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Comprehensive analysis of the interaction microbiome and prostate cancer: an initial exploration from multi-cohort metagenome and GWAS studies

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Abstract

Introduction Prostate cancer is one of the most common cancers in the United States with a high mortality rate. In recent years, the traditional opinion about prostate microbiome was challenged. Although there still are some arguments, an escalating number of researchers are shifting their focus toward the microbiome within the prostate tumor environment.

Methods We mined the data of the microbiome extracted from the metagenome, and it offers a broader taxonomic coverage and accurate functional profiling. We used Kraken2, a mapping tool, to mine the gut microbiota of prostate cancer patients. A two-sample Mendelian Randomization was conducted to reflect the association between gut microbiome and cancer.

Results In the study, we found the consistency of the special intratumor microbiome of both non-metastatic tumors and metastatic tumors. And we dig the gut microbiome in patients with different treatments. We found that some microbiotas may be associated with prostate cancer progression and a special microbiome in metastatic prostate cancer may exist. The anti-androgen therapy can significantly change both the intratumor and gut microbiome.

Conclusion With the progression and metastasis of prostate cancer, some intratumor microbiome changes. And anti-androgen influences both the intratumor and gut microbiome. Our discovery may help researchers further understand the progression, metastasis, and resistance of prostate cancer from the perspective of microbiome level.

Keywords Prostate cancer, Microbiome, Gut, Treatment, Androgen

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Introduction

In 2020, there were over 1.4 million newly diagnosed prostate cancer patients, and more than 375 thousand patients died of this terrible disease [1]. In America, the prostate is the most common cancer in men, and the mortality of prostate cancer is just lower than lung cancer [2]. In Asia, this situation is also not optimistic. In recent years, the prostate cancer incidence has still been increasing [3]. Exploration of the mechanism of prostate cancer formation and progression is becoming more and more important.

In the past, the urine was thought sterile. This stereotypical impression made the urologist surgeons and researchers pay no attention to the microbiome in prostate cancer. However, the association between microbiome and prostate cancer is attracting researchers' attention, especially after a study demonstrating the existence of an intratumoral microbiome was published in 2020 in *Science* [4]. This means researchers are paying more attention to the microbiome beyond gut diseases. Recent research has indicated that there is an association between microbiome and the incidence and progression of prostate cancer. The intestinal microbiota of patients could participate in metabolism and lead to resistance [5]. And some studies reported the role of microbiota in signaling [6, 7]. The signature of intratumoral microbiota was also reported, though the results are not consistent [8–11]. To further explore what role the microbiome plays in the progression, metastasis, and resistance in prostate cancer, it is important to broaden the source of the microbiome information. Due to the complexity of microbiota, bioinformatics plays an important role in identifying the characteristics and relevance of the microbiome in patients. As for metagenomics, which analyzes microbiota from the environment directly, it offers a broader taxonomic coverage and accurate functional profiling [12]. The data of microbiome extracted from metagenome were recently used to analysis with 16 S rRNA sequencing data in some research and performed well [13, 14]. We gained the signature of the microbiome in prostate cancer patients from the published articles and used similar tools to analyze the gut microbiome [15, 16]. Kraken2, a bioinformatics tool employed for the mapping and analysis of microbiota within the context of prostate cancer patients, is fast and precise while minimizing the consumption of computing resources [16]. This software has been extensively leveraged across a spectrum of prior research endeavors, thereby accruing a robust body of validation and scholarly recognition. Its user-friendly configuration and the facile interpretability of its output render it a highly accessible asset for subsequent investigative pursuits [17]. Kraken2 was also used in the intratumor microbiome data we have extracted in recent studies [18], providing us with valuable insights into this complex biological landscape.

With the development of bioinformatics, more tools can be used to study the risk factors of prostate cancer at a higher dimension. Mendelian randomization (MR) is a new tool evaluating the causal effects using genetic variants. Nonmodifiable genetic instruments ensure lifelong exposure, which can avoid both research bias and confounding environmental factors [19]. In this study, a two-sample MR is also used to evaluate the association between gut microbiome and prostate cancer. The results may offer a new vision of the influence of microbiota in the formation and progression of prostate cancer.

Methods

Intratumoral microbiome data

We searched Pubmed and extracted microbiome data from reliable studies. A study mining microbiome of 4164 metastases from the Hartwig Medical Foundation was included [18]. The Hartwig Medical Foundation is a project under the Center for Personalized Cancer Treatment (CPCT). Its goal was to systemically collect clinical data of patients with metastatic cancer while collecting biopsy metastatic lesions for whole genome sequencing. The data of prostate cancer patients was downloaded and screened using R packages "MicrobeDS" and "phyloseq".

TCGA, a landmark cancer genomics program, molecularly characterized over 20,000 primary cancers and matched normal samples. With comprehensive clinical data, it is widely used in many studies about cancer. A study extracting microbiome from The Cancer Genome Atlas Program (TCGA) using miRNA data was also included in [20]. The detailed microbiome data can be downloaded from the web link in their article (http://bic.jhlab.tw/).

Gut microbiome data

We searched the gut metagenome data from the National Center of Biotechnology Information (NCBI) BioProject database (https://www.ncbi.nlm.nih.gov/bioproject). The project names are PRJDB10718, PRJDB9379, PRJNA1077793. The MiSeq (Illumina) system was used to obtain 16s RNA. The detailed information was shown in the Table 1. We obtained the raw sequence data from Sequence Read Archive (SRA) database (https://www.ncbi.nlm.nih.gov/sra).

Microbial profiling pipeline

Preprocession

The workflow of bioinformatics was performed using default parameters unless we stated otherwise. All the whole metagenome sequencing (WMS) or 16 S rRNA reads were preprocessed using package "fastp", which filter out low quality, short reads, and trim reads in front

Table 1 The GWAS ID and details of the included studies

No.	ID	Trait	note	ncase	group_name	year	consortium	author	sex	population	unit	nsnp	sample_size	build	ncontrol	category	subcategory	ontology	mr	priority	pmid	sd
1	ieu-b-85	Prostate cancer	NA	79148	public	2018	PRACTICAL	Schumacher	Males	European	NA	20346368	140254	HG19/GRCh37	61106	Disease	Cancer	EFO:0001663	1	0	29892016	NA

and tail [21]. Program "fastQC" was used to spot potential problems in sequencing datasets.

Aligning sequencing reads

Bowtie 2, a fast and memory-efficient tool, was used for aligning sequencing reads to human reference sequences [22, 23]. We used genome assembly GRCh38 as human reference sequences and downloaded pre-built genome indexes "Human / GRCh38 no-alt analysis set" from the official website (https://bowtie-bio.sourceforge.net/bowtie2/index.shtml). And we collected all the sequencing that did not align to the human genome (GRCh38). "Samtools" was used to filter reads that did not map successfully and produce a binary alignment/map (BAM) file for the following analysis [24].

