

***Trichomonas vaginalis* and prostate cancer: A systematic review**

Trichomonas vaginalis e câncer de próstata: Uma revisão sistemática

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Abstract

Introduction: Prostate cancer (PC) is the second most frequent neoplasm in men accounting for 29% of tumor cases, at a rate of 1.4 million new cases and 375,000 deaths globally each year. Although its high prevalence, little is known about its etiology. Sexually transmitted infections (STIs) are one of the factors under discussion for a possible risk factor. Trichomoniasis is a prevalent STI caused by the pathogenic protozoan *Trichomonas vaginalis* that has been associated with the incidence of PC. **Objectives:** This review aims to determine whether the *T. vaginalis* is a risk factor for the development and/or progression of the disease. **Methodology:** A systematic review was conducted using the PubMed and Scielo databases. The following descriptors were used: “Prostate Cancer”; “Trichomonas vaginalis”; “Trichomonosis”; “Prostate”, all indexed in DeCS/MeSH. **Results and Discussion:** In total, 24 articles were included (8 in vitro studies; 1 in vivo study; 3 prospective studies; 9 case-control studies; 2 randomized clinical trials; and 1 systematic review and meta-analysis). **Conclusion:** Even though in vitro and in vivo studies analyzed credibly indicate the existence of this pathophysiology, these findings have not been reproduced in most populations studies conducted, throughout the years. More recent studies involving a bigger database indicates an association. This leads us to believe that new population studies should be conducted to obtain a consensus so that educational and preventive measures can be implemented.

Keywords: Prostatic neoplasms; *Trichomonas vaginalis*; Trichomonas infections; Prostate.

Resumo

Introdução: O câncer de próstata (CP) é a segunda neoplasia mais frequente nos homens, representando 29% dos casos de tumor, com uma taxa de 1,4 milhões de novos casos e 375.000 mortes por ano no mundo. Apesar de sua alta

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prevalência, pouco se sabe sobre sua etiologia. As infecções sexualmente transmissíveis (IST) são um dos fatores em discussão para um possível fator de risco. A tricomoníase é uma IST prevalente causada pelo protozoário patogênico *Trichomonas vaginalis* que tem sido associada à incidência de CP. Objetivo: Verificar se *T. vaginalis* é um fator de risco para o desenvolvimento e/ou de CP. Metodologia: Foi realizada uma revisão sistemática nas bases de dados PubMed e Scielo. Foram utilizados os seguintes descritores: “Prostate Cancer” e “Trichomonas vaginalis” “Trichomonosis”, “Prostate”, todos indexados no DeCS/MeSH. Resultados e Discussão: No total, foram incluídos 24 artigos (8 estudos in vitro; 1 estudo in vivo; 3 estudos prospectivos; 9 estudos caso-controle; 2 ensaios clínicos randomizados; e 1 revisão sistemática e meta-análise). Conclusão: Embora os estudos in vitro e in vivo analisados indiquem de forma crível a existência desta fisiopatologia, estes resultados não foram reproduzidos na maioria dos estudos populacionais realizados, ao longo dos anos. Estudos mais recentes envolvendo uma base de dados maior indicam uma associação. Novos estudos populacionais devem ser realizados para se obter um consenso para que medidas educativas e preventivas possam ser implementadas.

Palavras-chave: Neoplasias de próstata; *Trichomonas vaginalis*; Tricomoníase; Próstata.

