Biology Direct

RESEARCH

Open Access

Prostatitis, benign prostatic hyperplasia, and prostate cancer: a bidirectional Mendelian randomization study and clinical implications for these patients' populations

Yi Wang[1,2†], Guihua Chen[2†], Deng Li[2†], Dongliang Zhang[2*] and Qianwei Xing[1*]

Abstract

Background No authoritative books or guidelines are currently available for revealing the interrelationships of prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PCa). Moreover, no consensus on this issue has been reached among previously published epidemiological studies or meta-analyses.

Purpose We first took advantage of Mendelian randomization to clarify this issue and provide clinical implications for these patients' populations.

Methods Bidirectional two-sample and mediator Mendelian randomization were applied to explore the causal relationships among prostatitis, BPH, and PCa. Sensitivity analyses, including phenotype scanning, heterogeneity, pleiotropy, leave-one-out analysis, and the Steiger test, were conducted to evaluate the robustness and reliability of our results.

Results Our results revealed the interrelationships among prostatitis, BPH, and PCa via Mendelian randomization, confirming that genetic susceptibility to prostatitis or BPH could lead to increased risks of PCa directly or indirectly ($P < 0.05$). Moreover, mediator Mendelian randomization revealed four potential mediator pathways, including the prostatitis-BPH-PCa, the BPH-PCa-prostatitis, the PCa-prostatitis-BPH, and the PCa-BPH-prostatitis pathways. Based on these, we also provided clinical implications for prostatitis, BPH, and PCa patients' populations, respectively. Interestingly, a total of three vicious circles were revealed by us, including the prostatitis-BPH circle, the BPH-PCa circle, and the prostatitis-BPH-PCa circle. All of these three vicious circles contributed to the progression of benign prostate diseases to malignant diseases.

†Yi Wang, Guihua Chen and Deng Li contributed equally to this work.

*Correspondence:
Dongliang Zhang
zhangdlmn@163.com
Qianwei Xing
xingqianwei@ntu.edu.cn

Full list of author information is available at the end of the article

Conclusion We successfully clarified the interrelationships among prostatitis, BPH, and PCa, providing clinical implications for these patients' populations. A total of three vicious circles were also revealed by us to provide novel ideas for future drug development and guide clinical decision-making.

Significance

What is already known on this topic No authoritative books or guidelines are currently available for revealing the interrelationships of prostatitis, BPH, and PCa.

No consensus has been reached among previously published epidemiological studies or meta-analyses, due to their limitations.

Epidemiological researches investigating this issue still had controversies, and they were often case-control or retrospective cohort studies.

What this study adds We first took advantage of Mendelian randomization to explore the interrelationships among prostatitis, BPH, and PCa.

We provided clinical implications for prostatitis, BPH, and PCa patients' populations, respectively, based on mediator Mendelian randomization.

We identified a total of three vicious circles, contributing to the progression of benign prostate diseases to malignant diseases.

Our results provided novel ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment.

Keywords Prostatitis, Benign Prostatic Hyperplasia, Prostate Cancer, Mendelian randomization, Clinical implications

Introduction

Prostate diseases, including prostatitis, benign prostatic hyperplasia (BPH), and prostate cancer (PCa), are highly prevalent conditions affecting a sizable population of men globally [1]. As the malignant form of prostate disorders, PCa ranks as the second leading cause of cancer-related incidences and the fifth leading cause of cancer-related mortalities in the male population worldwide, based on the Global Cancer Statistics 2020 [2]. As a serious threat to the public and the aging male population globally, PCa so far has identified various epidemiology and risk factors, including age, smoking, family history, physical activity, etc [3]. Unexpectedly, prostatitis, or BPH, was also listed among them, although debates still existed [4, 5]. Actually, no authoritative books or guidelines are currently available for revealing their interrelationships. Therefore, a growing number of epidemiological studies or meta-analyses have made attempts to clarify this issue [6–8]. Due to the limitations of these methods, their conclusions remained controversial and incomplete, along with this issue being one of the most common tough questions for urologists in the face of accumulating inquiries from their patients suffering from prostate diseases.

Mendelian randomization, as a powerful and useful tool, utilizes genetic variants as instrumental variables to investigate causal relationships between exposures and outcomes, widely applied in tumor and non-tumor diseases [9–11]. There are various forms of Mendelian randomization, including two-sample Mendelian randomization [12], mediator Mendelian randomization [13], bidirectional Mendelian randomization, etc [14]. Zhong et al. applied two-sample Mendelian randomization to identify new blood metabolites linked to pancreatic ductal adenocarcinoma risks [15]. A bidirectional Mendelian randomization analysis by Dong et al. suggested that COVID-19 hospitalization would increase the risk of glioblastoma development [16]. Mediator Mendelian randomization emphasized the crucial roles of education in the relationships among income and smoking [17]. Obviously, Mendelian randomization seems to be more effective and comprehensive than epidemiological studies and meta-analyses at revealing the interrelationships of prostatitis, BPH, and PCa. Hence, in this article, we also performed Mendelian randomization using genome-wide association study data to explore the causal relationships among prostatitis, BPH, and PCa, providing clinical implications for these patients' populations and guiding clinical decision-making.

Materials and methods

Study design and data sources

The whole study design was detailed in Fig. 1, based on three basic Mendelian randomization assumptions [18]. In this article, we integrated two-sample Mendelian randomization and mediator Mendelian randomization to reveal the interrelationships of prostatitis, BPH, and PCa. The detailed information of these data sources was summarized in Table S1. In the discovery dataset, Prostatitis (GWAS ID: finn-b-N14_PROSTATITIS), BPH (GWAS ID: finn-b-N14_PROSTHYPERPLA), and PCa (GWAS ID: finn-b-C3_PROSTATE) summary data

