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UROLOGICAL ONCOLOGY

Genitourinary microbiomes and prostate cancer: a systematic review and meta-analysis of tumorigeneses and cancer characteristics

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Introduction We assessed the association of genitourinary microbiomes with prostate cancer (PCa) tumorigeneses and cancer characteristics.

Material and methods A systematic search and meta-analysis was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement. The primary endpoints were the association between relative abundance of genitourinary microbiomes and PCa compared to non-cancerous men/prostate specimen, high grade disease, and disease progression. The odds ratio (OR) was used as the summary statistic, and results were reported with 95% confidence intervals (CI).

Results Seventeen studies, comprising 2,195 patients were eligible for review and meta-analysis. The specific microbiomes in urine, prostate tissue, and prostate (or seminal) secretions were significantly more abundant in patients with PCa compared to men in the control groups in individual studies. Certain bacterial phyla, genuses, and species were significantly associated with PCa aggressiveness and disease progression in individual studies. The relative abundance meta-analysis of five urine microbiomes revealed no statistically significant differences between PCa patients and control groups (pooled OR, 1.35; 95% CI: 0.70–2.59).

Conclusions Our systematic review indicates that specific genitourinary microbiomes are more abundant in PCa and have a potential to predict/prognosticate disease aggressiveness and clinical outcomes. Nevertheless, these findings should be interpreted with caution owing to the significant heterogeneity among studies in terms of microbiome analysis method, assessed sample's characteristics, and individual biological behavior of microbiomes for analysis. Further studies are needed to validate these observations and shed more light on the role of the microbiome across the development and natural history of PCa.

Key Words: prostate cancer ‹› prostate adenocarcinoma ‹› microbiome ‹› microbiota ‹› prognosis

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer in men and the second leading cause of cancer death in the United States [1]. Recent evidence supports the hypothesis that chronic inflammation in the prostate microenvironment plays an important role in prostate carcinogenesis and prognosis [2].
Indeed, the microbiome has been shown cause and sustain chronic inflammatory microenvironment thereby generating reactive oxygen species and epigenetic alterations that promote prostate carcinogenesis [2]. A growing body of evidence supports an essential role of genitourinary microbiomes in dysregulations associated with PCa [3, 4] with an effect on a proinflammatory cascade affecting various processes within the extracellular environment [5]. Despite all these biologic evidences, the effect of microbiome on the risk of PCa is still to be uncovered.
In this systematic review and meta-analysis, we evaluated the association of genitourinary microbiomes with PCa tumorigeneses and disease severity.

MATERIAL AND METHODS

Search strategy

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [6]. In August 2023, a literature search on the PubMed, Scopus, and Cochrane Library databases was performed to identify reports investigating the association between genitourinary microbiome and PCa. The search terms used were (prostate cancer OR prostate neoplasm OR prostate carcinoma OR prostate tumor OR prostatic carcinoma OR prostatic cancer OR prostatic tumor OR prostatic neoplasm) AND (microbiota OR microbiome). We also checked the reference lists of relevant publications for additional pertinent publications. The international prospective register of systematic reviews (PROSPERO) was searched and indicated no relevant registered or published reviews. The protocol for this systematic review was registered in PROSPERO (CRD42023474549) and is available in full on the University of York website.

Inclusion criteria

The population, intervention, comparator, outcome, and study design (PICOS) approach was used to define the eligibility criteria. Studies were selected when patients with PCa (P: population) who were assessed for the presence of specific genitourinary microbiome (I: interventions) were compared with patients/prostate specimen without PCa (C: comparators) in terms of abundance of genitourinary microbiome and oncological survival outcomes (O: outcomes) using prospective or retrospective studies (S: study design). Furthermore, the association between genitourinary microbiomes and PCa aggressiveness (high-grade tumor) as well as progression (biochemical recurrence/metastatic disease) was evaluated. We excluded studies in other languages than English, meeting abstracts, case reports, review articles, replies, expert opinions, and commentaries and letters.

Data extraction

Two authors extracted the data from all eligible studies. The information contained the following characteristics: first author's name, publication year, region, recruitment period, study design, number of patients with available clinical and survival data, assessed specimen, microbiome analysis method, age, and predominant microorganism. The association of microbiomes abundance with PCa and disease characteristics were retrieved. All discrepancies regarding data extraction were resolved by consensus among co-authors.

Statistical analyses

We assessed the odds ratio (OR) from the analyses of individual studies and obtained a summary OR of the value microbiomes on prostate carcinogenesis. Heterogeneity among the outcomes of the included studies in this meta-analysis was assessed using Cochrane Q test and I^2 statistic. Significant heterogeneity was indicated by a $P < 0.05$ in Cochrane Q tests and a ratio >50% in I^2 statistics. Publication bias was assessed by Egger's test. Statistical analyses were performed using R version 4.0.3 (2020; R Foundation for Statistical Computing, Vienna, Austria).