Resumen

Introducción: El cáncer de próstata (CP) es la segunda neoplasia más frecuente en hombres, representando el 29% de los casos tumorales, con una tasa de 1,4 millones de nuevos casos y 375.000 muertes al año en todo el mundo. Apesar de su alta prevalencia, se sabe poco sobre su etiología. Las infecciones de transmisión sexual (ITS) son uno de los factores en discusión como posible factor de riesgo. La tricomoniasis es una ITS prevalente causada por el protozoo patógeno *Trichomonas vaginalis* que se ha asociado con la incidencia de CP. Objetivo: Verificar si *T. vaginalis* es un factor de riesgo para el desarrollo y/o CP. Metodología: Se realizó una revisión sistemática en las bases de datos PubMed y Scielo. Se utilizaron los siguientes descriptores: “Cáncer de Próstata” y “Trichomonas vaginalis”, “Trichomonosis”, “Próstata”, todos indexados en DeCS/MeSH. Resultados y discusión: En total se incluyeron 24 artículos (8 estudios in vitro; 1 estudio in vivo; 3 estudios prospectivos; 9 estudios de casos y controles; 2 ensayos clínicos aleatorizados; y 1 revisión sistemática y metanálisis). Conclusion: Aunque los estudios in vitro e in vivo analizados indican de manera creíble la existencia de esta fisiopatología, estos resultados no se han reproducido en la mayoría de estudios poblacionales realizados a lo largo de los años. Estudios más recientes que involucran una base de datos más grande indican una asociación. Es necesario realizar nuevos estudios poblacionales para llegar a un consenso que permita implementar medidas educativas y preventivas.

Palabras clave: Neoplasias de la próstata; *Trichomonas vaginalis*; Tricomoniasis; Próstata.

1. Introduction

Prostate cancer (PC) is the second most frequent neoplasm in men, accounting for 29% of tumor cases (Siegel et al, 2023). It most frequently diagnosed in 112 countries, at a rate of 1.4 million new cases and 375,000 deaths globally each year (Sung et al., 2021). For 2023, the estimate is 288,300 new cases and 34,700 deaths in the United States alone (Siegel et al, 2023).

Adenocarcinoma is a histological subtype among prostate cancers (95% of cases). It presents in the acinar form and is diagnosed histologically by the presence of small glands, typically smaller than benign glands, infiltrated with prominent nucleoli. The ductal form presents the formation of large glands showing papillary configurations (Vollmer, 2002). Other subtypes include neuroendocrine, urothelial carcinoma, carcinosarcoma, basal cell carcinoma, and stromal sarcoma.

The clinical picture is variable, with most diagnoses occurring in the localized stage, when the pathology is asymptomatic. More uncommonly, it can present with lower urinary tract symptoms (LUTS), such as hematuria or hematospermia, and even urinary urgency, nocturia and urinary excitation, more frequently associated with benign prostatic hyperplasia (BPH) (Hordern & Street, 2007). Among the 6% of patients diagnosed in the metastatic phase, bone pain is a possible symptom. In these cases, the inability to urinate, urinary incontinence, erectile dysfunction, weight loss, weakness or back pain due to spinal cord compression, pain associated with pathological fractures, fatigue caused by anemia or symptoms associated with chronic kidney disease may also be present (Collin et al, 2009).

Little is known concerning its etiology, though discussions concerning risk factors establish age above 65 years old. Family history, genetic mutations (such as the BRCA1 and BRCA2 mutation), familial conditions like Lynch syndrome, and Black ethnicity, which alone increases mortality rates by 2 to 4 times compared with the general population (Siegel et al., 2023). In terms of modifiable risk factors, much of the discussion focuses on the impact of diet, especially animal fat consumption,

considered an important factor in the development of PC (Kolonel et al, 1999). Obesity is also a risk factor for development of the disease and increased mortality (MacInnis & English, 2006). Smoking load particularly, is considered a determining factor in mortality, while no consensus exists regarding the clinical impact of other potential factors.

Sexually transmitted infection (STI) trichomoniasis is prevalent among people of low socioeconomic status, by the way and non-sexual transmission is considered rare. Caused by *Trichomonas*, a pathogenic protozoan of the Trichomonadidae family and a facultative anaerobic organism, its energy source consists of glucose, fructose, maltose, glycogen and starch, and it may maintain a glycogen reserve. Can synthesize certain amino acids, showing weak transamination activity. It shows good growth in pH range 5 to 7.5 and at temperatures from 20 to 40°C. Its habitat is the genitourinary tract of men and women, where it promotes infection; outside the tract, it does not survive (Neves, 2012). The disease vector and its pathogenesis depends on components of the cell surface of the host and parasite, and vaginal and urethral secretions. The flagellate possesses virulence mechanisms that depend on adherence and cytotoxicity, such as adhesins, cysteine-proteinases, integrins and glycosidases, but also possesses contact-dependent mechanisms.