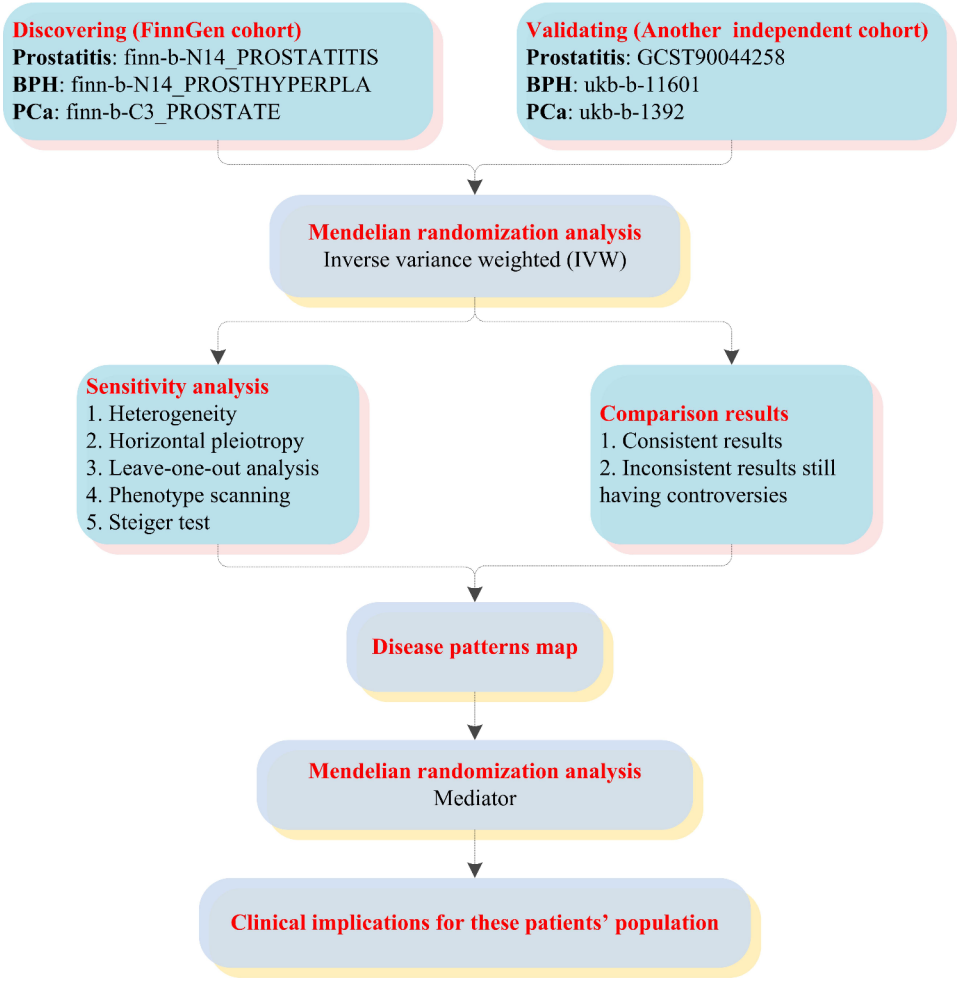

Fig. 1 The whole study design

were respectively obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/). Another independent cohort of prostatitis, BPH, and PCa were utilized as external validations. Prostatitis (GWAS Catalog ID: GCST90044258) summary data in the validation dataset were obtained from the GWAS Catalog database (https://www.ebi.ac.uk/gwas/home). BPH (GWAS ID: ukb-b-11601) and PCa (GWAS ID: ukb-b-1392) summary data in the validation datasets were obtained from the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/).

Ethical approval and research checklist

Since all of these data were openly accessible, patient consent had been obtained by corresponding studies, and ethical approval was not required for this study. The standards for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were followed while reporting this study (Table S2).

Selection of the genetic instrumental variables (IVs)

As detailed in Table S3, when the prostatitis (GWAS ID: finn-b-N14_PROSTATITIS) dataset, or the BPH (GWAS ID: finn-b-N14_PROSTHYPERPLA) dataset, or the PCa (GWAS ID: ukb-b-1392) dataset was used as exposure, we got single nucleotide polymorphisms (SNPs) significantly related to the outcome, based on the P values < 5E-06 and linkage disequilibrium (LD) threshold of clump kb = 10,000, r2 = 0.001. When the PCa (GWAS ID: finn-b-C3_PROSTATE) dataset or the BPH (GWAS ID: ukb-b-11601) dataset was used as exposure, we got single nucleotide polymorphisms (SNPs) significantly related to the outcome, based on the P values < 5E-08 and linkage disequilibrium (LD) threshold of clump kb = 10,000, r2 = 0.001. When the prostatitis (GWAS Catalog ID: GCST90044258) dataset was used as exposure, we got single nucleotide polymorphisms (SNPs) significantly related to the outcome, based on the P values < 5E-06 and linkage disequilibrium (LD) threshold of clump r2 = 0.001.

Then, the F-statistic was calculated, and its values < 10 were removed to reduce the bias from weak instrumental variables (IVs) [19]. Phenotype scanning was also applied to reduce the effects of confounding factors [20]. When the prostatitis (GWAS ID: finn-b-N14_PROSTATITIS; or GWAS Catalog ID: GCST90044258) dataset was used as exposures, we got the results of phenotype scanning and regarded SNPs also related to PCa, or BPH, or body mass index, or prostate specific antigen, or hypertension, or diabetes, or rheumatoid arthritis, or smoking, or alcohol as confounding factors, in combination with searching the PubMed database. When the BPH (GWAS ID: finn-b-N14_PROSTHYPERPLA; or GWAS ID: the ukb-b-11601) dataset was used as exposure, we got the results of phenotype scanning and regarded SNPs also related to PCa, or prostatitis, or body mass index, or prostate specific antigen, or hypertension, or diabetes, or rheumatoid arthritis, or smoking, or alcohol as confounding factors, in combination with searching the PubMed database. When the PCa (GWAS ID: finn-b-C3_PROSTATE dataset; or GWAS ID: ukb-b-1392) dataset was used as exposure, we got the results of phenotype scanning and regarded SNPs also related to BPH, or prostatitis, or body mass index, or hypertension, or diabetes, or smoking, or alcohol as confounding factors, in combination with searching the PubMed database. After removing SNPs also related to confounding factors in the exposure, the remaining SNPs were served as IVs.

Bidirectional two-sample mendelian randomization

The bidirectional two-sample Mendelian randomization was conducted by the "TwoSampleMR" R package in the R 4.2.1 environment. A total of 12 two-sample Mendelian randomization analyses were conducted in both the discovery datasets and the validation datasets, including the causality of prostatitis susceptibility to BPH; the causality of prostatitis susceptibility to PCa; the causality of BPH susceptibility to PCa; the causality of BPH susceptibility to prostatitis; the causality of PCa susceptibility to prostatitis; and the causality of PCa susceptibility to BPH, respectively. The inverse variance weighted (IVW) method with random effects was selected as the main result [21]. P values below 0.05 were regarded as statistically significant differences.

Sensitivity analysis

Sensitivity analyses were conducted to evaluate the robustness and reliability of our results, containing heterogeneity, pleiotropy, leave-one-out analysis, and the Steiger test. Heterogeneity was evaluated by the Cochran's Q test, and its values below 0.05 were regarded as significant heterogeneities [22]. Pleiotropy was calculated by the MR-Egger regression method, and $P < 0.05$ indicated that IVs could not only affect the exposures but also affect the outcomes, against the basic Mendelian randomization assumptions [23]. The leave-one-out method was conducted by removing each SNP sequentially to assess the robustness of our results [24]. A Steiger test was performed to confirm the directionality of the connection between exposures and outcomes [25]. $P < 0.001$ indicated the direction from exposure to outcome was highly plausible.

