 187,632 |     |
| Trichomoniasis                  | 0.004     |      |         |     |
| Without                         | 250,148   | 62,530 | 187,618 |     |
| With                            | 28        | 14    | 14      |     |
| Age (years)                     | 73.15 ± 11.41 | 73.21 ± 10.65 | 73.13 ± 11.65 | 0.129 |
| Age group (years)               | 0.999     |      |         |     |
| 18–44                           | 2,664     | 1.06  | 1,998   | 1.06 |
| 45–64                           | 50,292    | 20.10 | 37,719  | 20.10 |
| ≥ 65                            | 197,220   | 78.83 | 147,915 | 78.83 |
| Insurance premium (NT$)         | <0.001    |      |         |     |
| < 18,000                        | 245,698   | 98.21 | 184,044 | 98.09 |
| 18,000–34,999                   | 3,654     | 1.46  | 2,942   | 1.57 |
| ≥ 35,000                        | 824       | 0.33  | 646     | 0.34 |
| Depression                      | <0.001    |      |         |     |
| Without                         | 217,896   | 87.10 | 167,387 | 89.21 |
| With                            | 32,280    | 12.90 | 20,245  | 10.79 |
| CCI_R                           | 1.74 ± 2.96 | 1.71 ± 2.77 | 1.75 ± 3.03 | <0.001 |
| Season                          | <0.001    |      |         |     |
| Spring (Mar-May)                | 56,893    | 22.74 | 41,398  | 22.06 |
| Summer (Jun-Aug)                | 60,567    | 24.21 | 44,858  | 23.91 |
| Autumn (Sep-Nov)                | 72,621    | 29.03 | 55,955  | 29.82 |
| Winter (Dec-Feb)                | 60,095    | 24.02 | 45,421  | 24.21 |
| Location                        | <0.001    |      |         |     |
| Northern Taiwan                 | 99,711    | 39.86 | 73,236  | 39.03 |
| Central Taiwan                  | 71,555    | 28.60 | 54,677  | 29.14 |
| Southern Taiwan                 | 63,601    | 25.42 | 48,616  | 25.91 |
| Eastern Taiwan                  | 14,366    | 5.74  | 10,409  | 5.55  |
| Outlying islands                | 943       | 0.38  | 694     | 0.37  |
| Urbanization level              | <0.001    |      |         |     |
| 1 (Highest)                     | 75,256    | 30.08 | 56,320  | 30.02 |
| 2                               | 113,122   | 45.22 | 83,829  | 44.68 |
| 3                               | 17,865    | 7.14  | 13,746  | 7.33  |
| 4 (Lowest)                      | 43,933    | 17.56 | 33,737  | 17.98 |
| Level of care                   | <0.001    |      |         |     |
| Hospital center                 | 89,122    | 35.62 | 66,062  | 35.21 |
| Regional hospital               | 115,596   | 46.21 | 88,994  | 47.43 |
| Local hospital                  | 45,458    | 18.17 | 32,576  | 17.36 |

*Chi-square/Fisher exact test on categorical variables and t-test on continue variables*
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 1: AOR = 1.160, 95% CI = 1.124–1.189, P<0.001; urbanization level 2: AOR = 1.211, 95% CI = 1.179–1.235, P<0.001) but had significantly lower risk when diagnosed at a higher level of care (hospital center: AOR = 0.819, 95% CI = 0.796–0.902, P<0.001; regional hospital: AOR = 0.745, 95% CI = 0.724–0.808, P<0.001) instead.
### Table 2

Risk of BPH/prostate cancer and bladder cancer based on stated variables analyzed using multivariable logistic regression

