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Urinary microbiome profile in men with genitourinary malignancies

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Purpose: Recent advances in molecular biology technology have allowed identification of microbial communities in the urinary tract, and urinary microbiome is associated with various urological diseases. In this study, we aimed to characterize the urinary microbiome of genitourinary malignancies.

Materials and Methods: Metagenomic analysis of urinary DNA was performed in 85 patients including 30 with bladder cancer (BC), 27 with prostate cancer (PC), 12 with renal cancer (RC), and 16 with non-cancer (NC). 16S rRNA gene sequencing was conducted after amplification of the V3–V4 region.

Results: PC and RC had significantly lower Shannon index than BC, and beta diversity showed significantly different microbiome composition between four groups. We identified six genera of *Cutibacterium*, *Peptoniphilus*, *Sphingomonas*, *Staphylococcus*, *Micrococcus*, and *Moraxella*, which showed significantly different abundance between the four groups. When each of the malignancies were compared to NC at the species level, *Micrococcus* sp. was significantly increased in BC. We also identified 12 and five species with increased populations in PC and RC, respectively. Of these, *Cutibacterium acnes*, *Cutibacterium granulosum*, *Peptoniphilus lacydonensis*, and *Tessaracoccus* were significantly increased in both PC and RC.

Conclusions: Urinary microbiome composition was different depending on the type of genitourinary malignancies, and we identified bacteria that are significantly associated with each type of malignancy. Specifically, several bacterial species were associated both PC and RC, suggesting that PC and RC share a similar pathogenesis-related urinary microbiome.

Keywords: Metagenome; Microbiota; Urine; Urologic neoplasms

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INTRODUCTION

It is well established that chronic inflammation is one of the mediators for carcinogenesis, and specific pathogens are associated with development of malignant disease. Recent advances in molecular biology technology have allowed identification of a microbial communities in the human body. The microbiome interacts with host cells and plays an important role in human homeostasis. Studies have revealed that microbial imbalance, called dysbiosis, can lead to several pathologic conditions [1,2]. In genitourinary malignancies, there is well-known association between *schistosomiasis*

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infection and squamous cell carcinoma of the bladder [3]. Evidence also shows that inflammation is associated with carcinogenesis of prostate cancer [4,5].

Microbiomes reside in human bodies, and the microbiome composition varies by anatomical site. Although the Human Microbiome Project did not include investigation of the urinary microbiome, recent evidence changed the long-held paradigm that urine is sterile. Multiple studies have demonstrated the presence of urinary microbiome by culture- or molecular-based methods [6-8]. Dysbiosis of the urinary microbiome is associated with various urological disorders such as low urinary tract symptoms, interstitial cystitis, and chronic pelvic pain syndrome [9-11]. Several studies have investigated urinary microbiome in urologic cancers and have revealed different urinary microbiome compositions in urologic cancers, such as bladder cancer (BC) or prostate cancer (PC) [12-15]. While there was difference in the relative abundance of specific microorganisms, none of the prior studies have analyzed multiple urologic cancers at the same time. In this study, we aimed to characterize the urinary microbiome of three major genitourinary malignancies of PC, BC, and renal cancer (RC) compared to that of patients without malignant disease.

MATERIALS AND METHODS

1. Study population and sample collection

We prospectively collected clinical information and urine samples from patients undergoing surgical treatment for urologic malignant or benign disease. This study was approved by the Institutional Review Board of Ewha Medical Center (IRB no. 2018-05-041), and all patients provided informed consent for sample banking and genetic testing. The study protocol was carried out in accordance with the Declaration of Helsinki Guidelines. First void urine samples were collected the day of surgery and centrifuged at 200×g for 10 minutes, followed by 3,000×g for 20 minutes to remove cellular materials. The supernatants were stored at -70℃ until use.