Mediator mendelian randomization

As previously described [26, 27], a two-step Mendelian randomization was applied for the mediator Mendelian randomization analysis, containing two steps. Step one: Two-sample Mendelian randomizations were conducted among exposure and outcome (Beta1); among exposure and mediator (Beta2); and among mediator and outcome (Beta3), respectively. Step two: The direct and indirect effects were calculated using the formulas displayed below:

$$\text{direct effects} = \frac{\text{Beta1}}{\text{Beta1} + \text{Beta2} \times \text{Beta3}}$$

$$\text{indirect effects} = \frac{\text{Beta2} \times \text{Beta3}}{\text{Beta1} + \text{Beta2} \times \text{Beta3}}$$

Statistical analysis

All Mendelian randomization analyses and data visualization were conducted by the "TwoSampleMR" R package in the R 4.2.1 environment. P values below 0.05 were regarded as statistically significant differences.

Results

Study design and preparation for mendelian randomization

The whole study design was detailed in Fig. 1, and the characteristics of the enrolled datasets in Mendelian randomization in the discovery and validation datasets were summarized in Table S1. The standards for Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) were followed while reporting this study (Table S2). Moreover, the setting conditions for instrumental variables (IVs) of exposures in the discovery and validation datasets were detailed in Table S3. After adjusting for the confounding factors by phenotype scanning (Table S4 and Table S6), we obtained the final IVs of exposures in the discovery and validation datasets for further Mendelian randomization analyses (Table S5 and Table S7).

Bidirectional two-sample mendelian randomization results in the discovery dataset

As detailed in Fig. 2 and Table S3, for the causality of BPH susceptibility to PCa in the discovery dataset, our results showed that genetic susceptibility to BPH might increase the risks of PCa within the IVW method (beta=0.2479, 95% confidence interval (CI): 0.1251–0.3707; $P<0.001$; heterogeneity=2.965E-05; pleiotropy=pass; directionality=true). For the causality of BPH susceptibility to prostatitis in the discovery dataset, our results showed that genetic susceptibility to BPH might increase the risks of prostatitis within the IVW method (beta=0.5389, 95% CI: 0.3916–0.6862; $P<0.001$; heterogeneity=none; pleiotropy=pass; directionality=true). For the causality of PCa susceptibility to BPH in the discovery dataset, our results showed that genetic susceptibility to PCa might increase the risks of BPH within the IVW method (beta=0.1627, 95% CI: 0.0875–0.2378; $P<0.001$; heterogeneity=1.327E-07; pleiotropy=pass; directionality=true). For the causality of PCa susceptibility to prostatitis in the discovery dataset, our results showed that genetic susceptibility to PCa might increase the risks of prostatitis within the IVW method (beta=0.0964, 95% CI: 0.0115–0.1814; $P=0.026$; heterogeneity=none; pleiotropy=pass; directionality=true). For the causality of prostatitis susceptibility to BPH in the discovery dataset, our results showed that genetic susceptibility to prostatitis might increase the risks of BPH within the IVW method (beta=0.0791, 95% CI: 0.0198–0.1385; $P=0.009$; heterogeneity=none; pleiotropy=pass; directionality=true). However, no increased risks of PCa were observed in patients with any type of genetically predicted prostatitis (beta = -0.0153, 95% CI: -0.0916-0.0609; $P=0.693$; heterogeneity=none; pleiotropy=pass; directionality=true). Sensitivity analyses in the discovery dataset indicated the robustness and reliability of our results (Figure S1).

Bidirectional two-sample mendelian randomization results in the validation dataset

As detailed in Fig. 3 and Table S3, for the causality of BPH susceptibility to PCa in the validation dataset, our results showed that genetic susceptibility to BPH might increase the risks of PCa within the IVW method (beta=0.3949, 95% confidence interval (CI): 0.1478–0.6420; $P=0.002$; heterogeneity=0.006; pleiotropy=pass; directionality=true). For the causality of BPH susceptibility to prostatitis in the validation dataset, our results showed that genetic susceptibility to BPH might increase the risks of prostatitis within the IVW method (beta=117.4802, 95% CI: 56.1558-178.8047; $P<0.001$; heterogeneity=none; pleiotropy=pass; directionality=true). For the causality of PCa susceptibility to BPH in the validation dataset, our results showed that genetic susceptibility to PCa might increase the risks of BPH within the IVW method (beta=0.0513, 95% CI: 0.0133–0.0894; $P=0.008$; heterogeneity=0.004; pleiotropy=pass; directionality=true). However, no increased risks of prostatitis were observed in patients with any type of genetically predicted PCa (beta=0.8458, 95% CI: -16.0318-17.7234; $P=0.922$; heterogeneity=none; pleiotropy=pass; directionality=true). For the causality of prostatitis susceptibility to BPH in the validation dataset, our results showed that genetic susceptibility to prostatitis might increase the risks of BPH within the IVW method (beta=0.0005, 95% CI: 0.0002–0.007; $P=0.002$; heterogeneity=none; pleiotropy=pass; directionality=true). However, no increased risks of PCa