The clinical presentation of this STI is broad, and in men it is asymptomatic. In asymptomatic cases, the most locations for flagellates are the urethra and prostate. Because it has abundant glycogen, the male urogenital tract is the most common for parasite development. Underdiagnosis and undertreatment in asymptomatic disease can lead to complications, the most common of which are prostatitis (often nonspecific), balanoposthitis, and cystitis (Neves, 2012).

One important problem of nonspecific prostatitis is that it causes constant inflammation of the urethral and prostate region, besides more common complications, can result in prostatic cell lysis, inhibition of apoptotic factors and stimulation of the production of proto-oncogenes, and may induce the formation of cancer (Langston et al, 2019).

Within this hypothesis, several studies were conducted on the pathophysiology of the inflammatory process resulting from infection by *T. vaginalis* and its influence on the development and progression of PC; however, even though a large number of in vitro and animal model studies describe the pathophysiological aspect of this relation, population studies show a divergence of results. After two decades of decline, however, the incidence of this neoplasm grew by 3% from 2014 to 2019, resulting in 99,000 new cases, approximately half of which presented an advanced stage cancer (Siegel et al., 2023). Given these problematic indications, this review examines the relation between PC and *T. vaginalis* infection, to determine whether the latter is a risk factor for the development and/or progression of the disease.