2. DNA extraction and 16s rRNA gene sequencing

Supernatant was processed as previously describe [16]. DNA extraction was performed using a DNA extraction kit (PowerSoil DNA Isolation Kit, MO BIO, Carlsbad, CA, USA) following the manufacturer's instructions. Prepared DNA was used for PCR amplification of the V3–V4 hypervariable regions of the 16S ribosomal RNA genes using the primer set 16S_V3_F (5'-TCGTCGGCAGCGTCAGATGTGTATA-AGAGACAGCCTACGGGNGGCWGCAG-3') and 16S_V4_R (5'-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAG-GACTACHVGGGTATCTAATCC-3') [17,18]. The PCR products were used for construction of 16S rDNA gene libraries following the MiSeq System guidelines (Illumina Inc., San Diego, CA, USA). The 16S rRNA gene libraries for each sample were quantified using QIAxpert (QIAGEN, Hilden, Germany), and pyrosequencing was performed using the MiSeq System (Illumina Inc.) according to manufacturer recommendations.

3. Bioinformatics analysis

Sequencing data were processed using QIIME1.9.1 to assemble paired end reads into tags according to their overlap. In the pre-processing step, the primer was removed, and demultiplexing and quality filtering (Phred score ≥20) were applied. USEARCH7 was used to perform de-noising and chimera detection/filtering in operational taxonomic unit (OTU) grouping. Then, the Silva132 and National Center for Biotechnology Information databases were used to determine the OTUs with 97% similarity to the UCLUST and the close-reference analysis method; the OTU identifier also was determined. The OTU table was normalized by dividing each OTU by 16S copy number abundance. After filtering the generated OTU table using the Biological Observation Matrix format, the resulting sequences were clustered into OTUs based on a similarity threshold ≥97% using Python Nearest Alignment Space Termination. We have performed comparative OTU assignment with the database in terms of Phylum, Class, Order, Family, Genus, and Species separately using Ribosomal Database Project classifiers (Supplementary Fig. 1). We used the alpha_diversity.py program of QIIME to analyze alpha-diversity to understand local populations of the microbiome. Chao1 and Shannon index were used to estimate alpha diversity. Beta_diversity.py of QIIME was used to calculate beta diversity for estimating the correlation among other factors and microbes by Bray–Curtis. The comparisons of beta-diversity were performed with a pairwise permutational multivariate ANOVA (PERMANOVA) using the 'pairwise.adonis' function from the vegan R package. PERMANOVA is one of most widely used nonparametric methods to fit multivariate models to microbiome data. In this study, we performed the comparison of four groups. Therefore, the original p-values (p-value) were multiplied by four to obtain the Bonferroni-adjusted p-values. The taxonomic data were exported to Statistical Analysis of Metagenomic Profiles (STAMP) software to provide a statistical view of differences in abundant features between groups. To compare microbiome profile between each urologic cancer and the control group, STAMP analysis was performed. We

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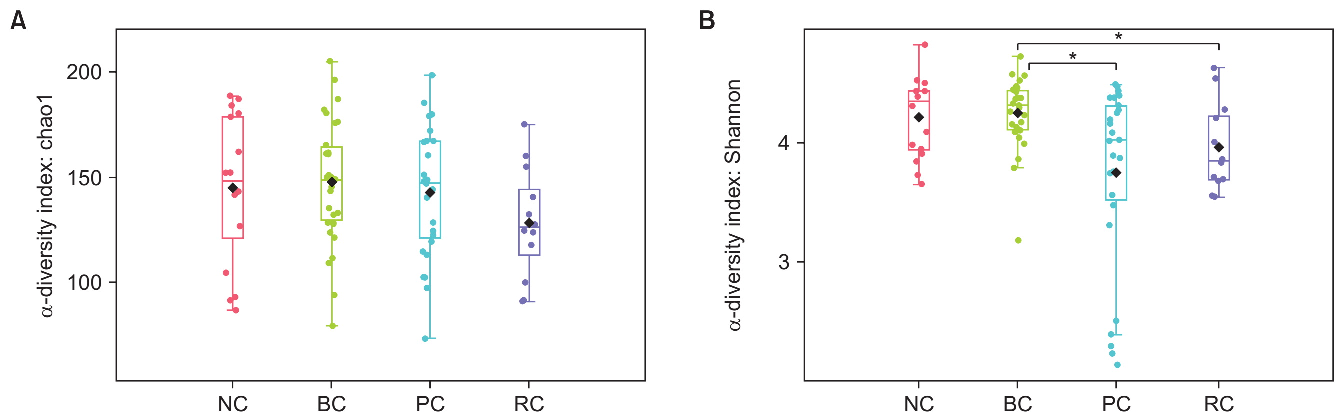