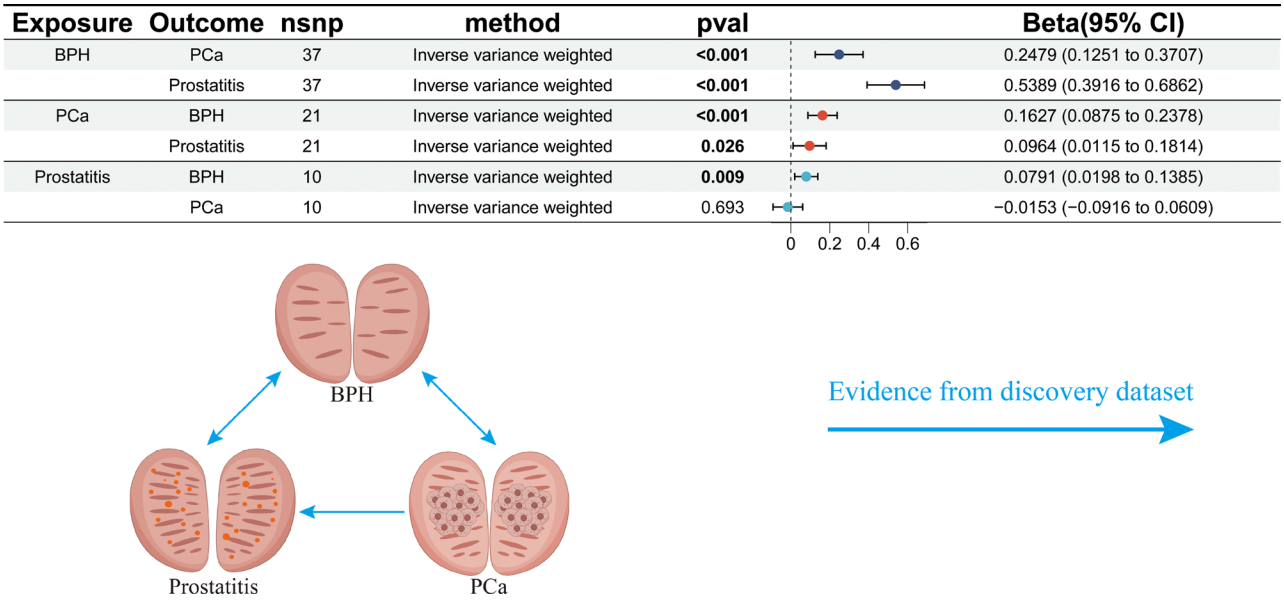

Fig. 2 Two-sample Mendelian randomization results in the discovery dataset

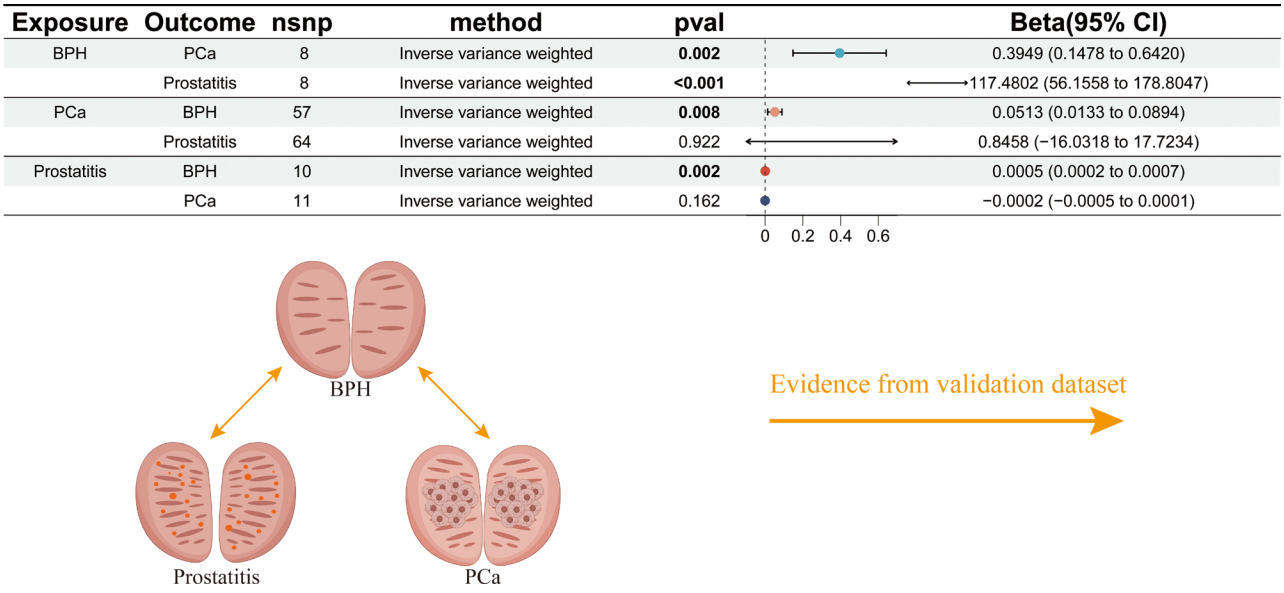

Fig. 3 Two-sample Mendelian randomization results in the validation dataset

were observed in patients with any type of genetically predicted prostatitis (beta = -0.0002, 95% CI: -0.0005-0.0001; *P*=0.162; heterogeneity=none; pleiotropy=pass; directionality=true). Sensitivity analyses in the validation dataset indicated the robustness and reliability of our results (Figure S2).

Mediator mendelian randomization results and clinical implications for these patients' populations

For prostatitis patients, BPH could serve as a mediator among prostatitis and PCa (indirect effects=100%), indicating the pathway from prostatitis to PCa was totally mediated by BPH, while PCa could not serve as a mediator among prostatitis and BPH (Fig. 4A). For BPH patients, prostatitis could not serve as a mediator among BPH and PCa, while PCa could serve as a mediator among BPH and prostatitis (indirect effects=4.2%; direct effects=95.8%), indicating the pathway from BPH to prostatitis was partially mediated by PCa (Fig. 4B). For PCa patients, prostatitis could serve as a mediator among PCa and BPH (indirect effects=4.5%; direct effects=95.5%), indicating the pathway from PCa to BPH was partially mediated by prostatitis. Moreover, BPH could also serve as a mediator among PCa and prostatitis (indirect effects=47.6%; direct effects=52.4%), indicating the pathway from PCa to prostatitis was about half mediated by BPH (Fig. 4C). All in all, a total of four potential mediator pathways were confirmed by our mediator Mendelian randomization results, including the prostatitis-BPH-PCa pathway, the BPH-PCa-prostatitis pathway, the PCa-prostatitis-BPH pathway, and the PCa-BPH-prostatitis pathway.

Clinical implications for prostatitis patients: prostatitis could lead to BPH directly, and it could also lead to PCa indirectly via the prostatitis-BPH-PCa pathway (indirect effects=100%), indicating the pathway from prostatitis to PCa was totally mediated by BPH. Obviously, effectively interrupting prostatitis progress to BPH might avoid the development of PCa, providing novel ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment. Unexpectedly, we found the prostatitis-BPH loop in combination with previous results.

Clinical implications for BPH patients: BPH could lead to PCa directly, and it could also lead to prostatitis directly or indirectly via the BPH-PCa-prostatitis pathway (indirect effects=4.2%; direct effects=95.8%), indicating the pathway from BPH to prostatitis was partially mediated by PCa. Obviously, we paid more attention to the progress of BPH to PCa, and effectively interrupting this progress might avoid the development of PCa, providing novel ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment. Unexpectedly, we found the BPH-PCa loop and the BPH-PCa-prostatitis loop in combination with previous results.

Clinical implications for PCa patients: PCa could lead to BPH directly or indirectly via the PCa-prostatitis-BPH pathway, and it could also lead to prostatitis directly or indirectly via the PCa-BPH-prostatitis pathway, resulting in the prostatitis-BPH-PCa vicious circle based on the PCa-prostatitis-BPH loop and the PCa-BPH-prostatitis loop. Obviously, effectively interrupting this vicious circle might inhibit the development of PCa, providing novel