Study quality assessment

We used The Newcastle-Ottawa Scale (NOS) to assess the quality of selected studies by two independent reviewers. The methodology comprises three components: group selection (0–4 points), Comparability (0–2 points), and exposure assessment (0–3 points) [7]. The maximum achievable score is 9 points, indicative of high methodological quality. Furthermore, Egger's test was conducted to evaluate the risk of publication bias [8].

RESULTS

Literature search process

A total of 536 studies were identified by our initial literature search, and 175 duplicates were removed. Three hundred thirteen and 31 studies were excluded after title/abstract and full-text evaluations, respectively. Finally, we identified 17 studies for qualitative and two studies for quantitative analyses (Figure 1).

Characteristics of the included studies

Tables 1 and 2 summarize the study characteristics and patients' clinical data, respectively. Thirteen studies were of retrospective design [3, 5, 9–19] and four studies were of prospective design [4, 20–22]. These studies were published between 2006 and 2023, with eight studies from Asia, four from Europe, four from North America, and one from Asia/Africa. In total, the 17 studies included 2195 patients who underwent genitourinary microbiomes assessment and outcome analysis in PCa patients.

Presence of Genus of microbiomes in PCa compared to non-cancerous men/prostate specimen

The genuses of *Enterococcus*, *Staphylococcus*, *Lactococcus*, *Carnobacterium*, *Streptococcus*, *Enterobacter*, *Geobacillus*, *Shewanella*, *Faecalibacterium*, *Neisseria*, *Agathobacter*, *Pseudomonas*, *Shigella*, *Subdoligranulum*, and *Blautia* were significantly more abundant in patients with PCa compared to men in the control groups [5, 10, 13, 14, 20].

Presence of Phylum of microbiomes in PCa compared to non-cancerous men/prostate specimen

The phyla of *Proteobacteria*, *Actinobacteria*, and *Firmicutes* were significantly more abundant in patients with PCa compared to men in the control groups [16].

Presence of Species of microbiomes in PCa compared to non-cancerous men/prostate specimen

The species of *Escherichia coli*, *Propionimicrobium lymphophilum*, *Uritidibacter ignavus*/*Corynebacterium coyleae*, *Cutibacterium acnes* SK137, *Acinetobacter lwoffii*, *Cutibacterium acnes*, *Peptoniphilus lacydonensis*, *Cutibacterium granulosum*, *Porphyromonas* sp. nov, *Varibaculum* sp. nov, *Peptoniphilus* sp. nov, *Fenollaria* sp. nov, *Peptoniphilus harei*, *Anaerococcus prevotii*, *Porphyromonas asaccharolytica*, *Fusobacterium nucleatum*, *Cupriavidus taiwanensis*, *Methylobacterium organophilum*, and *Ruminococcaceae_UCG_002* were significantly more abundant in patients with PCa compared to men in the control groups [3, 10–12, 20, 21, 22].

Association of genitourinary microbiomes with PCa aggressiveness (high-grade tumor)

Eight studies involving 1524 patients provided data on the association of genitourinary microbiomes with PCa pathologic grade [3, 4, 11, 12, 15, 17, 19, 21]. Unassigned *Streptococcus*, *Alloscardovia omnicolens*, *Ureaplasma urealyticum*, *Porphyromonas* sp. nov, *Varibaculum* sp. nov, *Peptoniphilus* sp. nov, *Fenollaria* sp. nov, *Peptoniphilus harei*, *Anaerococcus prevotii*, *Porphyromonas asaccharolytica*, *Fusobacterium nucleatum*, *Prevotella copri*, and *Nevskia ramose* were significantly more abundant in patients with high grade PCa. *Pediococcus pentosaceus*, *Listeria monocytogenes*, *Lactobacillus crispatus* ST1, *Bacillus halodurans*, and *Escherichia coli* were significantly correlated with low tumor grade in PCa patients.