Fig. 1. Difference in alpha diversity of the urinary microbiome. While the Chao1 index (richness) was not significantly different among the four groups (p=0.337; A), a diversity based on Shannon index (evenness) showed significant difference among the four groups (p=0.002; B). Boxes represent the interquartile ranges between the first and third quartiles, and the line inside the boxes represents the median; notches show the 95% confidence interval for the median. NC, non-cancer; BC, bladder cancer; PC, prostate cancer; RC, renal cancer. *p<0.05.

performed two-sided White's non-parametric t-test to identify differences in the urinary microbiome between each of the urologic cancers and the control group.

RESULTS

1. Sample information

This study comprised 104 male patients with 32 BC, 32 PC, 16 RC, and 24 non-neoplastic urologic disease as control (non-cancer, NC). After excluding 19 samples with sequencing read less than 5,000, 30 patients with BC, 27 patients with PC, 12 patients with RC, and 16 NC were included for final analysis. The average number of read counts per sample was 14,321; 19,102; 12,633; and 13,849 in BC, PC, RC, and NC, respectively. Patients were all male, but there was significant difference in age among groups (67.4, 68.1, 58.2, and 50.5 in BC, PC, RC, and NC, respectively. p<0.001). Detailed clinicopathological information is summarized in Supplementary Table 1.

2. Microbiome diversity and composition

To estimate the alpha diversity of the microbial communities, Chao1 and Shannon indices were calculated and used for further comparison of the differences among the four groups. Good's coverage was estimated to be 99.05% for all groups. While the Chao1 index (richness) was not significantly different between the four groups (p=0.337), a significant difference in Shannon index (evenness) among the four groups was noted (p=0.0023342). Although statistical significance was not observed between NC and other groups, PC had a significantly lower Shannon index than BC (p=0.012), and RC had a significantly lower Shannon index than BC (p=0.042; Fig. 1).

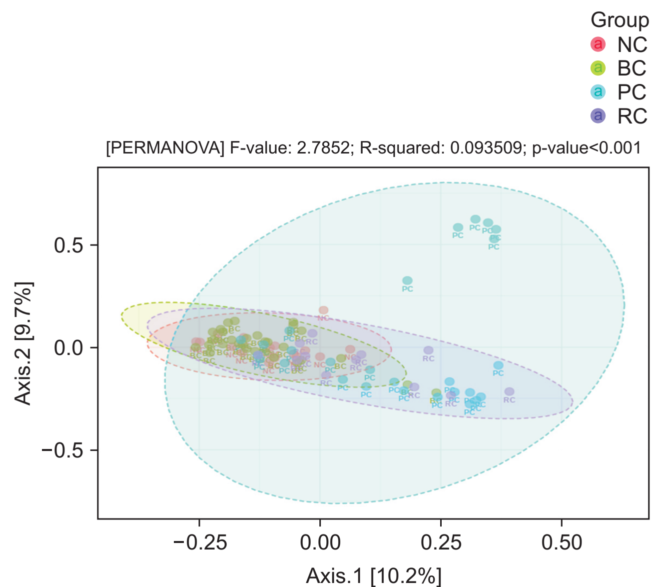

Fig. 2. Principal Coordinates Analysis plot of Bray–Curtis dissimilarity. Permutational multivariate ANOVA (PERMANOVA) analysis showed significant difference of urinary microbiome composition among the four groups. NC, non-cancer; BC, bladder cancer; PC, prostate cancer; RC, renal cancer.