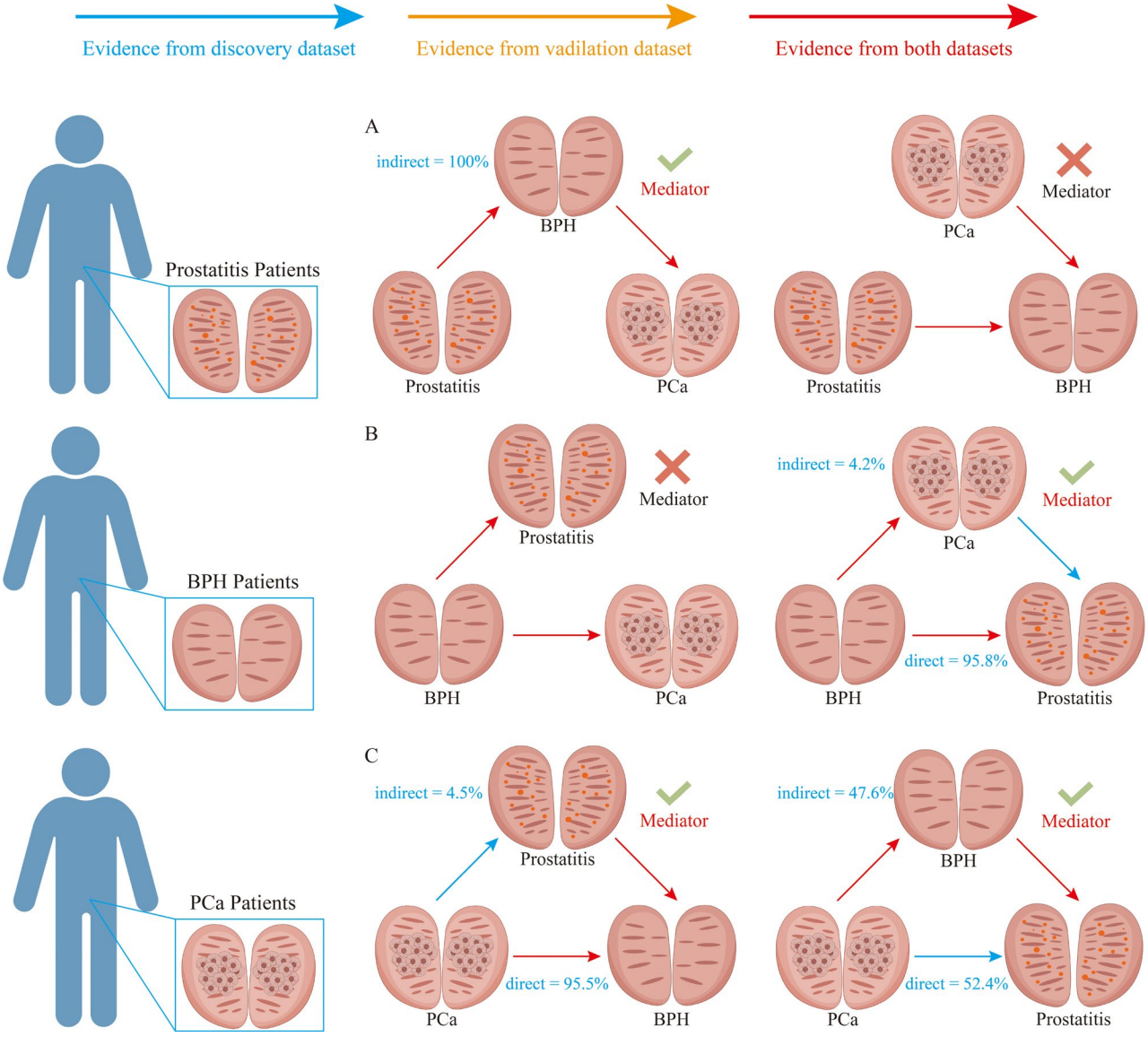

Fig. 4 Mediator Mendelian randomization analyses and clinical implications for (**A**) prostatitis; (**B**) BPH; (**C**) PCa patients' populations

ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment.

Summarized disease pattern map and clinical implications

Based on the above-mentioned results, a total of three vicious circles could be summarized by a disease pattern map in Fig. 5, including the prostatitis-BPH vicious circle (vicious circle 1), the BPH-PCa vicious circle (vicious circle 2), and the prostatitis-BPH-PCa vicious circle (vicious circle 3). All of these three vicious circles contributed to the progression of benign prostate diseases to malignant diseases. Obviously, the involved vicious circle would be markedly inhibited by effectively interrupting any part of the loop, providing novel ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment.

Discussion

In our clinical practices, we are often questioned by some anxious patients whether or not their benign prostate diseases (prostatitis or BPH) will progress to PCa or raise the risks of PCa. However, no authoritative books or guidelines are currently available for revealing their interrelationships. Moreover, no consensus has been reached among previously published epidemiological studies or meta-analyses [7, 28–30]. Hence, this issue remained one of the most common tough questions for urologists in the face of accumulating inquiries from their patients suffering from prostate diseases.

Due to their limitations, previous conclusions drew from epidemiological studies or meta-analyses remained controversial and incomplete. Epidemiological research investigating this issue still had controversies, and they

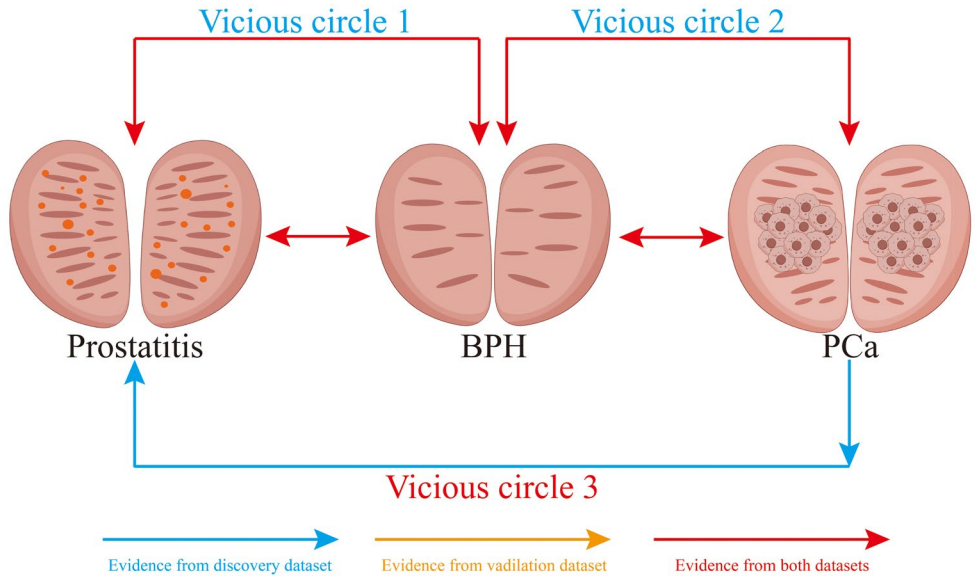

Fig. 5 Disease patterns map

were often case-control or retrospective cohort studies, which could not offer the same statistical power as randomized controlled trials. Weinmann et al. revealed significant associations among fatal PCa and any history of diagnosed BPH (odds ratio (OR)=1.4, 95% CI: 1.1–1.7), while no relationships were found with any history of prostatitis (OR=1.0, 95% CI: 0.79–1.4) [31]. Hung et al. suggested strong associations between PCa and prostatitis (adjusted OR=9.77, 95% CI: 3.09–30.9) or BPH (adjusted OR=24.9, 95% CI: 19.8–31.4) via logistic regression [6]. Although meta-analysis as a powerful tool could provide more reliable conclusions than a single study, it could only use limited data obtained from previously published articles. Our previous meta-analysis explored the relationships among prostatitis, BPH, and PCa, suggesting that prostatitis could increase the risks of BPH and that prostatitis or BPH could also increase the risks of PCa [7]. However, our meta-analysis results were incomplete, and the reversed relationships among prostatitis, BPH, and PCa were not involved due to the limitations of the meta-analysis.