Reads analysis

16 S rRNA reads and metagenome reads were analyzed with Kraken2, a rapid and multithreading axonomic sequence classifier that assigns taxonomic labels to sequences [16]. It can get on their website (https://benlangmead.github.io/aws-indexes/k2). A Kraken2 reference database named "PlusPF" was access on 30 June 2024. It is consistent of archaea, bacteria, viral, plasmid, human, UniVecCore, protozoa and fungi. Microbiota reads were extracted using Kraken2 from WMS reads or 16s RNA reads. After Kraken2 profiling, Bracken2 software was used to re-estimate genus-level abundances, applying a Bayesian model [15].

Depletion of known contaminants

To correct for false detection of microbiota, we adopted published list of possibility genera and removed both likely contaminants and mixed evidence contaminants [25]. And we searched studies about microbiome in prostate cancer and adopted reported microbiota into further consideration.

Bioinformatics: microbial analysis

Alpha and beta diversity estimations

Alpha diversity reflected the richness and diversity of the microbiome within the sample. The R package "vegan" (version: 2.6.6.1) was used to calculate the alpha diversity estimations. The Shannon and Simpson index were calculated to evaluate the richness and evenness of the microbiome [26, 27]. The Chao index, ACE index, and Pielou evenness were also calculated. The Chao index and ACE index estimate the richness of the sample or community [28, 29]. Pielou's evenness, the ratio of the actual Shannon index of a community to the maximum Shannon index, measures diversity along with species richness and is the most common measure of evenness [30]. An online tool was used for the figure graphing (https://www.genescloud.cn/chart/ChartOverview).

And packages "ggplot2" (version: 3.5.1), "ggprism" (version: 1.0.5) and "vegan" (version: 2.6.6.1) were used for beta diversity estimations and graph. The Bray-Curtis distance [31] and PCoA [32], reflecting the microbiome profiles, were shown in figure.

Microbial analysis

The public microbiome data of prostate cancer can get using R package "MicrobeDS". To analysis the consistent of microbiome, the packages "pheatmap" (version: 1.0.12) and "phyloseq" (version: 1.46.0) were used. Heatmap and barplot were used to reflect the component. A univariate cox regression analyses was conducted, and we tried to identify special cancer species using "survival" (version 3.7.0) and "survminer" (version: 0.4.9).

Survival analysis

We got the clinical data for survival analysis from TCGA database (https://portal.gdc.cancer.gov) to identify microbe signatures associated with prognosis. Kaplan-Meier (KM) curves were plotted by the "survminer" (version: 0.4.9) and it reflected the influence of these special microbiota in prognostic of prostate cancer. The Maximally Selected Rank Statistics was used for KM curves plotting.

MR

The data resources were obtained from MRC IEU OpenGWAS (https://gwas.mrcieu.ac.uk/; version: v8.5.1–2024-07-17), developed at the MRC Integrative Epidemiology Unit at the University of Bristol. The GWAS study we included was ieu-b-85 (Prostate cancer). The FinnGen (https://www.finngen.fi/fi/) project, commenced in autumn 2017, was also included. It was a public-private research collected from the Finnish Biobank and the Finnish Health Registry and included around 500,000 participants [33]. The majority of the FinnGen data in this study originated from Round 10. The data of gut microbiota can be accessed from GCST90032172 to GCST90032644, and the detail has been reported in a published article [34]. All of the p values are two tails. The R software (version 4.3.1) with the Two Sample MR package was used in the analysis. Figures were plotted by https://www.bioinformatics.com.cn (last accessed on 20 June 2024), an online platform for data analysis and visualization.

Result

Analysis of intratumoral microbiome

The microbiome of prostate cancer

In the microbiome data of TCGA, we explored the difference between the tumor tissue and non-tumor tissue (non-malignant adjacent prostate samples) [35]. Just as Fig. 1 showed, within the microbiome of TCGA-PRAD, the Proteobacteria emerged as the most abundant phylum. High abundance levels were also observed for Firmicutes, Actinobacteria, and Bacteroidetes. Among the five most abundant genera identified in the TCGA-PRAD microbiome were *Bacillus*, *Pseudomonas*, *Paenibacillus*, *Acinetobacter*, and *Corynebacterium*. Subsequently, we estimated the microbiome within prostate tumors using a variety of methodologies. We observed a significant difference in alpha-diversity ($p < 0.05$). The Shannon index, Simpson index, and Pielou's evenness all exhibited lower

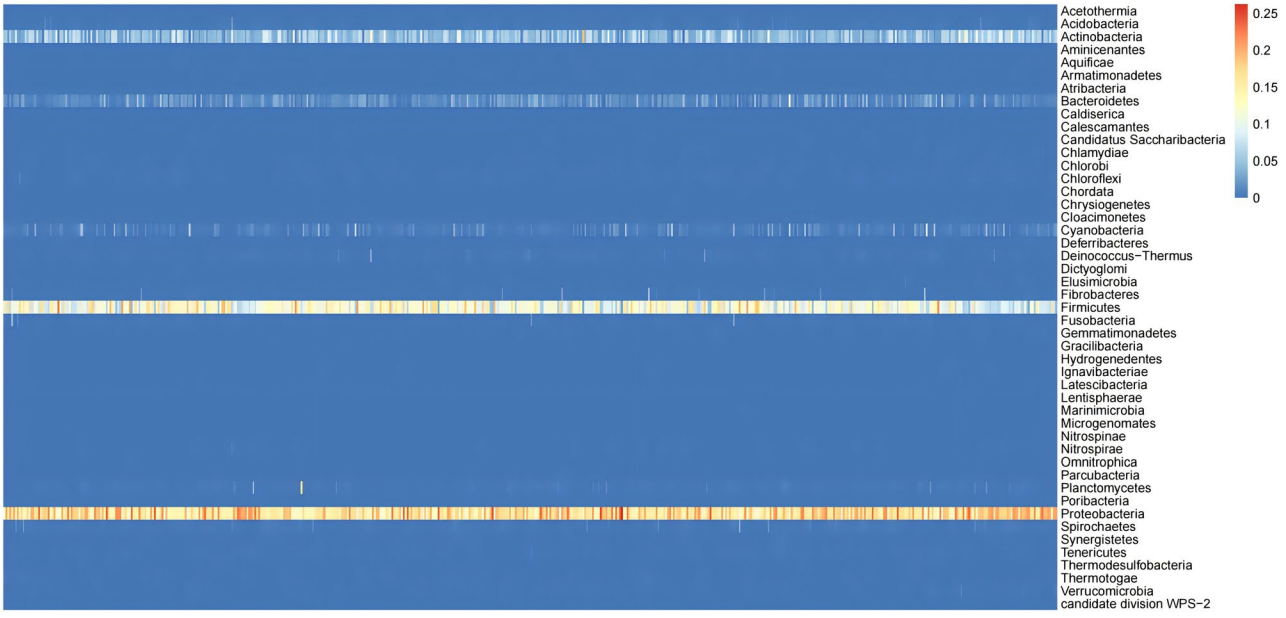

Fig. 1 The heatmap of microbiome in TCGA-PRAD at phylum level

in the tumor group, which meant community richness and community evenness were lower (Fig. 2A). In the beta-diversity analysis results, we discovered significant differences in intratumoral microbiome profiles ($p < 0.05$) (Fig. 2B and C).

