Unveiling the Etiology of Urological Tumors: A Systematic Review of Mendelian Randomization Applications in Renal Cell Carcinoma, Bladder Cancer, and Prostate Cancer

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ABSTRACT

Background: Our study aims to address two pivotal questions: "What are the recent advancements in understanding the etiology of urological tumors through Mendelian Randomization?" and "How can Mendelian Randomization be more effectively applied in clinical settings to enhance patient health outcomes in the future?"

Methods: In our systematic review conducted in April 2023, we utilized databases like PubMed and Web of Science to explore the influence of Mendelian Randomization in urological oncological diseases. We focused on studies published from January 2018, employing keywords related to urological tumors and Mendelian Randomization, supplemented with MeSH terms and manual reference checks. Our inclusion criteria targeted original research studies, while we excluded reports and non-relevant articles. Data extraction followed a PICO-based approach, and bias risk was independently evaluated, with discrepancies resolved through discussion. This systematic approach adhered to PRISMA guidelines for accuracy and thoroughness in reporting.

Results: From the initial 457 publications, we narrowed down to 43 full-text articles after screening and quality assessments.A deeper understanding of Mendelian Randomization can help us explore risk factors with a clear causal relationship to urological tumors.This insight may pave the way for future research in early diagnosis, treatment, and management of associated diseases.

Conclusion: Our review underscores the value of MR in urogenital tumor research, highlighting its efficacy in establishing causality and its potential to clarify disease mechanisms. Despite challenges like large sample sizes and variant identification, MR offers new perspectives for understanding and managing these tumors, suggesting a trend towards more inclusive and diverse research approaches.

INTRODUCTION

By 2030, cancer is anticipated to overtake cardiovascular diseases, becoming the leading cause of death across all age groups[1]. With population growth and aging, the incidence of urologic tumors continues to rise steadily. The latest epidemiological data reveals that urologic cancers account for 13.1% of all new cancer diagnoses and 7.9% of total cancer-related deaths. Among these, renal cell carcinoma (RCC), bladder cancer (BC), prostate cancer (PCa), and testicular cancer (TC) are the most prevalent types[2]. As a result, it becomes essential to investigate the etiology and risk factors of urologic tumors, formulate preventive strategies, evaluate prognosis, and pioneer new treatment methods.

The progression of urologic tumors is intricately influenced by various factors, such as age, gender, height, weight, childhood body size, lifestyle habits (including smoking and alcohol consumption), race, and underlying diseases[3,4]. Determining the connection and causality of these factors is a core challenge in epidemiological studies. For many years, randomized controlled trials (RCTs) have been esteemed as the gold standard for validating scientific theories. Yet, RCTs present inherent limitations due to their vulnerability to confounding factors, difficulty in applying targeted interventions, and the potential to confound or reverse causality[5]. Coupled with significant financial and temporal constraints, these drawbacks limit the practicality of RCTs. In contrast, Mendelian Randomization (MR) studies have recently gained traction in urologic tumor research, owing to their capability to minimize confounding influences and their high feasibility.

While the use of MR in investigating the etiology and risk factors of major urological tumors is on the rise, there remains a gap in the cohesive understanding of cancer-specific risk factors. Our study aims to address two pivotal questions: "What are the recent advancements in understanding

the etiology of urological tumors through Mendelian Randomization?" and "How can Mendelian Randomization be more effectively applied in clinical settings to enhance patient health outcomes in the future?"

To answer these questions, this systematic review was conducted to collate and analyze relevant evidence. Our primary objective is to determine the latest advancements in understanding the impact of MR on the etiology and clinical aspects of urological tumors, and to synthesize these findings into a comprehensive overview. Ultimately, this article presents an extensive review of the fundamental principles, strengths, and limitations of MR, highlighting its recent contributions to urological tumor research. The goal is to provide fresh insights and directions for future research in this field, potentially paving the way for more effective clinical applications of MR in urological oncology.

MATERIALS AND METHODS

Inclusion and Exclusion Criteria

We included articles if their title and/or abstract indicated an original research study, employing either quantitative or qualitative methods. The selected studies were expected to provide insights into the outcomes of MR in exploring the etiology of various urological tumors, as well as perspectives on the future applications of MR. The electronic abstracts of all retrieved articles were reviewed by three authors to ensure thorough evaluation. Duplicate references were removed to maintain the uniqueness of the dataset. We excluded studies that were not directly relevant to our research question, along with reports, comments, and letters, to maintain the focus and quality of our review. Mindful of potential selection, publication, and language biases in the

retrieval process, all relevant studies were subjected to a comprehensive full-text review for a detailed assessment.