For comparison of microbial composition, beta-diversity was calculated using Bray–Curtis dissimilarity. PERMANOVA analysis based on Bray–Curtis showed significant difference in urinary microbiome composition among the four groups (p<0.001; Fig. 2). At the phylum level, *Proteobacteria*, *Actinobacteria*, and *Firmicutes* were most abundant in all groups. The composition of the urinary microbiome of each group is shown in Supplementary Fig. 2.

3. Microbiome associated with urologic malignancies

In one-way ANOVA, 15 genera occupied more than 1%

of the overall bacterial population (Supplementary Table 2). Of 15 genera, the six *Cutibacterium*, *Peptoniphilus*, *Sphingomonas*, *Staphylococcus*, *Micrococcus*, and *Moraxella* were significantly different in abundance among the four groups (Fig. 3). We also identified 19 species with bacterial occupation more than 1%, and 12 species had significantly different abundance between the four groups (Table 1).

Taxon-based analysis revealed that the urine microbial communities were changed by disease at the species level. Thus, we compared each urologic malignancy with NC at the species level by STAMP analysis. When we compared NC and BC; seven species were more abundant in the BC group (Fig. 4A). Of these seven species, the difference was most pronounced in *Micrococcus* sp., which was significantly increased in the BC group (p=0.003). In comparison between NC and PC, we identified 18 species associated with PC and 12 species including *Acinetobacter lwoffii*, *Cutibacterium acnes*, *Peptoniphilus lacydonensis*, and *Cutibacterium granu-*