An analysis utilizing linear discriminant analysis effect size (LEfSe) revealed distinct microbiotas at the phylum, family, and genus level ($p < 0.05$) (Fig. 3A, B and C). Searching the List of Prokaryotic names with Standing in Nomenclature (LPSN) [36] and deleting low abundant microbiome, we included some possible families (Comamonadaceae, Cystobacteraceae, Enterobacteriaceae, Mycobacteriaceae, Paenibacillaceae and Peptostreptococcaceae) and genus (*Mycobacterium*, *Paenibacillus*, *Peptoclostridium*, *Saccharomonospora*, *Salmonella* and *Alicyclobacillus*) in following analysis. The Kaplan-Meier curves revealed a significant impact of the intratumor microbiome on the progression of prostate cancer, with differences observed at both the genus and phylum levels, as illustrated in Fig. 3D and E. Subgroup analysis of the PSA value ($<= 0.2$ ng/ml and > 0.2 ng/ml) and tumor pathology stage (T1/T2 and T3/T4) were shown in Supplemental Fig. 1. We also conducted a univariate Cox regression analysis on the highly abundant microbiota and identified that *Paenibacillus*, *Mycobacterium* and *Streptococcus* may be associated with biochemical recurrence. The detailed results of this analysis are presented in Supplemental Table 1.

The microbiome of metastatic cancer

In metastatic prostate cancer, we discovered that Staphylococcaceae, Streptococcaceae, Pseudomonadaceae, and Enterobacteriaceae were the most abundant families at the family level (Fig. 4). And it was discovered that *Staphylococcus*, *Streptococcus*, *Lactobacillus*, *Pseudomonas*, *Clostridium*, *Klebsiella*, and *Bacteroides* were rich in metastatic prostate cancer (Supplemental Fig. 2). We analyzed the intratumoral microbiota of metastatic prostate cancer but found no significant difference in alpha-diversity or beta-diversity among the samples at different biopsy sites (Fig. 5A, B and C).

Then we also conducted a comprehensive analysis of microbiota variations under various treatment modalities and discovered that anti-androgen therapy (androgen deprivation therapy and hormonal therapy) and immunotherapy can significantly alter the intra-cellular microbiome of patients (Fig. 6A and B, and 6C). To further elucidate the distinct within the metastatic prostate cancer microbiome, the LEfSe study was conducted. Notably, our analysis revealed that androgen deprivation therapy (ADT) and radiation therapy significantly modulate the intratumoral microbiome of metastatic prostate cancer patients. All the results were adjusted by False discovery

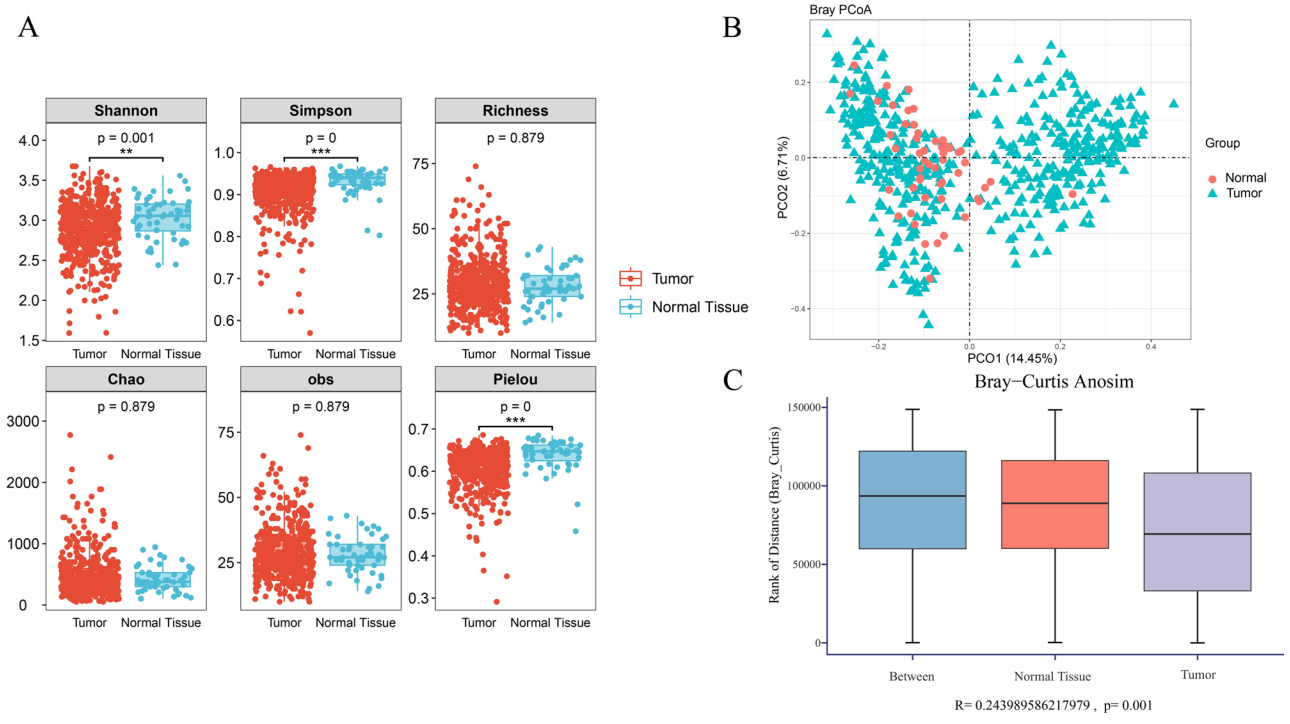

Fig. 2 (**A**) The alpha diversity of microbiome in TCGA-PRAD, including Shannon index, Simpson index, Richness, Chao, Obs, and Pielou's evenness. (**B**) The PCoA of TCGA-PRAD microbiome group by tumor tissue and non-tumor tissue. 3 (**C**) The Bray-Curtis distance of TCGA-PRAD microbiome group by tumor tissue and non-tumor tissue