Search Strategy

Our systematic review was centered on assessing the influence of MR in the etiology and clinical aspects of urological oncological diseases. In April 2023, we conducted a comprehensive search through electronic databases such as PubMed and Web of Science. This search was restricted to studies published after January 2018 and later updated to include any new publications. Our search strategy encompassed keywords like "Mendelian Randomization," "Urologic Tumors," "Prostate Cancer," "Bladder Cancer," "Kidney Cancer," and other related terms. We utilized MeSH terms and Boolean logic operators "AND" and "OR" to refine our article retrieval process. Additionally, reference lists from relevant literature were manually examined to identify original studies.

Screening Procedure

Following the search, 457 publications were identified.Subsequently, duplicate articles were removed, leading to the screening of 162 articles.Following abstract screening based on the inclusion/exclusion criteria, 63 articles were excluded.The remaining 99 publications were selected for an extensive review.Full texts of potentially relevant articles were reviewed by three authors to ascertain their eligibility for inclusion.After a quality assessment, 43 full-text articles were incorporated into the study(Figure 1).

Data Extraction and Analysis

Data extraction was collaboratively undertaken by two reviewers. Any discrepancies encountered were resolved through consultation. We employed a PICO (Population, Intervention, Comparison, Outcome)-based form for systematic information collection, which

included details such as author, publication year, country/region, comparison, study design, main findings/summaries, critical assessment, and risk of potential bias. Subsequently, three authors convened to discuss the study outcomes. The data synthesis was approached narratively, utilizing a thematic method to cohesively integrate studies of diverse methodologies, based on the nature of the evidence.

Narrative Synthesis

Given the substantial variation among the studies included in our review, a narrative synthesis (NS) approach was chosen. This decision followed a thorough discussion among the authors. NS is a versatile method capable of integrating both quantitative and qualitative research findings[6]. It is particularly favored in systematic reviews where there is significant heterogeneity among the experimental and non-experimental studies. In instances where quantitative data is not amenable to statistical synthesis due to its diverse nature, NS offers a practical alternative. The narrative synthesis applied in our review extends beyond merely focusing on intervention efficacy. It encompasses systematic evaluations addressing a broad spectrum of issues, providing a comprehensive and cohesive interpretation of the findings. This approach allows for a more nuanced understanding of the data, considering the varied methodologies and outcomes of the studies under review.

Data Presentation

The findings are systematically presented in the results section. The presentation is structured with subheadings, beginning with an overview of Mendelian Randomization, its limitations, and advantages. This is followed by a detailed examination of its applications in urological tumors, focusing on current research exploring the etiology of kidney, bladder, and prostate cancers.

Systematic Review Assessment

This systematic review was conducted in strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines , ensuring transparency and applicability in reporting[7]. The review process involved a consensus meeting among the authors to review and agree upon the PRISMA items.

RESULTS

Introduction to Mendelian Randomization

As sequencing technology advances and costs decrease, the procurement of tumor tissue and blood samples for genetic analysis is becoming increasingly common in leading medical facilities. Techniques such as targeted gene sequencing, liquid biopsy, and circulating tumor DNA (ctDNA) analysis are extensively utilized to gather genetic variation information[8]. Genetic testing holds significant potential in cancer management, offering benefits in early screening, preventive strategies, and the development of personalized treatment plans for cancer patients. This approach is particularly influential in improving the prognosis of individuals with cancers like breast and prostate cancer, extending its benefits to their families as well.In the realm of prostate cancer research, germline genetic testing, particularly of genes like BRCA1/2, has played a pivotal role in deepening our understanding of susceptibility to the disease9.In summary, as the collection and refinement of genetic variation data continue to evolve, the field of MR is undergoing a rapid expansion.