In this article, we took advantage of Mendelian randomization to explore the interrelationships among prostatitis, BPH, and PCa. Our Mendelian randomization results suggested that in both the discovery and validation datasets, genetic susceptibility to prostatitis could increase the risks of BPH, while no increased risks of PCa were observed in patients with any type of genetically predicted prostatitis; genetic susceptibility to BPH could increase the risks of PCa or prostatitis; genetic susceptibility to PCa could increase the risks of BPH, while genetic susceptibility to PCa could increase the risks of prostatitis merely in the discovery dataset. Consistent with previously published articles [32, 33] and our previous meta-analysis results [7], our results also shed light on the pathway via Mendelian randomization that prostatitis could increase the risks of BPH and that BPH could also increase the risks of PCa. Li et al. revealed that prostatitis might have a significant role in the clinical development and progression of BPH [32]. Nair-Shalliker et al. suggested that the risks of PCa were higher in men with a personal history of BPH (OR=2.29, 95% CI: 1.79–2.93) [33]. Inconsistent with previously published articles [34, 35] and our previous meta-analysis results [7], our results did not suggest significant associations among prostatitis and PCa via Mendelian randomization in both the discovery and validation datasets. Boehm et al. showed that prostatitis could increase the probability of detecting PCa even after adjusting for physician visits and PSA testing [34]. Wright et al. also revealed the significant distributions of prostatitis in PCa population-based cases and controls ($P<0.001$) [35]. Different from previously published articles, we first took advantage of Mendelian randomization in this article to explore the reversed relationships among prostatitis, BPH, and PCa, such as the causality of BPH susceptibility to prostatitis, the causality of PCa susceptibility to BPH, and the causality of PCa susceptibility to prostatitis.

Various attempts had been made to illuminate the potential mechanisms of the prostatitis-BPH-PCa pathway. Oseni et al. concluded that chronic inflammation was the common risk factor and molecular hallmark of prostatitis, BPH, and PCa; targeting inflammatory molecules or pathways could be potential treatments in patients with prostatic diseases [36]. Fiard et al. revealed that senescent cells, which were associated with the aging prostate and the senescence-related secretory phenotype, had been linked to both BPH and PCa, providing

opportunities for targeted therapies in the future [37]. From the genetic aspects, Glaser et al. found that BPH and PCa shared common inherited genetics, proving evidence that the significant associations in epidemiological studies were not entirely caused by the detection bias [38]. Other factors, such as oxidative stress, COX, or NO activity, might also play vital roles in the prostatitis-BPH-PCa pathway [39].

As for prostatitis patients, we noticed that prostatitis could lead to BPH directly, and it could also lead to PCa indirectly via the prostatitis-BPH-PCa pathway (indirect effects = 100%), indicating the pathway from prostatitis to PCa was totally mediated by BPH. Obviously, effectively interrupting prostatitis progress to BPH might avoid the development of PCa, providing novel ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment. Various attempts had also been made in previous articles. Di Silverio et al. compared combined therapy with rofecoxib (a COX-2 inhibitor) and finasteride (a 5α-reductase inhibitor) in treating BPH and found its advantages were significant in 4 weeks, providing an effective therapeutic strategy for interrupting prostatitis progress to BPH [40]. Basler et al. revealed in 2004 that COX-2 inhibitors could serve as promising therapeutic agents for PCa chemoprevention [41]. However, a double-blind randomized study by Flamiatos et al. in 2017 suggested that celecoxib (a selective COX-2 inhibitor) had no effects on prostaglandins, androgen receptor levels, or apoptosis in benign or malignant prostate tissues [42]. Effective therapeutic drugs for PCa prevention or treatment remained to be explored and developed.

As for BPH patients, we noticed that BPH could also lead to PCa directly, and effectively interrupting this progress might avoid the development of PCa, providing novel ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment. Various attempts had also been made in previous articles. Rittmaster et al. revealed that dutasteride (a licensed BPH drug) could suppress both serum and intraprostatic DHT levels in men with BPH or PCa at near-maximum levels [43]. During their 4-year study, Roehrborn et al. showed that dutasteride was linked to a lower risk of BPH progression in males with normal or enlarged prostates and mild-to-moderate symptoms [44]. A double-blind randomized study by Moore et al. further suggested that dutasteride could significantly reduce the volumes of PCa on T2-weighted MRI compared with placebo [45]. The above-mentioned information confirmed the idea that effectively interrupting the progress from BPH to PCa might avoid the development of PCa, and novel therapeutic drugs remained to be developed.

As for PCa patients, we noticed that PCa could lead to BPH directly or indirectly via the PCa-prostatitis-BPH pathway, and it could also lead to prostatitis directly or indirectly via the PCa-BPH-prostatitis pathway, resulting in the prostatitis-BPH-PCa vicious circle. Unexpectedly, a total of three vicious circles were revealed by us, including the prostatitis-BPH vicious circle (vicious circle 1), the BPH-PCa vicious circle (vicious circle 2), and the prostatitis-BPH-PCa vicious circle (vicious circle 3). All of these three vicious circles contributed to the progression of benign prostate diseases to malignant diseases. Obviously, the involved vicious circle would be markedly inhibited by effectively interrupting any part of the loop. However, how to effectively interrupt some parts of the loop remained to be explored and discussed by further studies.

The main strengths of this paper were that we first took advantage of Mendelian randomization to explore the interrelationships among prostatitis, BPH, and PCa, verified by a validation dataset, making our results more reliable. Moreover, mediator Mendelian randomization results provided clinical implications for prostatitis, BPH, and PCa patients' populations. Finally, a total of three vicious circles were revealed by us, and they all contributed to the progression of benign prostate diseases to malignant diseases, providing novel ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment. Several limitations should not be overlooked in a comprehensive understanding of our article. First, the whole study population was European, so bias might result in other study populations. Second, the causality of PCa susceptibility to prostatitis was only revealed in the discovery dataset, remaining to be verified in other validation datasets. Third, the prostatitis population was a mixture of various types in this article. So, we currently had difficulties in distinguishing them from each other. Finally, inconsistent with previously published articles and our previous meta-analysis results, our Mendelian randomization results did not suggest significant associations among prostatitis and PCa in both the discovery and validation datasets, remaining to be verified by high-quality and larger population research.