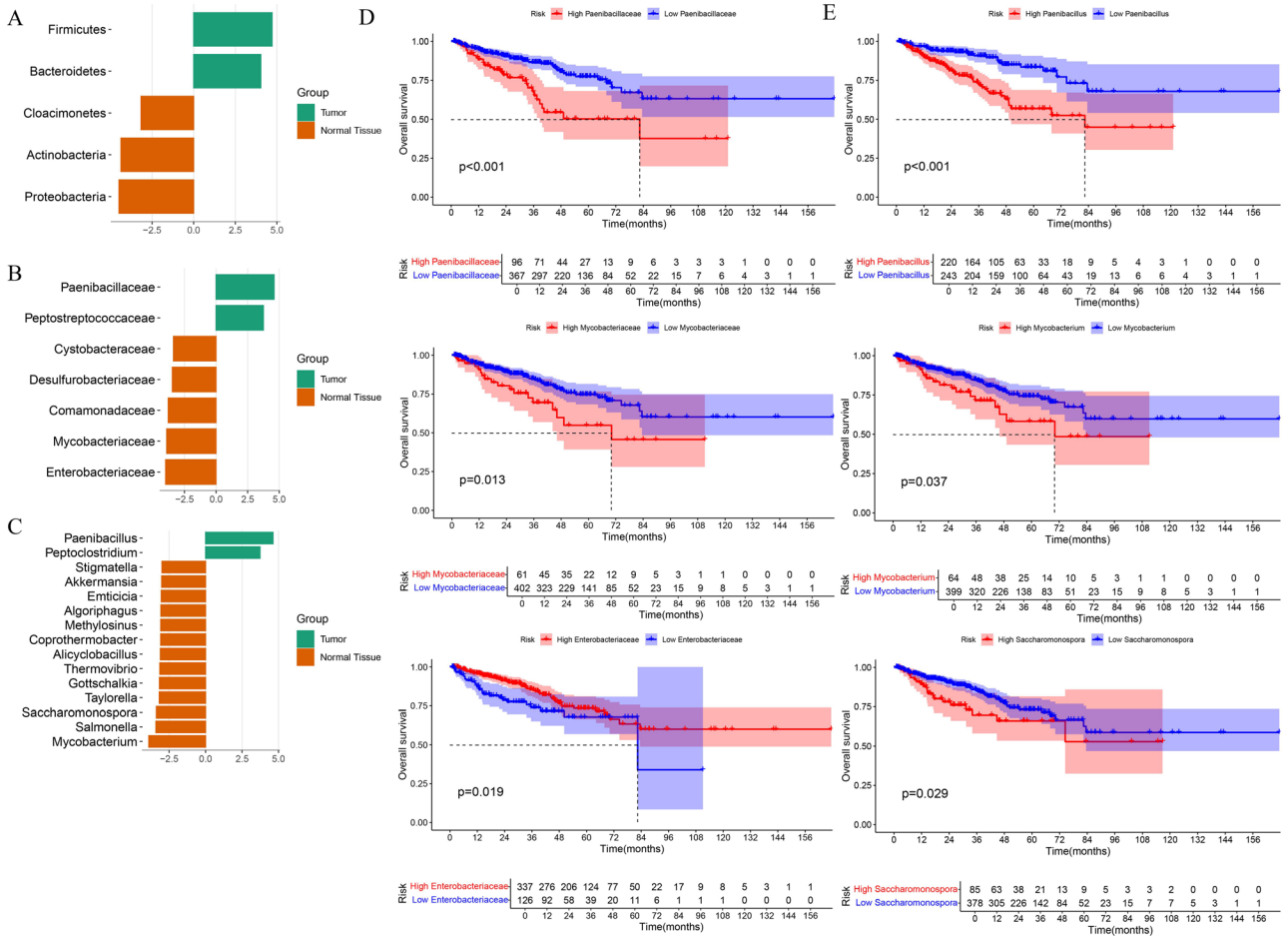

Fig. 3 (**A**) The LDA EFfect Size (LEfSe) analysis of microbiota group by tumor tissue and non-tumor tissue at phylum level ($p < 0.05$). (**B**) The LEfSe analysis of microbiota group by tumor tissue and non-tumor tissue at family level ($p < 0.05$). (**C**) The LEfSe analysis of microbiota between tumor and normal tissue at genus level ($p < 0.05$). (**D**) The positive result of Kaplan-Meier Survival Analysis group by microbiotas at family level. (**E**) The positive result of Kaplan-Meier Survival Analysis group by microbiotas at genus level

rate (FDR) and the significant result lists were shown in Fig. 6D and E. The relative abundance of *Olsenella*, *Myroides*, *Arcobacter*, *Collinsella* and *Parascardovia* was significantly elevated compared to other groups. Within the cohort receiving radiation therapy, *Leptotrichia*, *Olsenella*, *Parascardovia*, *Brachytbacterium*, and *Collinsella* were higher. Moreover, as an exploration study, we upload the result of the unadjusted p-value in Supplemental Fig. 3.

MR

The GWAS ID and details of the included studies was shown in Table 1. The MR outcome of ieu-b-85 was depicted in Fig. 7, Supplemental Fig. 4. In the two-sample MR analysis of ieu-b-85, 19 kinds of gut microbiota were identified to be correlated with prostate cancer. 9 of the identified gut microbiota species were associated with an increased risk of prostate cancer, while 10 were correlated with a decreased risk. However, none of these associations remained statistically significant after adjusting by FDR. The MR analysis result of the Finn database was shown in Supplemental Fig. 5.

Analysis of gut microbiome

In the previous analysis, we found distinct microbial profiles in the patients who received some specific therapeutic. Considering the multi-source of the microbiota in the tumor, comparing the microbiota composition outside the tumor may help us identify the key microbiota and provide new insights into prostate cancer. Consequently, we applied kraken2, a sequence classifier, to explore the gut microbiome of prostate cancer patients.