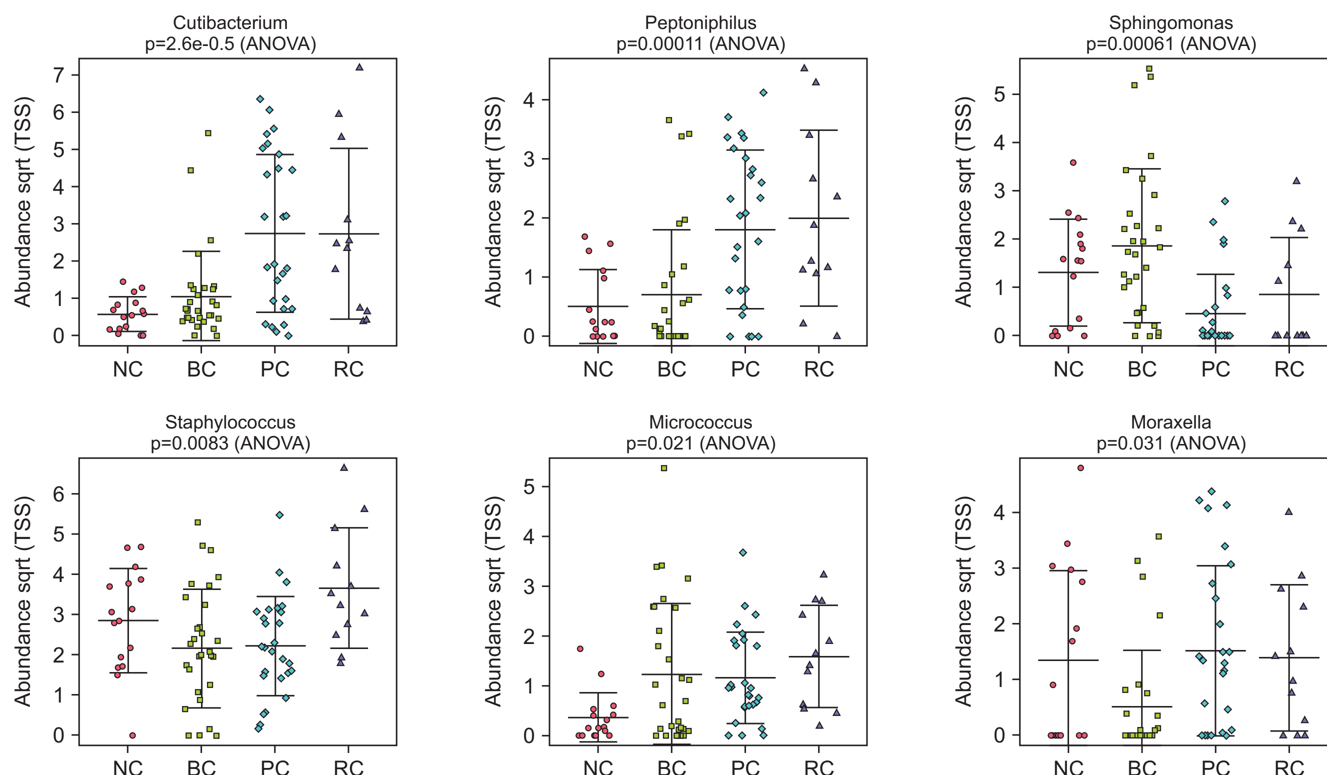

Fig. 3. One-way ANOVA performed at the genus level. Six genera were significantly different in abundance among the four groups. TSS, total sum scaling; NC, non-cancer; BC, bladder cancer; PC, prostate cancer; RC, renal cancer.

Table 1. One-way ANOVA in species level between four groups

Species	NC	BC	PC	RC	p-value
Cutibacterium granulosum	0.049	0.21	1.1	0.92	0.00002
Cutibacterium acnes	0.54	1.02	2.47	2.53	0.000048
Staphylococcus epidermidis	1.25	1	1.3	2.47	0.000075
Peptoniphilus lacydonensis	0.5	0.69	1.78	1.97	0.00014
Sphingomonas sp.	1.26	1.62	0.42	0.53	0.00082
Acinetobacter baumannii	1.24	1.27	0.55	0.24	0.00082
Acinetobacter populi	2.47	2.72	1.8	1.64	0.0033
Acinetobacter johnsonii	1	1.15	0.46	0.69	0.0071
Acinetobacter radioresistens	1.79	2.1	1.4	1.36	0.01
Acinetobacter lwoffii	1.43	1.75	3.23	1.61	0.012
Micrococcus sp.	0.36	1.23	1.16	1.59	0.021
Moraxella osloensis	1.35	0.51	1.52	1.37	0.031

NC, non-cancer; BC, bladder cancer; PC, prostate cancer; RC, renal cancer.