Fundamental Principles of Mendelian Randomization

MR is a potent analytical technique employed to determine causal links between risk factors and clinical outcomes. First introduced in 1986, it melds genetic information with epidemiological studies to draw causal connections between specific exposures and disease risks[10-12]. Executing an MR study involves intricate stages, such as defining the study design, garnering data from

clinical sources, identifying the exposure and outcome variables of interest, choosing the right genetic variants, and undertaking statistical analyses. Among these stages, selecting the genetic variants holds vital importance. Ideally, these variants should satisfy three core assumptions: Independence Assumption: The genetic variants must be free from confounding factors, Association Assumption: There should be a robust relationship between the genetic variants and the exposure under investigation, Exclusion Restriction Assumption: A direct association between the genetic factors and the outcome risk must not exist[13].

MR's core principle is rooted in the idea that genetic variations can influence exposure factors, subsequently shaping the development and advancement of diseases. When scientists establish a causal connection between a specific genetic variation and an exposure factor, it paves the way for inferring the causal effect between that exposure and the disease. This inference is achieved by examining how genetic variations correlate with disease outcomes within a population.

Classification of Mendelian Randomization Studies

Currently, commonly employed methods in MR research include classical MR, two-sample MR, bidirectional MR, and multivariable MR[14]. The classical MR, also known as single-sample MR, is the oldest and most established method. It involves assessing genetic variants, exposure factors, and outcomes within the same population at the individual level. However, due to inherent limitations in the association between risk factors and genotype results, it may result in false-positive results. Two-sample MR is the most extensively applied method, where genetic variant-exposure factor and genetic variant-disease risk data are obtained from two independent sample cohorts and analyzed as a whole. This approach has gained popularity due to its high feasibility and the accessibility of public databases. Bidirectional MR involves conducting an additional analysis after classical MR to investigate whether there is a reverse causal relationship between

exposure and outcome, aiming to further clarify the underlying relationships. Multivariable MR examines the relationships between genetic variants and multiple related phenotypes simultaneously and evaluates the independent causal effects of exposure factors on outcomes. This method is suitable for studying genetic variants that may lead to multiple phenotypic changes.

Advantages of Mendelian Randomization

The prominent advantage of MR research lies in its causal inference capabilities. First, genetic variants are not influenced by confounding factors such as environmental conditions, habits, social status, and economic situations which follow Mendelian inheritance patterns, allowing for more effective control of various biases. Second, the inherent relationship between individual's genotype and disease outcome is unquestionable, with the established directionality from "genetic variant to outcome", thereby avoiding the issue of reverse causality in this aspect[15].

Limitations of Mendelian Randomization

On one hand, current designs of MR studies exhibit several shortcomings[15,16] Firstly, identifying suitable genetic variants is a formidable challenge. For instance, in a lung cancer MR study, the exploration of associations between risk factors and SNPs yielded only 842 and 28 significant SNPs linked to BMI and smoking status, respectively, a small subset of the total SNPs[17]. Secondly, MR studies often grapple with low statistical power due to genetic polymorphism, necessitating large sample sizes to mitigate false positives. As Stephen observed, to detect a 1% causal effect of an instrumental variable (IV) on a trait, a sample of 30,000 cases is required for substantial statistical power (>95%) in a 1:1 case-control study [18]. Lastly, genetic variations only partly explain exposure effects, and the ambiguous linkage mechanisms further complicate the generalization of causal inferences. For example, Fan et al.'s research on schizophrenia and

prostate cancer risk used both meta-analysis and MR. Their meta-analysis suggested a decreased prostate cancer risk in schizophrenia patients, a finding not mirrored in MR studies. They highlighted the need for stronger evidence of SNP effects on schizophrenia and the potential influence of unidentified SNPs, urging caution in interpreting MR-derived causal relationships[19]. On the other hand, while MR studies are theoretically insulated from unobserved confounders, measurement errors, and reverse causality, practical applications, especially in traditional MR studies, reveal various potential biases and confounding factors. These include, but are not limited to, population stratification, pleiotropy, and horizontal pleiotropy, along with other less apparent confounders[20]. Population stratification arises when a specific genetic variation is associated with different disease risks across races or population groups, leading to misinterpretations of the genetic variation-disease relationship. Pleiotropy occurs when a genetic variant, used as an instrumental variable in MR studies, influences factors beyond the primary exposure and outcomes, thereby introducing biases in causal inference. Horizontal pleiotropy, as opposed to vertical pleiotropy which directly influences study outcomes, involves genetic variations that indirectly affect study results through multiple independent biological pathways. Many high-quality MR studies have recognized that issues like population stratification, residual pleiotropy, and other potential confounders significantly limit research, impacting the reliability of conclusions drawn[21,22]. These acknowledgments underscore the complexities involved in MR studies and highlight the need for cautious interpretation of their results.