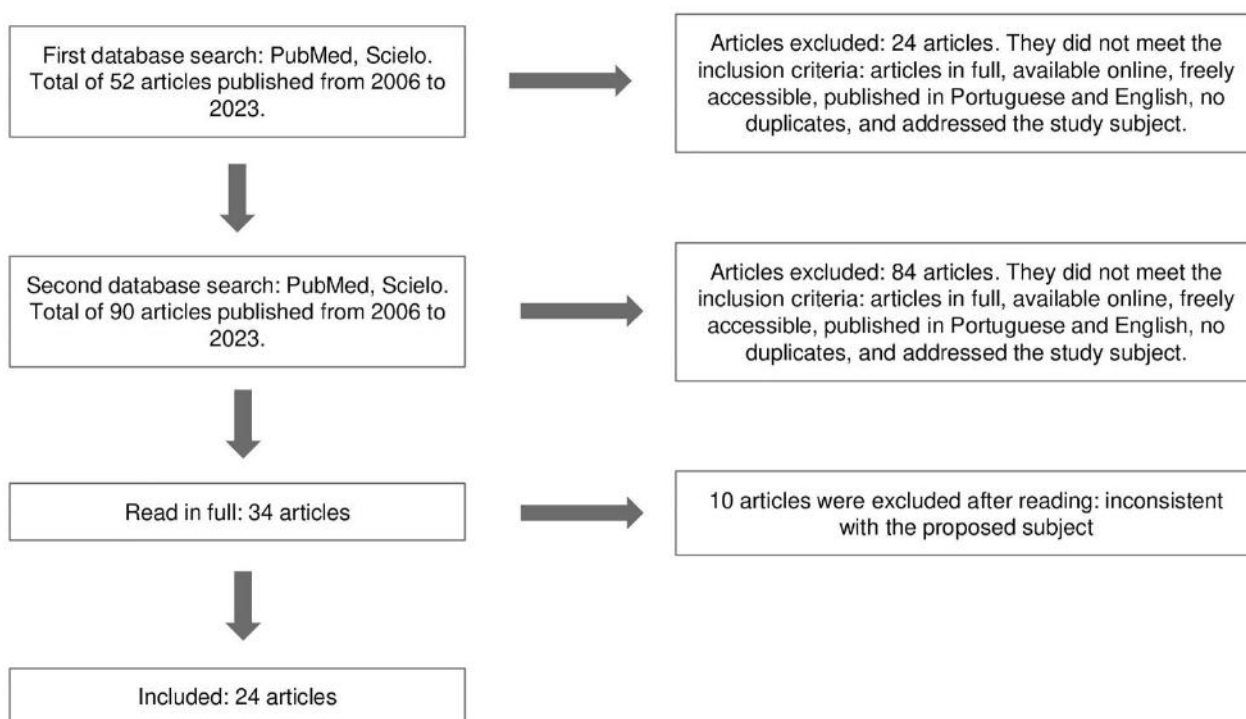
2. Methodology

A systematic review was conducted using the PubMed and Scielo databases, considering works published between 2002 and 2023. This review is an approach referenced in the methodology of Galvão and Ricarte (2019) that synthesizes the state of knowledge on the relationship between CP and *T. vaginalis*. The following descriptors were used: “Prostate Cancer”; “Trichomonas vaginalis”; “Trichomonosis”; and “Prostate”, all indexed in DeCS/MeSH. The first search involved the first two descriptors, and the second, the last two, in order to expand the results. The inclusion criteria for this review were: articles in full, available online, free access, published in Portuguese and English, no duplicates, and articles addressing the study subject.

3. Results and Discussion

The first search found 52 articles, 28 which met the inclusion criteria. The second found 90 articles, 6 which met the inclusion criteria. Ten of these articles were excluded because they presented similar themes, incomplete material, were written in other languages and/or were inconsistent with the subject (Figure 1).

Figure 1 – Flowchart of article search and selection.



Source: Authors.

Among the 24 selected articles, 6 (25.00%) are from 2019, 4 (16.66%) from 2020, 3 (12.50%) from 2016, 3 (12.50%) from 2021, 2 (8.33%) from 2009, 2 (8.33%) from 2012, 1 (4.17%) from 2006, 1 (4.17%) from 2014, 1 (4.17%) from 2017 and 1 (4.17%) from 2022 (Table 1).

Table 1 – Papers selected for systematic review.

Authors	Title	Types of studies	Key-information
Chen et al, 2012	Prospective study of effect modification by Toll-like receptor 4 variation on the association between <i>Trichomonas vaginalis</i> serostatus and prostate cancer	Prospective	No statistical association
Chung et al, 2020	Polarization of M2 Macrophages by Interaction between Prostate Cancer Cells Treated with <i>Trichomonas vaginalis</i> and Adipocytes	In vitro	Pathophysiology
Fowke et al, 2016	A prospective study of <i>Trichomonas vaginalis</i> and prostate cancer risk among African American men	Prospective	No statistical association
Han et al, 2016	Signalling pathways associated with IL-6 production and epithelial-mesenchymal transition induction in prostate epithelial cells stimulated with <i>Trichomonas vaginalis</i>	In vitro	Pathophysiology
Han et al, 2019	Inflammatory mediators of prostate epithelial cells stimulated with <i>Trichomonas vaginalis</i> promote proliferative and invasive properties of prostate cancer cells	In vitro	Positive association
Han et al, 2020	IL-6 produced by prostate epithelial cells stimulated with <i>Trichomonas vaginalis</i> promotes proliferation of prostate cancer cells by inducing M2 polarization of THP-1-derived macrophages	In vitro	Pathophysiology
Kamarkhani et al, 2021	Molecular Examination of <i>Trichomonas vaginalis</i> Infection and Risk of Prostate Cancer in the Biopsy of Patients with Different Prostate Lesions	Case-control	Negativity on biopsy
Kim et al, 2019	Comparison of Seropositivity to <i>Trichomonas vaginalis</i> between Men with Prostatic Tumor and Normal Men	Case-control	Positive association (seropositivity)