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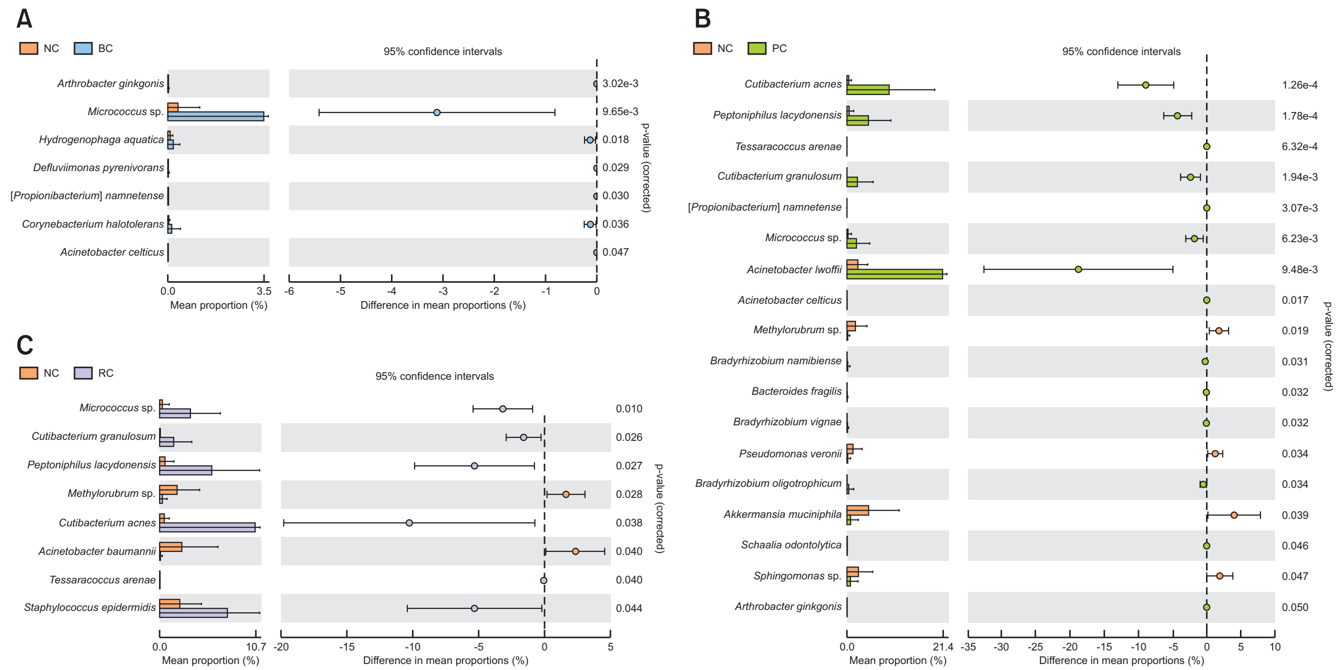

Fig. 4. Comparison of urinary microbiome at the species level. (A) Bladder cancer (BC) vs. non-cancer (NC). (B) Prostate cancer (PC) vs. NC. (C) Renal cancer (RC) vs. NC.

losum that were more highly enriched in the PC group (Fig. 4B).

Of the eight species that showed different abundance between RC and NC, the six *C. acnes*, *P. lacydonensis*, *Micrococcus* spp., *C. granulosum*, *Tessaracoccus arenae*, and *Staphylococcus epidermidis* were more highly enriched in the RC group (Fig. 4C).

DISCUSSION

Dysbiosis of the microbiome contributes to carcinogenesis through several mechanisms including DNA damage, production of carcinogenic metabolites, and stimulation of inflammation [19]. It has been demonstrated that the gut microbiome is associated with various gastrointestinal malignancies, such as esophageal, gastric, colorectal, and pancreatic cancer [20,21]. Regarding urologic malignancies, the bladder is constantly in contact with urine, and dysbiosis of the urinary microbiome could influence the microenvironment and carcinogenesis of the bladder as the gut microbiome influences the development of gastrointestinal tract malignancies. Several studies have investigated the urinary microbiome in BC [13,14,22,23]. However, the results of these studies are not consistent. Although these studies identified several organisms, which were significantly associated with BC, we did not find specific organisms associated with BC in common with those in previous studies. This might be due to the various stages and grades of BC, and the small number of patients included in the studies. Our study also identified seven species that were more highly enriched in BC. However, STAMP analysis shows that most of these species were present in extremely low proportion compared to species associated with PC and RC.