Conclusions

All in all, we first took advantage of Mendelian randomization to explore the interrelationships among prostatitis, BPH, and PCa, confirming that genetic susceptibility to prostatitis or BPH could lead to increased risks of PCa directly or indirectly. Moreover, mediator Mendelian randomization revealed four potential mediator pathways, including the prostatitis-BPH-PCa pathway, the BPH-PCa-prostatitis pathway, the PCa-prostatitis-BPH pathway, and the PCa-BPH-prostatitis pathway. Based on these, we also provided clinical implications for prostatitis, BPH, and PCa patients' populations, respectively. Interestingly, a total of three vicious circles were revealed

by us, and they all contributed to the progression of benign prostate diseases to malignant diseases, providing novel ideas for drug development and new therapeutic strategies for clinical PCa prevention or treatment.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13062-024-00575-x.

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Supplementary Material 7

Supplementary Material 8

Supplementary Material 9

Acknowledgements
None declared.

Author contributions
Y.W & GH.C & D.L: Manuscript writing/editing; Y.W & GH.C & D.L: Data analysis; QW.X & DL.Z: Data collection or management; QW.X & DL.Z: Protocol/project development. All the co-authors agreed to publish the final version of this manuscript.

Funding
This study was supported by grants from Jiangsu Provincial Research Hospital(YJXYY202204-YSB36).

Data availability
Prostatitis, BPH, and PCa summary data were obtained from the GWAS Catalog database (https://www.ebi.ac.uk/gwas/home) with an ID of GCST90044258 and the IEU OpenGWAS project (https://gwas.mrcieu.ac.uk/) with the GWAS IDs of finn-b-N14_PROSTATITIS, finn-b-N14_PROSTHYPERPLA, finn-b-C3_PROSTATE, ukb-b-11601, and ukb-b-1392, respectively.

Declarations

Ethics approval and consent to participate
None declared.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Urology, Affiliated Hospital of Nantong University, No.20 West Temple Road, Nantong, Jiangsu Province 226001, China
[2]Department of Urology, Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine, No.85 Wujin Road, Shanghai 200080, China

Received: 5 September 2024 / Accepted: 2 December 2024
Published online: 19 December 2024

References

1. Gasmi A, Bjørklund G, Noor S, Semenova Y, Dosa A, Pen JJ, Menzel A, Piscopo S, Wirth N, Costea DO. Nutritional and surgical aspects in prostate disorders. Crit Rev Food Sci Nutr. 2023;63(21):5138–54.
2. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global Cancer statistics 2020: GLOBOCAN estimates of incidence and Mortality Worldwide for 36 cancers in 185 countries. Cancer J Clin. 2021;71(3):209–49.
3. Bergengren O, Pekala KR, Matsoukas K, Fainberg J, Mungovan SF, Bratt O, Bray F, Brawley O, Luckenbaugh AN, Mucci L, et al. 2022 update on prostate Cancer epidemiology and risk Factors-A systematic review. Eur Urol. 2023;84(2):191–206.
4. Ørsted DD, Bojesen SE. The link between benign prostatic hyperplasia and prostate cancer. Nat Reviews Urol. 2013;10(1):49–54.
5. Sandhu JS. Prostate cancer and chronic prostatitis. Curr Urol Rep. 2008;9(4):328–32.
6. Hung SC, Lai SW, Tsai PY, Chen PC, Wu HC, Lin WH, Sung FC. Synergistic interaction of benign prostatic hyperplasia and prostatitis on prostate cancer risk. Br J Cancer. 2013;108(9):1778–83.
7. Zhang L, Wang Y, Qin Z, Gao X, Xing Q, Li R, Wang W, Song N, Zhang W. Correlation between Prostatitis, Benign Prostatic Hyperplasia and prostate Cancer: a systematic review and Meta-analysis. J Cancer. 2020;11(1):177–89.
8. Kim SH, Kwon WA, Joung JY. Impact of Benign Prostatic Hyperplasia and/or Prostatitis on the risk of prostate Cancer in Korean patients. World J men's Health. 2021;39(2):358–65.
9. Chen C, Wang P, Zhang RD, Fang Y, Jiang LQ, Fang X, Zhao Y, Wang DG, Ni J, Pan HF. Mendelian randomization as a tool to gain insights into the mosaic causes of autoimmune diseases. Autoimmun rev. 2022;21(12):103210.
10. McGrath IM, Montgomery GW, Mortlock S. Insights from mendelian randomization and genetic correlation analyses into the relationship between endometriosis and its comorbidities. Hum Reprod Update. 2023;29(5):655–74.
11. Sun JX, Xu JZ, Liu CQ, An Y, Xu MY, Zhong XY, Zeng N, Ma SY, He HD, Hu J, et al. The association between human papillomavirus and bladder cancer: evidence from meta-analysis and two-sample mendelian randomization. J Med Virol. 2023;95(1):e28208.
12. Shen S, Gao X, Song X, Xiang W. Association between inflammatory bowel disease and rosacea: a bidirectional two-sample mendelian randomization study. J Am Acad Dermatol 2023.
13. Carter AR, Sanderson E, Hammerton G, Richmond RC, Davey Smith G, Heron J, Taylor AE, Davies NM, Howe LD. Mendelian randomisation for mediation analysis: current methods and challenges for implementation. Eur J Epidemiol. 2021;36(5):465–78.
14. Noordam R, Hamer MA, Pardo LM, van der Nat T, Kiefte-de Jong JC, Kayser M, Slagboom PE, Uitterlinden A, Zillikens MC, Beekman M, et al. No Causal Association between 25-Hydroxyvitamin D and features of skin aging: evidence from a bidirectional mendelian randomization study. J Invest Dermatol. 2017;137(11):2291–7.
15. Zhong H, Liu S, Zhu J, Xu TH, Yu H, Wu L. Elucidating the role of blood metabolites on pancreatic cancer risk using two-sample mendelian randomization analysis. Int J Cancer 2023.
16. Dong J, Wang S, Xie H, Mou Y, Zhu H, Peng Y, Xi J, Zhong M, Xie Z, Jiang Z, et al. COVID-19 hospitalization increases the risk of developing glioblastoma: a bidirectional mendelian-randomization study. Front Oncol. 2023;13:1185466.
17. Shi X, Yuan W, Cao Q, Cui W. Education plays a crucial role in the pathway from poverty to smoking: a mendelian randomization study. Addiction (Abingdon England). 2023;118(1):128–39.
18. Burgess S, Small DS, Thompson SG. A review of instrumental variable estimators for mendelian randomization. Stat Methods Med Res. 2017;26(5):2333–55.
19. Chen L, Yang H, Li H, He C, Yang L, Lv G. Insights into modifiable risk factors of cholelithiasis: a mendelian randomization study. Hepatology (Baltimore MD). 2022;75(4):785–96.
20. Lin J, Zhou J, Xu Y. Potential drug targets for multiple sclerosis identified through mendelian randomization analysis. Brain. 2023;146(8):3364–72.
21. Burgess S, Butterworth A, Thompson SG. Mendelian randomization analysis with multiple genetic variants using summarized data. Genet Epidemiol. 2013;37(7):658–65.
22. Hemani G, Bowden J, Davey Smith G. Evaluating the potential role of pleiotropy in mendelian randomization studies. Hum Mol Genet. 2018;27(R2):R195–208.