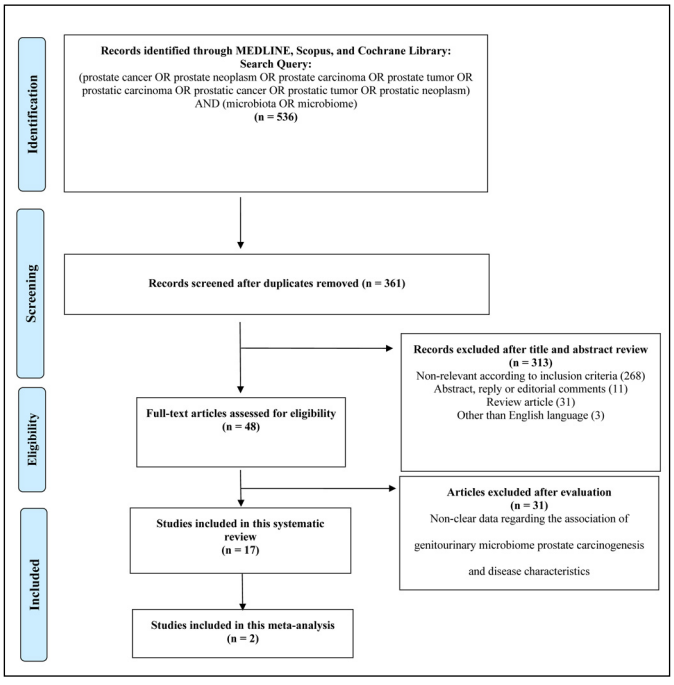

Figure 1. *PRISMA flow chart for article selection process to analyze the the association of genitourinary microbiome and prostate carcinogenesis and disease characteristics.*

Table 1. *Studies' characteristics in17 studies assessing the association of genitourinary microbiome with prostate cancer*

Author	Year	Region	Recruitment period	Design	Specimen	Pts[a]	Microbiome analysis
Alexeyev et al. [19]	2006	Europe	1982–1996	Retrospective	Prostate tissue	352	16S DNA nested PCR assay
Yu et al. [20]	2015	Asia	NA	Prospective	Urine, EPS, Seminal fluid	34	PCR-DGGE
Cavarretta et al. [5]	2017	Europe	2011–2013	Retrospective	Prostate tissue	16	Massive ultradeep pyrosequencing
Shrestha et al. [21]	2018	North America	NA	Prospective	Urine	129	16S DNA PCR
Alanee et al. [4]	2019	North America	NA	Prospective	Urine	30	16S rRNA high-throughput NGS
Feng et al. [18]	2019	Asia	NA	Retrospective	Prostate tissue	65	Metagenomic and meta transcriptomic analysis
Feng et al. [17]	2019	Asia/Africa	NA	Retrospective	Prostate tissue	22	Metagenomic and meta transcriptomic analysis
Ma et al. [14]	2019	Asia	2015–2016	Retrospective	Prostatic fluid	59	16S rRNA gene sequencing
Ma et al. [12]	2020	North America	NA	Retrospective	Prostate tissue	242	RNA sequencing
Ahn et al. [22]	2022	Asia	NA	Prospective	Urine	27	Metagenomic analysis of urinary DNA
Hurst et al. [3]	2022	Europe	2012–2020	Retrospective	Urine, Prostate tissue	318[b]	Anaerobic culture, population-level 16S analysis, RNA sequencing, whole genome DNA sequencing
Salachan et al. [13]	2022	Europe	2004–2019	Retrospective	Prostate tissue	94	RNA sequencing
Sarkar et al. [11]	2022	Asia	NA	Retrospective	Prostate tissue	77	16S rRNA amplicon sequencing and qPCR analyses
Tsai et al. [10]	2022	Asia	NA	Retrospective	Urine	185	16S rRNA sequencing
Kim et al. [16]	2023	Asia	NA	Retrospective	Prostate tissue	23	16S rRNA sequencing
Kim et al. [9]	2023	Asia	NA	Retrospective	Prostate tissue	26	16S rRNA-based NGS
Lee et al. [15]	2023	North America	NA	Retrospective	Urine	311	Multiplex PCR for bacterial genotoxin genes[c]

NA – not available; PCR – polymerase chain reaction; PCR-DGGE – polymerase chain reaction-denaturing gradient gel electrophoresis; EPS – expressed prostatic secretions; NGS – next-generation sequencing
[a]patients with available survival data
[b]discovery, n = 215 patients; validation, n = 103
[c]bacterial genotoxin genes: Colibactin (polyketone synthase [pks] gene island: clbN and clbB), cytotoxic necrotizing factor (cnf1) toxin, and cytolethal distending toxin B (cdtB)