The landscape of MR studies is evolving. The expansion of global genetic databases, coupled with advancements in statistical algorithms, cross-disciplinary collaboration, and enhanced understanding of disease mechanisms, are gradually addressing MR's inherent design limitations.

Researchers are now more effectively combining biological insights with bioinformatics and laboratory experiments, leading to refined interpretations of MR study outcomes. Innovative methods, such as multivariable mediating MR and Egger regression, are being adopted to combat biases and confounders more effectively in MR analyses [23,24]. These improvements are steadily enhancing the reliability of MR studies, reinforcing their potential as a valuable research tool.

The Current Application Status of MR in Urological Tumors

As mentioned earlier, due to its advantages in causal inference and other aspects, Mendelian MR has been widely applied in cancer research, including studies on urological tumors. Through MR studies, researchers can assess the risk factors, clarify causal relationships, identify potential prognostic biomarkers, and provide important clues for early disease prevention and scientific management of urological tumors.

Behavioral habits play a crucial role in the progression of urological tumors, and exploring their causal relationships is crucial for early prevention and treatment of these tumors. The association between obesity and urological tumors has been increasingly highlighted. Papavasileiou et al. conducted MR studies and reviews on kidney cancer, prostate cancer, bladder cancer, and testicular cancer, analyzing the biological mechanisms and concluding that overweight and obesity are significant risk factors for urological tumors[3]. Chen et al. found that low intake of dried fruits is a risk factor for oral/pharyngeal, lung, squamous cell lung, breast, ovarian, pancreatic, and cervical cancers, but there is no apparent causal relationship with lung adenocarcinoma, endometrial cancer, thyroid cancer, prostate cancer, bladder cancer, and brain cancer[25]. Additionally, previous studies have indicated a negative correlation between milk intake and colorectal cancer, bladder cancer, and breast cancer risk, but a positive correlation with prostate cancer[26]. To investigate the potential causal relationship between milk intake and

cancer, Susanna et al. conducted a two-sample MR study and found that milk intake may reduce the risk of colorectal cancer, while there is no apparent causal association with bladder cancer, breast cancer, and prostate cancer[27]. Coffee, as a popular beverage, has long been studied for its relationship with tumor risk, but the relationship between coffee and caffeine intake and urological tumors remains controversial[28-30]. Deng et al. conducted a two-sample MR study based on the UK Biobank (n=420,838) and the FinnGen consortium (n=175,121) and found no significant causal association between coffee consumption and bladder cancer risk[31]. Similarly, Wang et al. conducted an MR study utilizing the Prostate Cancer Association Group to Investigate Cancer-Associated Alterations in the Genome (PRACTICAL) consortium and FinnGen data to investigate the causal relationship between coffee consumption and renal cell carcinoma risk[32]. In another study, Li et al. performed a meta-analysis using a large sample size (n=13,230) from the FinnGen consortium and international cancer research institutions, employing a two-sample MR approach to analyze the causal association between coffee intake and renal cell carcinoma risk[33]. The results indicated that there was no significant causal relationship between coffee or caffeine intake and the risks of renal cell carcinoma and prostate cancer .

The relationship between urological tumors and nutritional factors has always been a hot topic in scientific research. Recently published MR studies have also delved into this area. A two-sample MR study from Peking Union Medical College revealed that elevated serum zinc levels may increase the risk of prostate cancer, and serum copper levels are positively associated with the risk of clear cell renal cell carcinoma, while there is no significant association with bladder cancer risk[34]. Moreover, a large-scale MR study with data from over 600,000 cancer patients showed no significant association between serum vitamin E levels and the risk of colorectal

cancer, esophageal cancer, lung cancer, oral and pharyngeal cancer, ovarian cancer, pancreatic cancer, breast cancer, prostate cancer, kidney cancer, and bladder cancer, suggesting that vitamin E supplementation may not be beneficial for the prevention of urological cancers[35].