We initially investigated the gut microbiome in suspected prostate cancer patients. A bar plot was used to describe the consistency of the gut microbiome, presented in Fig. 8. Our previous study indicated that anti-androgen therapy and nuclear therapy may influence the microbiome of patients. Subsequently, we explored the gut microbiota in the patients with radiation therapy and anti-androgen therapy. However, no statistically

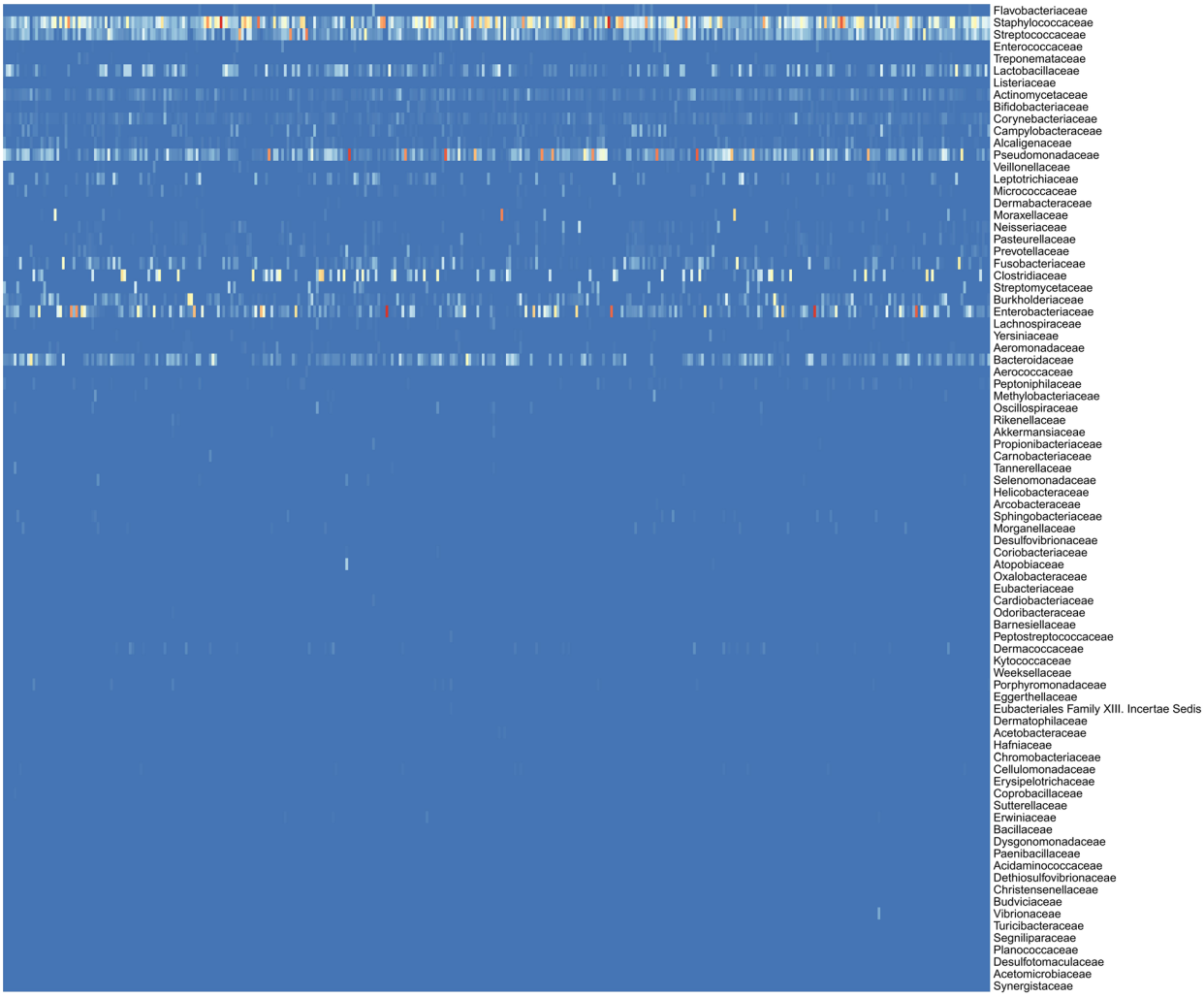

Fig. 4 The heatmap of microbiome in metastasis prostate cancer at family level

significant differences were observed after applying the FDR correction to the p-values. As an exploration study, we tried to analyze the data based on the unadjusted p-values. And the difference microbiotas were depicted in Fig. 9.

Discussion

The relationship between the microbiome and prostate cancer is still on debate. Till now, few trials have been conducted, and whether a special prostate microbiome exists is still being doubted [37]. Although the urinary was thought sterile in tradition, some special microbiotas were still found in prostate cancer. In the majority of studies preceding this discussion, *Propionibacterium* was identified as the dominant microorganism [11, 38, 39], which is also reported associated with prostate inflammation. As for normal microbiota, *Streptococcaceae* was found with a lower abundance in tumor tissue while *Staphylococcaceae* was higher [11].However, most of the findings were obtained by traditional nucleic acid amplification tests like PCR or 16 S rRNA. The amplification bias may distort the bacterial composition and quantify, and it also could not capture viruses [9]. In recent years, the metagenome has entered people's field of vision. Some studies using metagenome analysis tools reported some low-abundance microbiota such as *Acinetobacterter*, *Pseudomonas*, *Firmicutes* and *Actinobacteria* [9, 10]. Tumorigenic including cytomegalovirus and human papillomavirus were also reported [10]. The newly discovered low-abundance microbiota may help us understand more about the microenvironment of cancers and their interaction.

In our study of the intratumor microbiome, we classified the change of alpha and beta diversity between tumor and normal tissue. The community richness and community evenness were lower in tumor tissue, and this phenomenon has been observed in many other types of tumor [40–42]. A possible explanation was that injury to the prostatic epithelium or reductions androgen regulated secretory capability promote pathogenic organisms