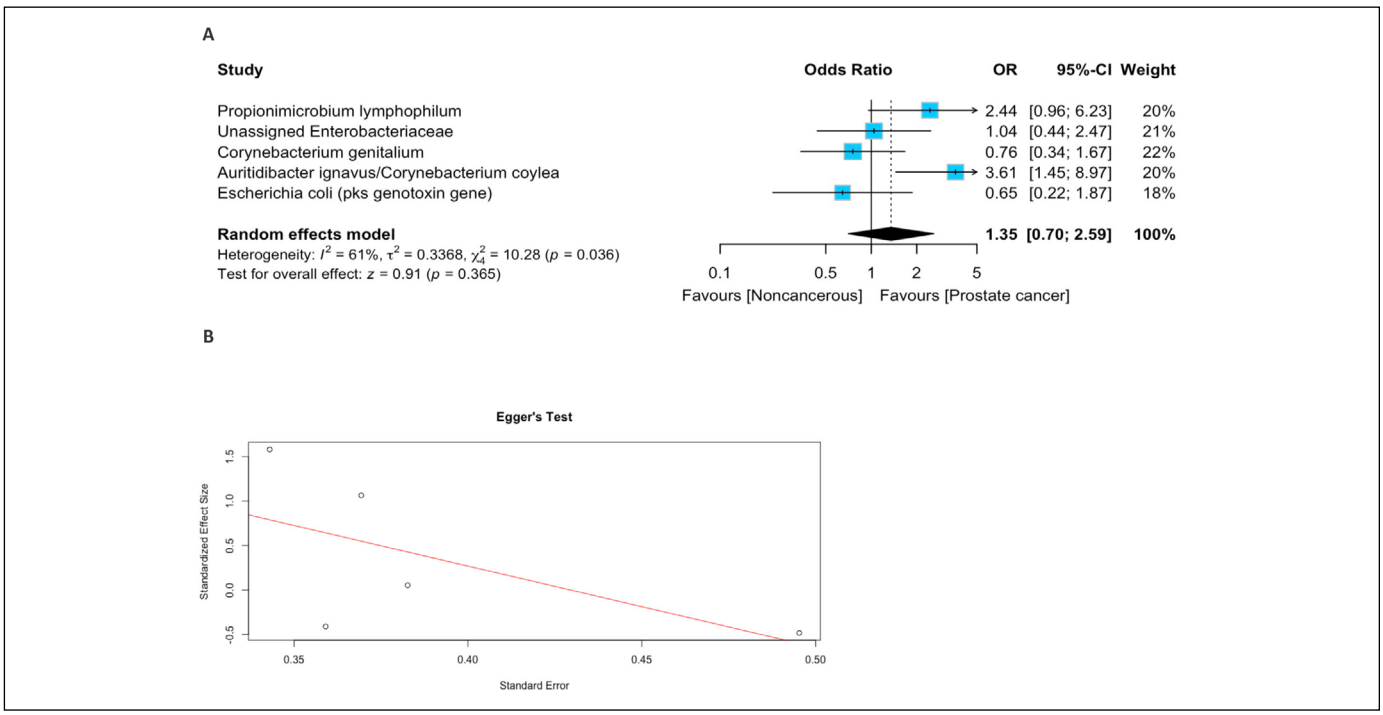

Figure 2. *Forest plot* **(A)** *and Egger's test plot* **(B)** *of six reports on two studies [15, 21] showing the association between urinary microbiomes abundance and prostate cancer.*

Table 2. *Patients' characteristics in 17 studies assessing the association of genitourinary microbiome with prostate cancer*