Kim et al, 2021a	Involvement of Macrophages in Proliferation of Prostate Cancer Cells Infected with <i>Trichomonas vaginalis</i>	In vitro	Pathophysiology
Kim et al, 2021b	Proliferation of Mouse Prostate Cancer Cells Inflamed by <i>Trichomonas vaginalis</i>	In vivo	Pathophysiology
Kushwaha et al, 2020	Inflammation driven tumor-like signaling in prostatic epithelial cells by sexually transmitted <i>Trichomonas vaginalis</i>	In vitro	Pathophysiology
Langston et al, 2019	<i>Trichomonas vaginalis</i> infection and prostate-specific antigen concentration: Insights into prostate involvement and prostate disease risk	Case-control	No statistical association
Marous et al, 2017	<i>Trichomonas vaginalis</i> infection and risk of prostate cancer: associations by disease aggressiveness and race/ethnicity in the PLCO Trial	Randomized clinical trials	No statistical association
Najafi et al, 2019	Is there association between <i>Trichomonas vaginalis</i> infection and prostate cancer risk?: A systematic review and meta-analysis	Systematic review and meta-analysis	No statistical association
Saleh et al, 2020	<i>Trichomonas vaginalis</i> serostatus and prostate cancer risk in Egypt: a case-control study	Case-control	Positive association with no impact on mortality
Shui et al, 2016	<i>Trichomonas vaginalis</i> infection and risk of advanced prostate cancer	Case-control	No statistical association about mortality
Stark et al, 2009	Prospective study of <i>Trichomonas vaginalis</i> infection and prostate cancer incidence and mortality: Physicians' Health Study	Prospective	Positive association with impact on mortality
Sutcliffe et al, 2009	Trichomonosis and subsequent risk of prostate cancer in the Prostate Cancer Prevention Trial	Randomized clinical trials	No statistical association
Sutcliffe et al, 2012	Trichomonosis, a Common Curable STI, and Prostate Carcinogenesis - A Proposed Molecular Mechanism	In vitro	Pathophysiology
Sutcliffe, 2006	Plasma antibodies against <i>Trichomonas vaginalis</i> and subsequent risk of prostate cancer	Case-control	Positive association (seropositivity)
Tsang et al, 2019	Association between <i>Trichomonas vaginalis</i> and prostate cancer mortality	Case-control	No impact on mortality
Two et al, 2014	<i>Trichomonas vaginalis</i> homolog of macrophage migration inhibitory factor induces prostate cell growth, invasiveness, and inflammatory responses	In vitro	Positive association
Vicier et al, 2019	Elevated Serum Cytokines and <i>Trichomonas vaginalis</i> Serology at Diagnosis Are Not Associated With Higher Gleason Grade or Lethal Prostate Cancer	Case-control	No impact on mortality
Yang et al, 2022	Association between trichomoniasis and prostate and bladder diseases: a population-based case-control study	Case-control	Positive association

Source: Authors.

The types of studies analyzed: 8 (33.33%) in vitro studies; 1 (4.17%) in vivo study; 3 (12.50%) prospective studies; 9 (37.50%) case-control studies; 2 (8.33%) randomized clinical trials; and 1 (4.17%) systematic review and meta-analysis.

The initial evidence of an association between *T. vaginalis* and PC dates back to 2006, a case-control study was conducted within the Health Professionals Follow-up Study (an all-male study designed to complement the all-female Nurses' Health Study) on 691 patients in the United States (Sutcliffe, 2006). They reported a 1.05 higher prevalence of seropositivity for *T. vaginalis* in patients with PC by measuring IgG in patients diagnosed with PC and control patients (OR=2.05; 95% CI: 1.05–4.02; p interaction=0.11). Since 2006, this association has been studied using different models and approaches to determine its pathophysiology and potentially important clinical findings linking these two pathologies (Sutcliffe, 2006).

In vitro studies

Eight in vitro studies were conducted, when Sutcliffe et al. (2012) returned to elucidate the pathophysiology of the data they had previously reported (Sutcliffe, 2006), which suggested that an alteration in the PIM 1-HMGA1-COX 2 cascade that could lead to carcinogenesis (Sutcliffe et al., 2009), though no further investigation was conducted. In 2014, it was reported that *T. vaginalis* macrophage migration inhibitory factor, (TvMIF) showed tautomeric action (Twu et al., 2014).). This protein has 47% similarity with human MIF (HuMIF), a pro-inflammatory cytokine. Thus, TvMIF acts by inhibiting macrophage migration,

and through binding to the human CD74 MIF receptor with high affinity, comparable to that of HuMIF, it can trigger extracellular-signal-regulated kinase (ERK) activation, serine threonine kinase (Akt) and B-cell leukemia/lymphoma 2 protein (Bcl-2)-associated phosphorylation death at a physiologically relevant concentration, thus increasing the growth and invasion of PC (Twu et al., 2014).