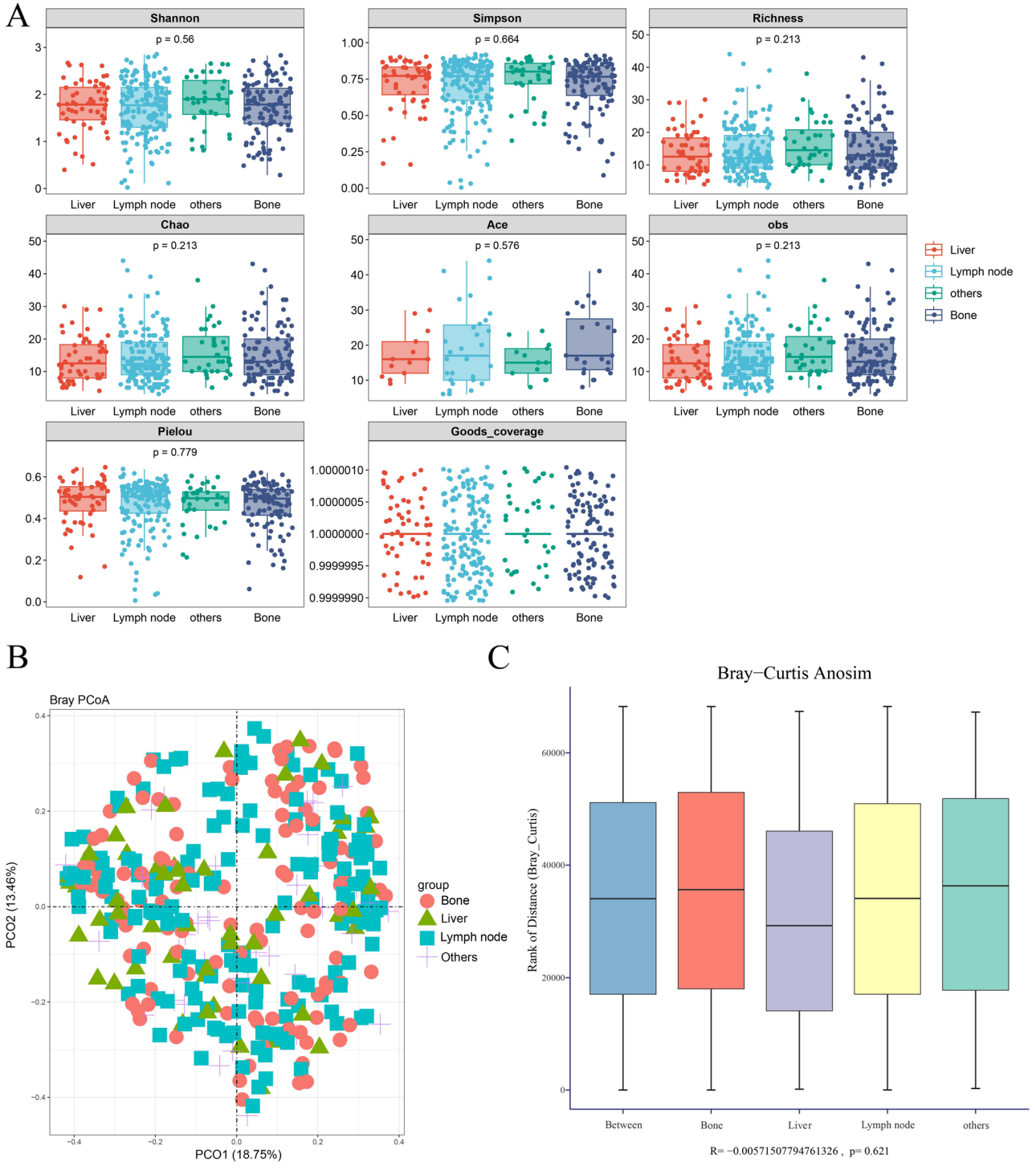

Fig. 5 (**A**) The alpha diversity of microbiome in metastasis prostate cancer, including Shannon index, Simpson index, Richness, Chao, Obs, and Pielou's evenness, group by biopsy site. (**B**) The PCoA of metastasis prostate cancer microbiome group by tumor tissue and non-tumor tissue, group by biopsy site. (**C**) The Bray-Curtis distance of metastasis prostate cancer microbiome group by biopsy site

[43]. It can also be an explanation for the observed disparities of beta diversity. The opportunistic bacteria immigrate to the tumor microenvironment (TME) and inhibit abundant indigenous microbiota.

Although plenty of studies identified the microbiome in primary prostate cancer studies, the data of metastatic prostate cancer was still absent. We extracted the microbiome data from a recent pan-cancer study and found that *Staphylococcus* and *Streptococcus* were the

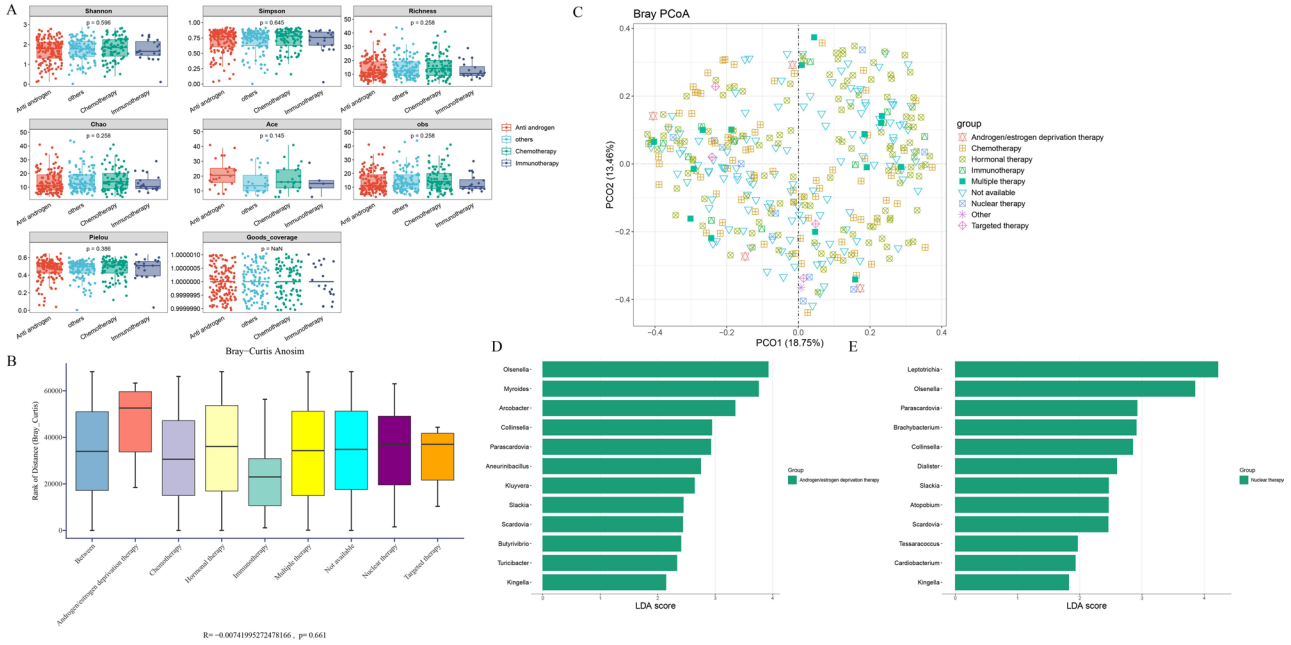

Fig. 6 (**A**) The alpha diversity of microbiome in metastasis prostate cancer, including Shannon index, Simpson index, Richness, Chao, Obs, and Pielou's evenness, group by treatment type. (**B**) The PCoA of metastasis prostate cancer microbiome group by tumor tissue and non-tumor tissue, group by treatment type. (**C**) The Bray-Curtis distance of metastasis prostate cancer microbiome group by treatment type. (**D**) The LEfSe analysis of microbiota between androgen deprivation patients and other treatments patients. (**E**) The LEfSe analysis of microbiota between nuclear treatment patients and other treatments patients