Author	Pts characteristics (n)	Age, year	Predominant microorganism	Microbiomes associated with the condition			
				Microbiome distribution		High grade PCa	
				In favour of PCa	In favour of BPH		
Alexeyev et al. [19]	BPH[a] (352)	NA	*Propionibacterium acnes*	*Propionibacterium acnes* (NS)	-	NS	NS
Yu et al. [20]	BPH (21), PCa (13)	Mean: 66.7	*E. coli, Enterococcus*	*Escherichia coli* in EPS (S), *Enterococcus* in EPS and seminal fluid (S)	*Escherichia coli* in urine (S), *Enterococcus* in urine (S)	NA	NA
Cavarretta et al. [5]	PCa (16)	Median: 65	*Propionibacterium* sp. *Corynebacteriaceae* sp. *Staphylococcus* sp.	*Staphylococcus* sp. (S)	NS	NA	NA
Shrestha et al. [21]	BPH (63), PCa (66)	Mean: 62.8	*Streptococcus anginosus, Anaerococcus lactolyticus, Anaerococcus obesiensis, Actinobaculum schaalii, Varibaculum cambriense, Propionimicrobium lymphophilum.*	*Propionimicrobium lymphophilum* (S), *Uritidibacter ignavus/ Corynebacterium coyleae* (S)	Unassigned *Enterobacteriaceae* (S), *Corynebacterium genitalium* (S)	Unassigned *Streptococcus* (S), *Alloscardovia omnicolens* (S), *Ureaplasma urealyticum* (S)	NA
Alanee et al. [4]	BPH (16), PCa (14)	NA	*Bacteria, Firmicutes, Bacilli, Lactobacillales, Streptococcaceae, Streptococcus*	NS	Taxonomy: *Firmicutes*, *Erysipelotrichia*; *Erysipelotrichales*, *Erysipelotrichaceae*, *Clostridium_ XVIII* (S). Taxonomy: *Firmicutes*, *Clostridia*, *Clostridiales*, *Lachnospiraceae*, *Clostridium_ XlVa* (S). Taxonomy: *Firmicutes*; *Clostridia*; *Clostridiales*; *Ruminococcaceae*; *Clostridium_IV* (*Acetanaerobacterium*, *Faecalibacterium*) (S).	NS	NA
Feng et al. [18]	PCa (65)	Mean: 68.4	*Escherichia, Propionibacterium, Acinetobacter, Pseudomonas*	NS	NS	NS	*Pseudomonas* (three RNA genes) negatively associated with metastasis
Feng et al. [17]	High risk PCa (22)	NA	*Escherichia, Propionibacterium, Pseudomonas*	NA[b]	NA	NA	NA
Ma et al. [14]	BPH (27), PCa (32)	Mean: 68.2	*Bacillus, Enterococcus, Lactococcus*	*Lactococcus* (S), *Carnobacterium* (S), *Streptococcus* (S), *Enterobacter* (S), *Geobacillus* (S)	*Alkaliphilus* (S), *Cronobacter* (S)	NA	NA
Ma et al. [12]	PCa (242)	NA	NA	*Cutibacterium acnes* SK137[f]	*Cutibacterium acnes* KPA171202[f], *Variovorax paradoxus* S110[f]	Pediococcus pentosaceus[c] (S), Listeria monocytogenes[c] (S), Lactobacillus crispatus ST1[c] (S), and Bacillus halodurans[c] (S), Nevskia r amose[d] (S)	Rhodococcus erythropolis PR4[e] (S), Delftia acidovorans SPH-1[e] (S), Methylobacterium radiotolerans JCM 2831[e] (S), Stenotrophomonas maltophilia K279a[e] (S), Meiothermus silvanus DSM 9946[e] (S)

Table 2. *Continued*

Author	Pts characteristics (n)	Age, year	Predominant microorganism	Microbiomes associated with the condition			
				Microbiome distribution		High grade PCa	
				In favour of PCa	In favour of BPH		
Ahn et al. [22]	PCa (27)	NA	*Cutibacterium, Peptoniphilus, Sphingomonas, Staphylococcus, Micrococcus, Moraxella*	*Acinetobacter lwoffii* (S), *Cutibacterium acnes* (S), *Peptoniphilus lacydonensis* (S), *Cutibacterium granulosum* (S)	*Akkermansia muciniphila* (S), *Sphingomonas* sp. (S), *Pseudomonas* (S), *Methylorubrum* sp. (S)	NA	NA
Hurst et al. [3]	PCa (318)[g]	NA	Phyla *Firmicutes*, phyla *Actinobacteria*, phyla *Bacteroidetes*	*Porphyromonas* sp. nov. (S), *Varibaculum* sp. nov. (S), *Peptoniphilus* sp. nov. (S), *Fenollaria* sp. nov. (S), *Peptoniphilus harei* (S), *Anaerococcus prevotii* (S), *Porphyromonas asaccharolytica* (S), *Fusobacterium nucleatum* (S)	NS	*Porphyromonas* sp. nov. (S), *Varibaculum* sp. nov. (S), *Peptoniphilus* sp. nov. (S), *Fenollaria* sp. nov. (S), *Peptoniphilus harei* (S), *Anaerococcus prevotii* (S), *Porphyromonas asaccharolytica* (S), *Fusobacterium nucleatum* (S)	*Porphyromonas* sp. nov. (S), *Varibaculum* sp. nov. (S), *Peptoniphilus* sp. nov. (S), *Fenollaria* sp. nov. (S), *Peptoniphilus harei* (S), *Anaerococcus prevotii* (S), *Porphyromonas asaccharolytica* (S), *Fusobacterium nucleatum* (S)
Salachan et al. [13]	PCa (94)	Median: 65.7	*Enterobacter hormaechei, Streptococcus pneumoniae, Acinetobacter baumannii, Mycobacterium sp., Salmonella enterica, Escherichia coli, Campylobacter jejuni, Clostridioides difficile, Mycobacterium abscessus, Bacillus cereus*	*Shewanella* (S)	*Staphylococcus saprophyticus* (S), *Vibrio parahaemolyticus* (S)	*Microbacterium* species[h] (S)	NS
Sarkar et al. [11]	BPH (28), PCa (49)	Mean: 65	*Prevotella copri, Cupriavidus campinensis, Propionibacterium acnes*	*Cupriavidus taiwanensis* (S), *Methylobacterium organophilum* (S)	*Kocuria palustris* (S), *Cellvibrio mixtus* (S)	*Prevotella copri* (S)	NA
Tsai et al. [10]	BPH (123), PCa (62)	Mean: 71.1	*Alcaligenes, Pseudomonas, Lactobacillus, Akkermansia, Cetobacterium*	*Faecalibacterium* (S), *Staphylococcus* (S), *Ruminococcaceae_UCG_002* (S), *Neisseria* (S), *Agathobacter* (S), *Pseudomonas* (S), *Escherichia* (S), *Shigella* (S), *Subdoligranulum* (S), *Blautia* (S), *Pseudomonas* (S)	*Sphingomonas* (S)	NA	NA
Kim et al. [16]	BPH (10), PCa (13)	Mean: 71.8	*Proteobacteria, Bacteroidetes, Firmicutes*	*Proteobacteria* (S), *Actinobacteria* (S), *Firmicutes* (S)	*Deferribacteres* (S)	NA	NA
Kim et al. [9]	PCa (26)	Mean: 73	*Proteobacteria, Bacteroidetes,* and *Firmicutes*	NA	NA	NA	*Lactobacillus*[i] (S)