23. Bowden J, Davey Smith G, Burgess S. Mendelian randomization with invalid instruments: effect estimation and bias detection through Egger regression. Int J Epidemiol. 2015;44(2):512–25.
24. Burgess S, Bowden J, Fall T, Ingelsson E, Thompson SG. Sensitivity analyses for robust causal inference from mendelian randomization analyses with multiple genetic variants. Epidemiol (Cambridge Mass). 2017;28(1):30–42.
25. Hemani G, Tilling K, Davey Smith G. Orienting the causal relationship between imprecisely measured traits using GWAS summary data. PLoS Genet. 2017;13(11):e1007081.
26. Relton CL, Davey Smith G. Two-step epigenetic mendelian randomization: a strategy for establishing the causal role of epigenetic processes in pathways to disease. Int J Epidemiol. 2012;41(1):161–76.
27. Röhnisch HE, Kyrø C, Olsen A, Thysell E, Hallmans G, Moazzami AA. Identification of metabolites associated with prostate cancer risk: a nested case-control study with long follow-up in the Northern Sweden Health and Disease Study. BMC Med. 2020;18(1):187.
28. Ørsted DD, Bojesen SE, Nielsen SF, Nordestgaard BG. Association of clinical benign prostate hyperplasia with prostate cancer incidence and mortality revisited: a nationwide cohort study of 3,009,258 men. Eur Urol. 2011;60(4):691–8.
29. Langston ME, Horn M, Khan S, Pakpahan R, Doering M, Dennis LK, Sutcliffe S. A systematic review and Meta-analysis of associations between clinical prostatitis and prostate Cancer: new estimates Accounting for Detection Bias. Cancer Epidemiol Biomarkers Prevention: Publication Am Association Cancer Res Cosponsored Am Soc Prev Oncol. 2019;28(10):1594–603.
30. Hennis AJ, Wu SY, Nemesure B, Leske MC. Urologic characteristics and sexual behaviors associated with prostate cancer in an african-caribbean population in Barbados, west indies. Prostate cancer. 2013;2013:682750.
31. Weinmann S, Shapiro JA, Rybicki BA, Enger SM, Van Den Eeden SK, Richert-Boe KE, Weiss NS. Medical history, body size, and cigarette smoking in relation to fatal prostate cancer. Cancer Causes Control: CCC. 2010;21(1):117–25.
32. Li J, Li Y, Cao D, Huang Y, Peng L, Meng C, Wei Q. The association between histological prostatitis and benign prostatic hyperplasia: a single-center retrospective study. Aging male: Official J Int Soc Study Aging Male. 2022;25(1):88–93.
33. Nair-Shalliker V, Yap S, Nunez C, Egger S, Rodger J, Patel MI, O'Connell DL, Sitas F, Armstrong BK, Smith DP. Adult body size, sexual history and adolescent sexual development, may predict risk of developing prostate cancer: results from the New South Wales Lifestyle and evaluation of risk study (CLEAR). Int J Cancer. 2017;140(3):565–74.
34. Boehm K, Valdivieso R, Meskawi M, Larcher A, Schiffmann J, Sun M, Graefen M, Saad F, Parent M, Karakiewicz PI. Prostatitis, other genitourinary infections and prostate cancer: results from a population-based case-control study. World J Urol. 2016;34(3):425–30.
35. Wright JL, Lin DW, Stanford JL. Circumcision and the risk of prostate cancer. Cancer. 2012;118(18):4437–43.
36. Oseni SO, Naar C, Pavlović M, Asghar W, Hartmann JX, Fields GB, Esiobu N, Kumi-Diaka J. The molecular basis and clinical consequences of chronic inflammation in Prostatic diseases: Prostatitis, Benign Prostatic Hyperplasia, and prostate Cancer. Cancers 2023, 15(12).
37. Fiard G, Stavrinides V, Chambers ES, Heavey S, Freeman A, Ball R, Akbar AN, Emberton M. Cellular senescence as a possible link between prostate diseases of the ageing male. Nat Reviews Urol. 2021;18(10):597–610.
38. Glaser A, Shi Z, Wei J, Lanman NA, Ladson-Gary S, Vickman RE, Franco OE, Crawford SE, Lilly Zheng S, Hayward SW, et al. Shared inherited Genetics of Benign Prostatic Hyperplasia and prostate Cancer. Eur Urol open Sci. 2022;43:54–61.
39. Sciarra A, Di Silverio F, Salciccia S, Autran Gomez AM, Gentilucci A, Gentile V. Inflammation and chronic prostatic diseases: evidence for a link? Eur Urol. 2007;52(4):964–72.
40. Di Silverio F, Bosman C, Salvatori M, Albanesi L, Proietti Pannunzi L, Ciccariello M, Cardi A, Salvatori G, Sciarra A. Combination therapy with rofecoxib and finasteride in the treatment of men with lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH). Eur Urol. 2005;47(1):72–8. discussion 78–79.
41. Basler JW, Piazza GA. Nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective inhibitors for prostate cancer chemoprevention. J Urol. 2004;171(2 Pt 2):S59–62. discussion S62-53.
42. Flamiatos JF, Beer TM, Graff JN, Eilers KM, Tian W, Sekhon HS, Garzotto M. Cyclooxygenase-2 (COX-2) inhibition for prostate cancer chemoprevention: double-blind randomised study of pre-prostatectomy celecoxib or placebo. BJU Int. 2017;119(5):709–16.
43. Rittmaster R, Hahn RG, Ray P, Shannon JB, Wurzel R. Effect of dutasteride on intraprostatic androgen levels in men with benign prostatic hyperplasia or prostate cancer. Urology. 2008;72(4):808–12.
44. Roehrborn CG, Nickel JC, Andriole GL, Gagnier RP, Black L, Wilson TH, Rittmaster RS. Dutasteride improves outcomes of benign prostatic hyperplasia when evaluated for prostate cancer risk reduction: secondary analysis of the REduction by DUtasteride of prostate Cancer events (REDUCE) trial. Urology. 2011;78(3):641–6.
45. Moore CM, Robertson NL, Jichi F, Damola A, Ambler G, Giganti F, Ridout AJ, Bott SR, Winkler M, Ahmed HU, et al. The Effect of Dutasteride on magnetic resonance imaging defined prostate Cancer: MAPPED-A Randomized, Placebo Controlled, double-blind clinical trial. J Urol. 2017;197(4):1006–13.

Publisher's note