	pvalue	OR
Acetobacteraceae	0.036	1.448(1.025−2.046)
Bacteroidessp002160055	0.010	0.922(0.866−0.981)
Barnesiellaceae	0.047	1.049(1.001−1.100)
Barnesiella	0.045	1.048(1.001−1.096)
Brachyspirae	0.043	1.154(1.005−1.325)
Brevibacillaceae	<0.001	0.659(0.526−0.827)
Brevibacillales	<0.001	0.639(0.507−0.804)
CAG−110	<0.001	0.871(0.806−0.942)
CAG−273sp003534295	0.038	1.048(1.003−1.096)
CAG−452sp000434035	0.044	0.940(0.885−0.998)
Chromobacteriaceae	0.028	0.726(0.546−0.966)
Enteroscipio	0.045	1.100(1.002−1.208)
Firmicutes I	0.017	0.467(0.250−0.872)
Flavobacteriales	0.022	1.245(1.032−1.502)
Lawsonibactersp000492175	<0.001	1.430(1.171−1.747)
Pararhizobium	0.041	0.814(0.668−0.991)
Staphylococcus	0.030	0.804(0.660−0.979)
UBA1375sp002305795	0.047	1.111(1.001−1.234)
UBA3282sp002493835	0.044	0.750(0.567−0.993)

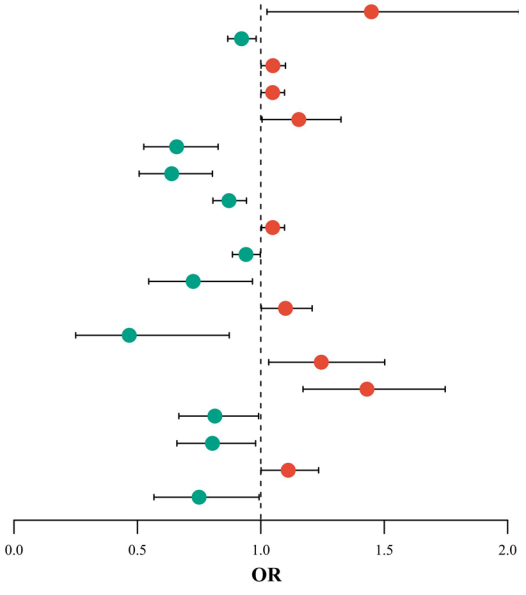

Fig. 7 The forest plot of significant results in MR analysis (ieu-b-85)

highest genus, but they existed on normal human skin and were normal environmental pollutants. We also identified some genera, such as *Lactobacillus*, *Pseudomonas*, and *Clostridium*, which may associated with metastasis of cancer, which has been reported in other cancers. Some past studies may be helpful to explain the specific mechanism. *Clostridium*, plays an important role in the cancer progression through androgen receptor signaling [44]. *Bacteroides*, were found associated with a greater risk of prostate cancer in a study of the gut microbiome [45]. *Streptococcus* and *Lactobacillus*, were also found enriched in the fecal samples of CRPC patients [5]. Interestingly, we found no difference among the samples from different biopsy sites. And we supposed that a special

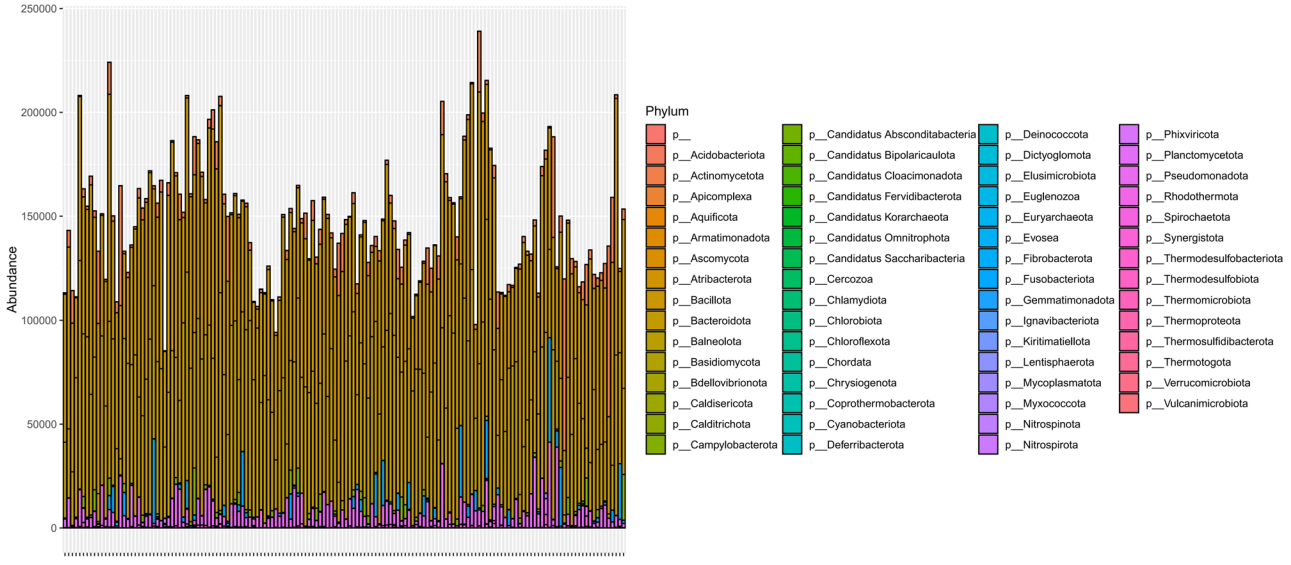

Fig. 8 The bar plot of gut microbiome in suspected prostate cancer (p_: phylum)