Table 2. *Continued*

Author	Pts characteristics (n)	Age, year	Predominant microorganism	Microbiomes associated with the condition			
				Microbiome distribution		High grade PCa	
				In favour of PCa	In favour of BPH		
Lee et al. [15]	PCa (311)	Mean: 65	*Escherichia coli*	NS	NS	*Escherichia coli* (S)	NA

BPH – benign prostatic hyperplasia; PCa – prostate cancer; NS – non-significant; OR – odds ratio; S – statistically significant; NA – not available; EPS – expressed prostatic secretions
a352 patients with BPH: 171 patients later developed prostate cancer and 181 patients did not progress to cancer
bstatistically significant increase in the richness of the bacterial communities within the African vs Australian samples
cnegatively correlated with Gleason score
dpositively correlated with Gleason score
enegatively correlated with TNM cancer staging
fpro-tumor microbes in prostate cancer cell
g404 (urine sample) + 204 (prostate tissue)
hover-abundant in pathologically advanced T3 tumors compared to T2
irelatively higher population of *Lactobacillus* in patients without biochemical recurrence
fhigher proportion of low-grade cancer in those men positive for urinary genotoxin and higher-grade cancer in those genotoxin negative

Association of genitourinary microbiomes with PCa progression (biochemical recurrence/ metastatic disease)

Six studies involving 855 patients provided data on the association of genitourinary microbiomes with PCa progression (biochemical recurrence/metastatic disease) [3, 9, 12, 13, 18, 19]. *Pseudomonas, Porphyromonas* sp. nov, *Varibaculum* sp. nov, *Peptoniphilus* sp. nov, *Fenollaria* sp. nov, *Peptoniphilus harei, Anaerococcus prevotii, Porphyromonas asaccharolytica,* and *Fusobacterium nucleatum* were significantly more abundant in PCa patients who experienced disease progression compared to those who did not. *Lactobacillus* was significantly more abundant in patients who did not experience biochemical recurrence compared to those who did.

Meta-analysis

Six reports on two studies with 440 patients were included in the relative abundance meta-analysis of urine microbiomes between PCa patients compared to men in the control groups [15, 21]. There was no association between urinary microbiomes and PCa risk (pooled OR: 1.35; 95% CIs: 0.70–2.59). The Chi-square and I^2 tests showed significant heterogeneity ($p = 0.03$). Egger's test revealed no significant publication bias ($p = 0.9$). Study quality assessment results was presented in Table 3.

DISCUSSION

We performed a systematic review of the association of genitourinary microbiomes with the PCa tumorigeneses and disease severity. This approach led to several interesting findings.

We found that the specific microbiomes in urine, prostate tissue, and prostate (or seminal) secretions were significantly more abundant in patients with PCa compared to men in the control groups in individual studies. Indeed, genitourinary microbiomes have been suggested to serve as carcinogenic microorganisms, stimulating prostate tumorigenesis through prostatic inflammation developing proliferative inflammatory atrophy [23]. Moreover, intraprostatic microbiomes have been shown to induce expression of regulatory T-cells, which suppress the activation and proliferation of effector T-cells, thereby suppressing the immune system [12]. However, the extracellular matrix shaped by the tumor which provides an immune suppressive microenvironment and favourable conditions for certain microorganisms' settlement might justify the higher microbiome abundance in PCa [16, 24].