T. vaginalis could be an important factor in tumor progression due to changes in the macroenvironment that induced IL-6 production and mesenchymal epithelium transition (Han et al., 2016). It was observed increased production in IL-1 β , IL-6, CCL2, CXCL8, PGE2 and COX2 by RWPE-1 cells (normal prostatic epithelium) when stimulated by *T. vaginalis*, increases in the proliferation, invasion and migration of PC cells, and increases in markers associated with the epithelial-mesenchymal transition, suggesting that *T. vaginalis* infection is one of the factors that creates not only a favorable macroenvironment (Han et al., 2016), but also a microenvironment favorable to the proliferation and invasion of PC (Han et al., 2019).

Recently, in 2020 and 2021, four studies determined a positive association between *T. vaginalis* and PC, through IL-6 production following infection (Han et al., 2020), leading to the polarization of M2 macrophages, and progression of neoplastic cells and greater neoplasm aggressiveness (Han et al., 2020; Chung et al., 2020). The study findings also indicate that PC cells show greater sensitivity to *T. vaginalis* compared with healthy prostatic epithelium (Kushwaha et al., 2020), leading to an exacerbation of PC through an inflammatory process caused by *T. vaginalis* that can lead to metaplasia (Kim et al., 2021a).

In vivo studies

Using PC cells from *T. vaginalis*-infected mice, in 2021, researchers in Seoul observed increased production of CXCL1 and CCL2 inflammatory cytokines, and an increase in CXCR2, CCR2, and gp130 receptors, leading to greater migration, proliferation and invasion by PC. These alterations decreased following treatment with antibodies specific for *T. vaginalis*; however, they still presented a more aggressive character than cells with no contact with the parasite. The study's findings indicate an association between *T. vaginalis* and the invasion and proliferation of PC through a cytokine cascade (Kim et al., 2021b).

Prospective studies

Three prospective studies were analyzed. In the first, which formed part of the Health Professionals Follow-up Study, a prospective study that indicated an association between seropositivity for *T. vaginalis* and PC risk (OR=1.23; 95% CI: 0.94–1.61) and high-grade cancer (OR for Gleason 7-10 scores=1.10; 95% CI: 0.72–1.68), though neither result was significant. However, a significantly higher risk of diagnosing advanced disease (OR=2.17; 95% CI: 1.08–4.37), and neoplasms that could ultimately progress to distant metastases or death specific to the disease were determined (OR=2.69; 95% CI: 1.37–5.28) (Stark et al., 2009).

In the second, observed the same group of patients from the 2006 study, investigating the pathophysiology of the association between *T. vaginalis* and PC through the modifying effect on Toll-like receptor 4 (TLR4) and its variants by *T. vaginalis* infection in prostatic epithelium that led to metaplasia. The study observed no association between carriers of the rs4986790 variant (p interaction=0.07) or in homozygous men for the wild-type SNP variant (OR=1.23; 95% CI: 0.86–1.77); however, a positive association was observed between variant carriers (OR=4.16; 95% CI: 1.32–13.1), leading to the hypothesis that TLR4 variants influence the relationship between *T. vaginalis* and PC risk, and inflammation plays a role in this association (Chen et al., 2012).

The final study from 2016, again part of the Health Professionals Follow-up Study, involved 881 men and reported no significant associations or trends between *T. vaginalis* serological levels and PC risk or aggressive PC diagnosis in African-

American men (all $p > 0.05$) (Fowke et al., 2016).

Case-control studies

Case-control studies were the format most used to assess this issue. The first was conducted in 2016, involved 327 patients, 146 of whom had advanced or metastatic PC, and showed no risk between these parameters and *T. vaginalis* infection. However, the study did not evaluate serological status as a risk factor for neoplasia development, an issue in this review, while raising the hypothesis that this was a protective factor and suggesting further research (OR=0.57; 95% CI: 0.30–1.08) (OR=0.51; 95% CI: 0.28–0.93) (Sutcliffe et al, 2006, Shui et al., 2016).