| Variables             | Crude OR | 95% CI | 95% CI | P     | Adjusted OR | 95% CI | 95% CI | P     |
|-----------------------|----------|--------|--------|-------|-------------|--------|--------|-------|
| **Trichomoniasis**    |          |        |        |       |             |        |        |       |
| Without               | Reference|        |        |       | Reference    |        |        |       |
| With                  | 3.000    | 1.430  | 6.294  | 0.004 | 2.999       | 1.426  | 5.301  | 0.002 |
| **Age group (years)** |          |        |        |       |             |        |        |       |
| 18–44                 | Reference|        |        |       | Reference    |        |        |       |
| 45–64                 | 1.000    | 0.914  | 1.094  | 0.999 | 1.015       | 0.923  | 1.107  | 0.782 |
| ≥ 65                  | 1.000    | 0.915  | 1.092  | 0.999 | 1.006       | 0.919  | 1.098  | 0.794 |
| **Insured premium (NT$)** |        |        |        |       |             |        |        |       |
| < 18,000              | Reference|        |        |       | Reference    |        |        |       |
| 18,000–34,999         | 0.722    | 0.665  | 0.784  | < 0.001 | 0.745   | 0.688  | 0.799  | < 0.001 |
| ≥ 35,000              | 0.823    | 0.697  | 0.971  | 0.021 | 0.836       | 0.701  | 0.979  | 0.019 |
| **Depression**        |          |        |        |       |             |        |        |       |
| Without               | Reference|        |        |       | Reference    |        |        |       |
| With                  | 3.286    | 1.846  | 4.959  | < 0.001 | 3.124   | 1.808  | 4.838  | < 0.001 |
| **CCI_R**             | 0.996    | 0.993  | 0.999  | 0.006 | 1.000       | 0.998  | 1.005  | 0.058 |
| **Season**            |          |        |        |       |             |        |        |       |
| Spring                | Reference|        |        |       | Reference    |        |        |       |
| Summer                | 0.936    | 0.912  | 0.960  | < 0.001 | 0.938   | 0.902  | 0.953  | < 0.001 |
| Autumn                | 0.796    | 0.776  | 0.816  | < 0.001 | 0.790   | 0.758  | 0.805  | < 0.001 |
| Winter                | 0.863    | 0.841  | 0.886  | < 0.001 | 0.862   | 0.824  | 0.878  | < 0.001 |
| **Location**          |          |        |        |       |             |        |        |       |
| Northern Taiwan       | Reference|        |        |       | Reference    |        |        |       |
| Central Taiwan        | 0.854    | 0.835  | 0.873  | < 0.001 | 0.853   | 0.833  | 0.873  | < 0.001 |
| Southern Taiwan       | 0.853    | 0.833  | 0.873  | < 0.001 | 0.852   | 1.011  | 1.094  | 0.012 |
| Eastern Taiwan        | 1.052    | 1.011  | 1.094  | 0.012 | 0.992       | 0.858  | 1.148  | 0.919 |
| Outlying islands      | 0.992    | 0.858  | 1.148  | 0.919 | Had multicollinearity with urbanization level|
| **Urbanization level**|          |        |        |       |             |        |        |       |
| 1 (Highest)           | 1.113    | 1.082  | 1.144  | < 0.001 | 1.160   | 1.124  | 1.189  | < 0.001 |
| 2                     | 1.156    | 1.127  | 1.186  | < 0.001 | 1.211   | 1.179  | 1.235  | < 0.001 |
| 3                     | 0.991    | 0.951  | 1.033  | 0.685 | 0.987       | 0.952  | 1.036  | 0.924 |
| 4 (Lowest)            | Reference|        |        |       | Reference    |        |        |       |
| **Level of care**     |          |        |        |       |             |        |        |       |
| Hospital center       | 0.883    | 0.861  | 0.905  | < 0.001 | 0.819   | 0.796  | 0.902  | < 0.001 |
| Regional hospital     | 0.756    | 0.738  | 0.775  | < 0.001 | 0.745   | 0.724  | 0.808  | < 0.001 |
| Local hospital        | Reference|        |        |       | Reference    |        |        |       |

**P:** Chi-square/Fisher exact test on categorical variables and t-test on continue variables; OR = odds ratio, CI = confidence interval, Adjusted OR: adjusted for variables listed in the table

### 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 = 1.326–
5.301; with depression: AOR = 3.104, 95% CI = 1.706–5.972; 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.