Table 3. *Newcastle-Ottawa Scale Assessment of Study Quality in 17 Studies Investigating the Association Between Genitourinary Microbiome and Prostate Cancer*

Author	Selection	Comparability	Exposure	Overall score
Alexeyev et al. [19]	2	1	1	4
Yu et al. [20]	3	1	1	5
Cavarretta et al. [5]	3	1	2	6
Shrestha et al. [21]	3	1	2	6
Alanee et al. [4]	3	1	2	6
Feng et al. [18]	2	1	2	5
Feng et al. [17]	2	1	2	5
Ma et al. [14]	2	1	1	4
Ma et al. [12]	2	1	1	4
Ahn et al. [22]	2	1	2	5
Hurst et al. [3]	2	1	2	5
Salachan et al. [13]	3	1	2	6
Sarkar et al. [11]	3	1	2	6
Tsai et al. [10]	2	1	1	4
Kim et al. [16]	3	1	2	6
Kim et al. [9]	3	1	2	6
Lee et al. [15]	3	1	1	6

The methodology comprises three components: group selection (0–4 points), Comparability (0–2 points), and exposure assessment (0–3 points). The maximum achievable score is 9 points, indicative of high methodological quality.

There is also some evidence supporting an antitumor effect for specific microbiomes in various cancers, supporting the hypothesis that the microbiomes may play a protective role with regard to PCa [25, 26]. For example, *Lactobacillus* species might exert antitumor effects by the release of protective factors such as indole-3-lactic acid, which has been shown to accelerate programmed cell death of tumor cells in the large intestine [27]. These results are in line with our findings that intra-prostatic *Lactobacillus* species were more abundant in low grade PCa and in patients with a lower likelihood to experience biochemical recurrence [9, 12]. Nevertheless, the antitumor role of genitourinary microbiomes in prostate is not yet clear with frequent contaminants in sequencing-based microbiome studies [13]. Thus, the results of all studies and of this meta-analysis should be considered as preliminary.

At the microbiome species level, our meta-analysis revealed no difference in the abundance of the microbiome of PCa patients and men in the control groups. These findings might be explained by the different biological behaviors of microbiomes with propensity towards carcinogenesis. In addition to the local inflammatory effect of carcinogenic microbiomes, some microorganisms such as *Escherichia coli* might selectively colonize and grow in hypoxic and necrotic tumor areas producing cytotoxic protein cytolysin A (ClyA) for tumor cells kill [28].

According to our systematic review, certain bacterial phyla, genuses, and species were significantly associated with PCa aggressiveness and disease progression. While degradation of androgen deprivation-relevant drugs, androgen-producing bacteria, and biosynthesis of menaquinone by specific microbiomes constitute the possible mechanisms of disease progression and resistance to treatment in PCa patients, the mechanisms that account for the association between specific local microbiomes and PCa grade remain unknown [29].

Our study has a number of important limitations. The reporting bias might have led to negative results not being published, and the majority of included studies used retrospective designs, which increase the risk of selection bias. Furthermore, heterogeneity was observed in both the microbiome analysis techniques and the assessed specimens, alongside limited data on PCa treatment details, thus constraining the value of these results. A number of factors affecting the human microbial ecosystem, such as diet, ethnicity, and geography may also influence the results. Additionally, the scarcity of quantitative data in the majority of studies led us to utilize only two studies for the meta-analysis. Conducting a meta-analysis with just two studies represents a potential limitation of our study. Finally, nonstandardization of microbiomes classification makes drawing a definitive conclusion from these studies difficult.

CONCLUSIONS

Specific genitourinary microbiomes are more abundant in patients with PCa compared to men in the control groups, and associated with disease aggressiveness in PCa patients in individual studies. These studies should be considered as hypothesis generating requiring validation and in-depth analysis. Specially, standardization of microbiome assessment and reporting as well as functional predictive validated models are necessary.

CONFLICT OF INTERESTS

Authors declare no conflict of interest.

References

1 Siegel RL, Miller KD, Fuchs HE, et al. Cancer statistics, 2022. CA Cancer J Clinic. 2022; 72: 7-33.

2 Sfanos KS, Yegnasubramanian S, Nelson WG, et al. The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol. 2018; 15: 11-24.

3 Hurst R, Meader E, Gihawi A, et al. Microbiomes of Urine and the Prostate Are Linked to Human Prostate Cancer Risk Groups. Eur Urol Oncol. 2022; 5: 412-419.

4 Alanee S, El-Zawahry A, Dynda D, et al. A prospective study to examine the association of the urinary and fecal microbiota with prostate cancer diagnosis after transrectal biopsy of the prostate using 16sRNA gene analysis. Prostate. 2019; 79: 81-87.

5 Cavarretta I, Ferrarese R, Cazzaniga W, et al. The Microbiome of the Prostate Tumor Microenvironment [Figure presented]. Eur Urol. 2017; 72: 625-631.

6 Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol. 2009; 62: e1–34.