In 2018, a new study involving 749 men from the Health Professionals Follow-Up Study, the population of seven of the studies evaluated here, observed no association between serological status for *T. vaginalis* and mortality from PC or all causes (Tsang et al, 2019).

The following year, a study was conducted to determine how high levels of cytokines and antibodies to *T. vaginalis* at the time of PC diagnosis were related to aggressiveness and lethality, involving 324 patients. This study also discarding any association and did not evaluate *T. vaginalis* as a risk factor, like the 2016 study ($p > 0.05$) (Vicier et al., 2019). Another study of the same scope, conducted in Korea on 183 men, revealed the presence of antibodies to *T. vaginalis* were 1.7% higher in men with prostate tumors ($p = 0.001$) (Kim et al., 2019). However, in the same year, another study involving 732 US military personnel reported that even though the findings did not determine any association between *T. vaginalis* and the prostate gland, these should be reviewed due to elevated PSA in men with a high serological load for *T. vaginalis* ($p = 0.125$) (Langston et al, 2019).

More recently, in 2020 and 2021, two more case-control studies were published. An Egyptian study, involving 445 men, identified that while only 8.3% of controls were seropositive for trichomoniasis, this proportion rose to 19% in PC patients, and was associated with PSA levels and tumor stage; however, no impact on prognosis or mortality was observed ($p < 0.001$ and $p < 0.05$) (Saleh et al., 2020). In Iran, 250 samples of prostate lesions were analyzed using PCR, all were negative; however, studies that reported associations between these two factors used serology for *T. vaginalis*, thus PCR may not be the most appropriate technique to determine an association (Kamarkhani et al., 2021).

In 2022, a large case-control study was conducted using the National Health Insurance Program database in Taiwan, involving 253,176 patients. It determined a significant association ($p = 0.016$) between *T. vaginalis* and PC, which was more intense when the patient had both *T. vaginalis* and depression (Yang et al., 2022).

Randomized clinical trials

Although this form of research is the most adequate to address this relation, only two randomized clinical trials were conducted. Within the Health Professionals Follow-Up Study set out to confirm their initial findings by conducting a randomized clinical trial involving 616 control patients and 18 patients with PC. No relation was observed between these parameters (OR=0.83; 95% CI: 0.63-1.09), while for men with high seropositivity, the OR was 0.97 (95% CI: 0.70-1.34). In 2017, again with patients previously studied within the Health Professionals Follow-up Study, this time involving 1126 patients with PC and 1216 control patients. No association between *T. vaginalis* infection and the PC was observed; moreover, none were observed for risk of Gleason 7 (OR=0.87; 95% CI: 0.55–1.37), nor for more advanced PC in Caucasian men (OR=0.90; 95% CI: 0.58–1.38), nor for risk of any PC in African-American men (OR=1.06; 95% CI: 0.67–1.68) (Sutcliffe et al, 2009, Marous et al., 2017).

Systematic review and meta-analysis

In 2019, a meta-analysis was performed which concluded that the risk for PC is 17.51% higher in individuals with

previous exposure to *T. vaginalis* (OR=1.17; 95%CI: 1.01–1.36) (Najafi et al., 2019); however, these findings are not significant.

4. Conclusion

Following the systematic analysis of published articles concerning the relation between *T. vaginalis* infection and PC, at this time, none of the studies indicate a significant association. However, it should be highlighted that 8 of the 24 articles analyzed were conducted within the Health Professionals Follow-up Study, a group of men with knowledge concerning STIs, their transmission, protection against transmission, access to medication, and a high socioeconomic status, all factors of great importance in the history of *T. vaginalis* infection. In contrast, all the in vitro and in vivo studies analyzed credibly indicate the existence of this pathophysiology. Even though these findings have not been reproduced in surveyed populations, the large number of studies and the presence of the recent Taiwanese study, which had the largest database among the studies analyzed, indicates a significant association. This leads us to believe that new population studies should be conducted to obtain a consensus so that educational and preventive measures can be implemented.

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