Table 3
Risk of BPH/prostate cancer and bladder cancer stratified by variables listed in the table by using multivariable logistic regression

| 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                             | 1,998      | 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                             | 2,942      | 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       | 1.706 | 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                             | 4,119      | 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       | 0.898 | 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      | 1.762 | 118.976 | 0.008 |

P: Chi-square/Fisher exact test on categorical variables and t-test on continue variables; Adjusted OR = Adjusted odds ratio: adjusted for the variables listed in Table 2; CI = confidence interval

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; PCa: 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 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) (Fig. 2).
Schistosoma haematobium cytokines found in trichomoniasis, including IL-6 and IL-8, are also associated with a higher risk of developing BC. 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 response promotes cell proliferation, sustains inflammation, and stimulates the growth of prostate cancer cells. Levels of inflammatory cytokines are present in several cancers, including PCa. IL-6 plays an important role in inducing PCa. Repeated cell damage and repair in chronic inflammation is likely to play an important role in inducing BPH. In women, 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. A similar inflammatory reaction was also noted in T. vaginalis-infected prostatic epithelial cells in some in vitro studies. Repeated cell damage and repair in chronic inflammation is likely to play an important role in inducing BPH. Furthermore, the alteration in cytokine expression during chronic inflammation may have effects on cell growth and proliferation of the prostate epithelium and stroma.

**Discussion**

We designed this case-control study based on nationwide data from Taiwan NHIRD. We found that T. vaginalis infection was significantly associated with BPH and PCa in a male population. Therefore, 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 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.

The mechanism of T. vaginalis inducing BPH and PCa still remains unclear. Several studies have demonstrated different possible mechanisms. In women, 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. A similar inflammatory reaction was also noted in T. vaginalis-infected prostatic epithelial cells in some in vitro studies. Repeated cell damage and repair in chronic inflammation is likely to play an important role in inducing BPH. Furthermore, the alteration in cytokine expression during chronic inflammation may have effects on cell growth and proliferation of the prostate epithelium and stroma. T. vaginalis possibly induces carcinogenesis of the prostate. The infected prostatic epithelial cells produce IL-6 in chronic inflammation. In early studies, an elevated serum IL-6 level was noted in patients with advanced PCa. The positive correlation between IL-6 receptor expression and cell proliferation has been reported. IL-6 also induces epithelial-mesenchymal transition (EMT) in breast cancer growth and metastasis, and the same reaction may also occur in prostatic epithelial cells. In addition, more than one study has demonstrated that IL-6 could enhance androgen receptor (AR) activity and AR gene expression, which is also related to prostate cancer growth.

Twu et al. demonstrated that T. vaginalis macrophage migration inhibitory factor (TvMIF) plays an important role in inducing PCa. There are already studies that have proven that higher macrophage migration inhibitory factor (HuMIF) levels are present in several cancers, including PCa. 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.

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.
Our 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 [28]. Moreover, depression can also cause cytokine dysregulation and increased serum IL-6 concentration [28], 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 histological and TNM classification of PCa and BC, serum sex hormone concentrations, family history, or personal history such as 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 [29], 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 [30]. 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.

**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.

**Abbreviations**

AOR: adjusted odds ratio; AR: androgen receptor; BC: bladder cancer; BMI: body mass index; BPH: benign prostate hyerplasia; CCL2: chemokine ligand 2; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EMT: epithelial-mesenchymal transition; FGF-2: fibroblast growth factor 2; GUC: genitourinary cancers; HPFS: Health Professionals Follow-up Study; HuMIF: human macrophage migration inhibitory factor; IL: interleukin; LHID2005: Longitudinal Health Insurance Database 2005; NHI: National Health Insurance; NHIRD: National Health Insurance Research Database; NT$: New Taiwan Dollars; OR: odds ratio; PCa: prostate cancer; STI: sexually transmitted infection; *T. vaginalis*: *Trichomonas vaginalis; TvMIF: Trichomonas vaginalis* macrophage migration inhibitory factor; UTI: urinary tract infection

**Declarations**

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**Availability of data and materials**

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.

**Authors’ contributions**

HCL, HYY and CCC conceived the idea and wrote the first draft manuscript. RYS and KYH contributed to the manuscript. WCC and CHC research data collection and statistical analyses. All authors read and approved the final manuscript.

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**Ethics approval:**

This study was approved by the Institutional Review Board of Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan (TSGHIRB No. 2-105-05-082).

**Consent for publication:**

Because the patient identifiers were encrypted before their data were used for research purposes to protect confidentiality, the requirement for written or verbal consent from patients for data linkage was waived.

**Conflicts of Interest:** The authors declare no competing interests.

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**Figures**

The flowchart of the study design (nested case-control study) from National Health Insurance Research Database in Taiwan.
Figure 2
Risk of BPH/prostate or bladder cancer stratified by trichomoniasis and depression status using logistic regression

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