The microbiome of PC is studied most widely among urologic malignancies. Chronic inflammation of the prostate is proposed to contribute to the development of PC, and a previous study on the urinary microbiome of PC identified several microorganisms that are associated with urinary tract infection and prostatitis [12]. In PC, one of the species of interest is *C. acnes*, which also is known as *Propionibacterium acnes*. *C. acnes* is associated with infectious skin disease such as acne vulgaris. The association between *C. acnes* and PC has long been discussed. *C. acnes* was one of the predominant microorganisms cultured from PC tissue [24], and a recent molecular method found that *Cutibacterium* was the most abundant genus in both normal and cancer tissues of radical prostatectomy specimens [25]. Although the role of *C. acnes* in PC is inconclusive, activation of inflammatory pathways including NF-kB, IL-6, STAT3, and COX2 by *C. acnes* has been suggested as an immunological change associated with development of PC [26]. In a recent epidemiologic study, a diagnosis of acne in late adolescence significantly increased the risk of PC, suggesting the association between *C. acnes* and PC [27]. In line with previous

studies, our urinary microbiome analysis also showed that PC had a significantly higher abundance of *C. acnes* compared to NC. Intriguingly, *C. acnes* and *S. epidermidis* were significantly higher in RC in STAMP analysis. Both *C. acnes* and *S. epidermidis* are main commensal skin bacteria and associated with the pathophysiology of acne [28]. In addition, enrichment of *C. acnes*, *C. granulosum*, *P. lacydonensis*, and *T. arenae* were observed both in PC and RC, and these cancers might have similar carcinogenesis or microenvironment associated with the microbiome. In a population-based study, the incidence of PC was higher in men with RC than in those without, suggesting a common underlying etiology in both PC and RC [29]. For example, androgen signaling is one of the important pathways in PC. Many studies found the role of androgen receptors in RC, and there are multiple ongoing clinical trials that examine therapeutic agents targeting androgen receptor in RC [30].

In this study, we analyzed the urinary microbiome of patients with genitourinary malignancies. Although several studies investigated urinary microbiome in genitourinary malignancies, no previous study has analyzed various types of major genitourinary malignances at the same time under the same condition. Specifically, less is known about the microbiome of RC. To the best of our knowledge, no prior study has examined the urinary microbiome in RC.

Our study is not devoid of limitation. Individuals included in NC were not healthy people but also underwent surgery for urologic benign disease. In addition, patients in NC were younger than those in the cancer group. Considering that microbiome composition can change with age, a study with an age-matched control group would be ideal for microbiome analysis. However, when we performed PERMANOVA analysis in our data, microbiome composition was not significantly associated with age in the NC group ($p=0.675$) or the entire cohort ($p=0.286$; Supplementary Fig. 3). One of the main limitations of studies that utilize 16S rRNA sequencing technique is that it does not differentiate between dead and living bacteria. The identification of bacteria could be the result of DNA fragmentation of dead bacteria, which could be derived from circulation or other body sites. Nevertheless, the identification of bacterial DNA indicates the presence of bacteria at some location in the human body. We speculate that identification of a certain kind of bacteria or bacterial community, which has significant abundance in genitourinary malignancies, provides valuable information for understanding the pathogenesis of genitourinary malignancies.

CONCLUSIONS

In conclusion, our results suggest that major genitourinary malignancies have a different urinary microbiome composition than in patients without such malignancy. We identified bacteria that are significantly associated with each type of genitourinary malignancy. Specifically, several bacterial species were associated with both PC and RC, suggesting that PC and RC share a similar pathogenesis-related urinary microbiome. The urinary microbiome can contribute to the pathophysiology of genitourinary malignancies, and it has potential for diagnostic and therapeutic utilization.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: Hyun Kyu Ahn and Kwang Hyun Kim. Data acquisition: Hyun Kyu Ahn and Kwang Hyun Kim. Statistical analysis: Kwangmin Kim and Junhyung Park. Data analysis and interpretation: Kwangmin Kim, Junhyung Park, and Kwang Hyun Kim. Drafting of the manuscript: Hyun Kyu Ahn and Kwang Hyun Kim. Critical revision of the manuscript: Hyun Kyu Ahn and Kwang Hyun Kim. Supervision: Kwang Hyun Kim. Approval of the final manuscript: all authors.

SUPPLEMENTARY MATERIALS

Supplementary materials can be found via https://doi.org/10.4111/icu.20220124.

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