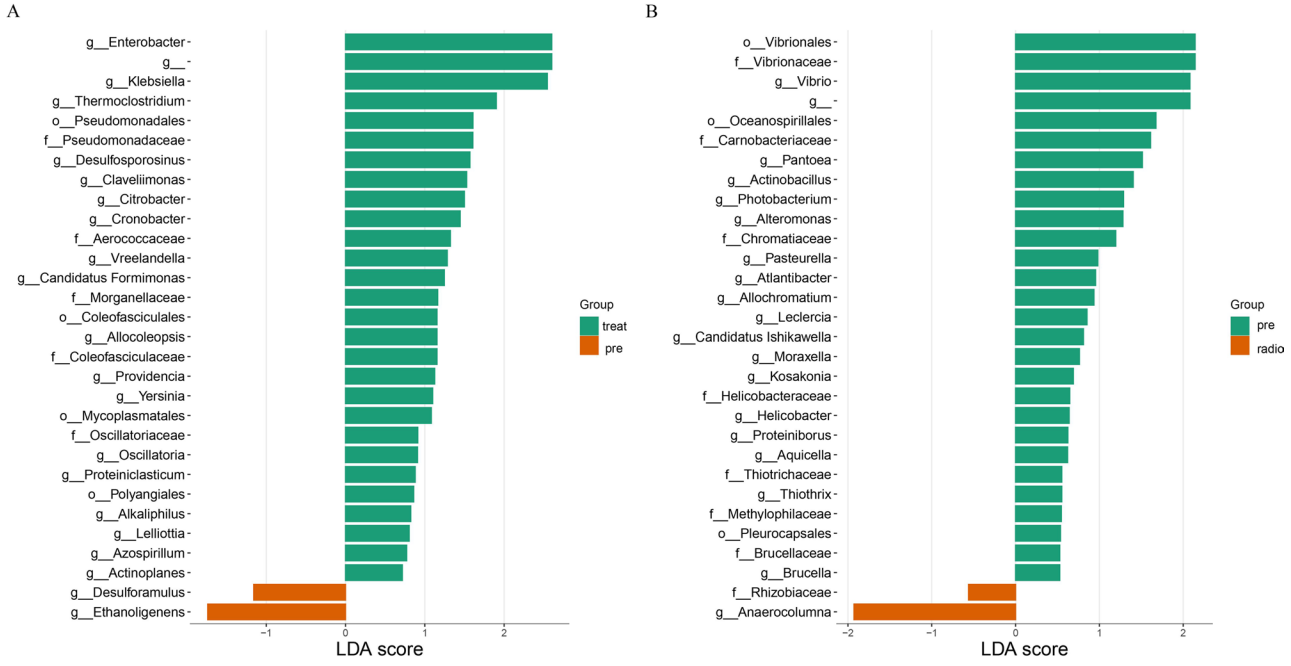

Fig. 9 (**A**) The LEfSe analysis of gut microbiota in anti-androgen treatment patients before and after treating (o_: order; f_: family; g_: genus). (**B**) The LEfSe analysis of gut microbiota in radio treatment patients before and after treating (o_: order; f_: family; g_: genus)

prostate microbiome may exist and keep its special features even if it spreads to different sites. Then we tried to explore the aftermath of distinct treatment types. Anti-androgen therapy, a first-line treatment of advanced prostate cancer, showed a great benefit to patients. But unfortunately, almost all the patients receive the hormonal therapy or androgen deprivation therapy will advance to castration-resistant prostate cancer (CRPC) within 3 years [46]. How to maintain the sensitivity of prostate cancer to anti-androgen therapy is a great challenge for us. In this study, we found *Olsenella*, *Arcobacter*, *Parascardovia*, and other microbiotas have higher abundance after hormonal treatment. In fact, it has been found endocrine resistance by gut bacteria androgen biosynthesis [5]. In intratumor microbiota, some bacteria which can synthesize androgen may also increase as an alternative. Also, the lack of androgen can change the immunity statement, and higher androgen levels could suppress antitumor immunity [47]. Also, the intratumor microbiome could reflect the metabolism, the change of

abundance shows the change of environment in cancer just as a nonliving material. And the little change may not be detected using normal instruments.

Nowadays, the interaction of whole body microbiome is getting researchers attention [48]. As for the intratumor microbiome, four potential sources have been proposed, including hematogenous spread, lymphatic drainage, normal adjacent tissue (NAT), and mucosal barriers [49]. We also study the gut microbiome and try to demonstrate the links between the gut and tumor microbiota. Both the analysis of 16sRNA microbiome data and the MR study didn't show significance after the p value adjusting by FDR. As an exploratory study, we decided to analyze the original p value.

Although some studies suggest gut microbiota plays a role in prostate cancer, but not much study has studied the mechanism under the association. Recent studies offer a possible vision. A major metabolite of microbiota called short chain fatty acids can activate insulin-like growth factor 1 (IGF-1) production and IGF-1 signaling pathway promotes the growth of prostate cancer [7]. The interleukin-6 (IL6) signaling pathway and activator of transcription 3 (STAT3) axis activated by LPS may also promote cancer growth. A former study has found that in CRPC patients, some gut microbiota may produce a bacterial enzyme that synthesizes androgenic steroids and lead to endocrine treatment resistance [5]. And other studies reported phylum Firmicutes, like *Lactobacillus*, can be responsible for testosterone regulation in patients [50, 51].

Conclusion

In summary, we offered a new vision of the microbiome in prostate cancer. We discovered the possibility of special prostate microbiota existence. The anti-androgen treatment can also influence both the intratumor and gut microbiome. This discovery could help researchers further understand the mechanism of progression, metastasis and treatment.

Abbreviations

RNA	Ribonucleic acid
MR	Mendelian Randomization
CPCT	Center for Personalized Cancer Treatment
TCGA	The Cancer Genome Atlas Program
NCBI	National Center of Biotechnology Information
SRA	Sequence Read Archive
WMS	Whole metagenome sequencing
BAM	Binary Alignment/Map
KM	Kaplan-Meier
LEfSe	Linear discriminant analysis effect size
LPSN	The List of Prokaryotic names with Standing in Nomenclature
ADT	Androgen deprivation therapy
FDR	False discovery rate
GWAS	Genome-Wide Association Studies
PCR	Polymerase Chain Reaction
NAT	Normal adjacent tissue
IGF-1	Insulin-like growth factor 1
IL6	Interleukin-6
LPS	Lipopolysaccharides
CRPC	Castration-Resistant Prostate Cancer
PCoA	Principal Co-ordinates Analysis

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12967-024-05937-7.

Supplementary Material 1: The subgroup LEfSe analysis of (A) PSA value (<=0.2 ng/ml and >0.2 ng/ml) (B) Tumor pathology stage (T1/T2 and T3/T4).

Supplementary Material 2: The heatmap of microbiome in metastasis prostate cancer at genus level.

Supplementary Material 3: The LEfSe analysis of microbiota in metastasis prostate cancer grouped by treatment not adjusted by FDR. A) Anti-androgen therapy; B) Chemotherapy; C) Imunnotherapy; D) Target therapy; E) Nuclear therapy.

Supplementary Material 4: The detail result of the MR (ieu-b-85).

Supplementary Material 5: The forest plot of significant results in MR analysis (FinnGen).

Supplementary Material 6

Acknowledgements

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Author contributions

Y.G.C contribute to the article searching and data acquisition. Y.G.C and L.C.Z contribute to data cleaning. Y.G.C, P.H, X.J.C, M.L.T contribute to data analysis. Y.G.C drafted this manuscript. X.Q.D and W.S.G revised the manuscript. All authors contributed to the article and approved the submitted version. Y.G.C, X.Q.D, and W.S.G contributed equally to this work.

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Data availability

All the human data we used in this article is open to access. And the detail is declared in the article.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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