7 Lo CK-L, Mertz D, Loeb M. Newcastle-Ottawa Scale: Comparing reviewers' to authors' assessments. BMC Med Res Methodol. BMC Med Res Methodol. 2014; 14: 45.

8 Lin L, Chu H. Quantifying publication bias in meta-analysis. Biometrics. 2018; 74: 785-794.

9 Kim JH, Seo H, Kim S, et al. Biochemical Recurrence in Prostate Cancer Is Associated with the Composition of Lactobacillus: Microbiome Analysis of Prostatic Tissue. Int J Mol Sci. 2023; 24: 10423.

10 Tsai K-Y, Wu D-C, Wu W-J, et al. Exploring the Association between Gut and Urine Microbiota and Prostatic Disease including Benign Prostatic Hyperplasia and Prostate Cancer Using 16S rRNA Sequencing. Biomedicines. 2022; 10: 2676.

11 Sarkar P, Malik S, Banerjee A, et al. Differential Microbial Signature Associated With Benign Prostatic Hyperplasia and Prostate Cancer. Front Cell Infect Microbiol. 2022; 12: 894777.

12 Ma J, Gnanasekar A, Lee A, et al. Influence of intratumor microbiome on clinical outcome and immune processes in prostate cancer. Cancers (Basel). 2020; 12: 1-23.

13 Salachan P V, Rasmussen M, Fredsøe J, et al. Microbiota of the prostate tumor environment investigated by whole-transcriptome profiling. Genome Med. 2022; 14: 9.

14 Ma X, Chi C, Fan L, et al. The microbiome of prostate fluid is associated with prostate cancer. Front Microbiol. 2019; 10: 1664

15 Lee J, Wickes BL, Fu J, et al. Prevalence of genotoxic bacteria in men undergoing biopsy for prostate cancer. Prostate. 2023; 83: 663-669.

16 Kim JH, Seo H, Kim S, et al. Malignant Prostate Tissue Is Associated with Different Microbiome Gene Functions. Diagnostics (Basel). 2023; 13: 278.

17 Feng Y, Jaratlerdsiri W, Patrick SM, et al. Metagenomic analysis reveals a rich bacterial content in high-risk prostate tumors from African men. Prostate. 2019; 79: 1731-1738.

18 Feng Y, Ramnarine VR, Bell R, et al. Metagenomic and metatranscriptomic analysis of human prostate microbiota from patients with prostate cancer. BMC Genomics. 2019; 20: 146.

19 Alexeyev O, Bergh J, Marklund I, et al. Association between the presence of bacterial 16S RNA in prostate specimens taken during transurethral resection of prostate and subsequent risk of prostate cancer (Sweden). Cancer Causes Control. 2006; 17: 1127-1133.

20 Yu H, Meng H, Zhou F, et al. Urinary microbiota in patients with prostate cancer and benign prostatic hyperplasia. Arch Med Sci. 2015; 11: 385-394.

21 Shrestha E, White JR, Yu S-H, et al. Profiling the Urinary Microbiome in Men with Positive versus Negative Biopsies for Prostate Cancer. J Urol. 2018; 199: 161-171.

22 Ahn HK, Kim K, Park J, et al. Urinary microbiome profile in men with genitourinary malignancies. Investig Clin Urol. 2022; 63: 569-576.

23 De Marzo AM, Marchi VL, Epstein JI, et al. Proliferative inflammatory atrophy of the prostate: Implications for prostatic carcinogenesis. Am J Pathol. 1999; 155: 1985-1992.

24 Yuan Z, Li Y, Zhang S, et al. Extracellular matrix remodeling in tumor progression and immune escape: from mechanisms to treatments. Mol Cancer. 2023; 22: 48.

25 Peng Z, Cheng S, Kou Y, et al. The Gut microbiome is associated with clinical response to Anti-PD-1/PD-L1 immunotherapy in gastrointestinal cancer. Cancer Immunol Res. 2020; 8: 1251-1261.

26 Routy B, Le Chatelier E, Derosa L, et al. Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science (1979). 2018; 359: 91-97.

27 Sugimura N, Li Q, Chu ESH, et al. Lactobacillus gallinarum modulates the gut microbiota and produces anti-cancer metabolites to protect against colorectal tumourigenesis. Gut. 2022; 71: 2011.

28 Jiang S-N, Phan TX, Nam T-K, et al. Inhibition of tumor growth and metastasis by a combination of Escherichia coli-mediated cytolytic therapy and radiotherapy. Mol Ther. 2010; 18: 635-642.

29 Terrisse S, Zitvogel L, Kroemer G. Effects of the intestinal microbiota on prostate cancer treatment by androgen deprivation therapy. Microb Cell. 2022; 9: 190-194.