The causal relationship between urological tumors and treatment-related biomarkers is another focus of MR research. Some case-control studies have shown a close relationship between peripheral blood leukocyte telomere length (LHL) and the survival of urological tumor patients, but their relationship remains controversial. Previous studies often measured LHL in blood samples taken after diagnosis, which may be influenced by pre-existing diseases and detection time. To eliminate the impact of these confounding factors, Chen et al., Machiela et al., and Xu et al. conducted case-control and MR studies on bladder cancer, renal cell carcinoma, and prostate cancer, respectively[36-38]. The results showed that LHL does not play an important role in the etiology of bladder cancer. However, longer LHL may lead to a higher risk of renal cell carcinoma, while shorter LHL may contribute to the occurrence of prostate cancer and poorer treatment outcomes. This highlights the prognostic and clinical value of LHL in risk stratification of renal cell carcinoma and prostate cancer patients. Further elucidation of its mechanisms will help determine more effective treatment strategies and improve prognosis.

Recent MR studies have also examined sociocultural factors. Scholars analyzed 14 urological and reproductive-related diseases and found that education level plays a crucial role in non-tumor and reproductive-related diseases, but the causal relationship is not evident in urological tumors[39].

Advances in the Application of MR in Renal Cell Carcinoma

In recent years, the incidence of renal cell carcinoma has been increasing at a rate of approximately 1.1% per year, imposing a heavy burden on society[40]. The latest MR studies have

revealed causal associations between obesity-related biomarkers, renal dysfunction, and renal cancer, providing new insights for the prevention and management of renal cell carcinoma.

The relationship between obesity and the progression of renal cell carcinoma is strongly interconnected. It is crucial to identify obesity-related biomarkers that are closely associated with the risk of developing renal cell carcinoma for its prevention, early diagnosis, and treatment. To investigate the causal relationship between obesity-related factors and renal cell carcinoma, Johansson et al. employed the MR study method to comprehensively explore various indicators, including obesity indices, blood pressure, lipid levels, type 2 diabetes, insulin, and glucose-related markers[41]. The results indicated that high BMI, high diastolic blood pressure, and high fasting insulin levels may play a role in the etiology and progression of renal cell carcinoma, while the remaining factors were not significantly associated with the risk of developing the disease . Chen et al. conducted a large-scale two-sample MR study (n > 4000) to investigate the key regulatory factors of obesity and diabetes, insulin-like growth factors (IGFs), and pointed out that individuals with high IGF-1 predicted by genetics had a 45% lower risk of developing renal cell carcinoma compared to the control group (95% CI, 0.48-0.62), while IGF-3 levels did not show a significant impact[42,43]. Additionally, previous observational studies have indicated a significant correlation between lipid-lowering drugs and the risk of renal cell carcinoma, but the causal relationship remains uncertain. Therefore, Liu et al. conducted a drug target MR analysis and molecular-specific MR analysis based on renal cell carcinoma cases (n = 6530) and European ancestry controls (n = 911,435)[44]. The study found that the decrease in low-density lipoprotein caused by statins may not have a protective effect on the incidence of renal cell carcinoma, while the use of prostate cancer SK9 inhibitors such as evolocumab may reduce the risk of developing renal cell carcinoma. In conclusion, early weight and blood pressure control,

as well as the use of lipid-lowering drugs that enhance IGF-1 expression and prostate cancer SK9 inhibitors, may prevent the occurrence of renal cell carcinoma.

Previous studies have shown a significant correlation between renal dysfunction and a high risk of developing and a high mortality rate associated with renal cell carcinoma[46,47]. There may also be a bidirectional causal relationship between the two, and clarifying the causal relationship is crucial for the prevention and treatment of renal cell carcinoma[45]. Glomerular filtration rate is one of the diagnostic indicators of renal dysfunction. A bidirectional MR study conducted by Lin et al. demonstrated a significant negative causal effect of estimated glomerular filtration rate based on creatinine on the risk of renal cell carcinoma (OR = 0.007, 95% CI: 0.26-0.569)[46]. Conversely, reverse MR indicated that renal cancer may also reduce kidney function through shared genetic mechanisms with estimated glomerular filtration rate based on cystatin C[45]. Additionally, after excluding body composition, the serum urate and urine albumin/creatinine ratio may significantly increase the risk of renal cell carcinoma (OR = 14.503, 95% CI: 2.546-96.001). These findings suggest a bidirectional causal relationship between renal dysfunction and the occurrence of renal cell carcinoma, emphasizing the importance of the joint prevention and treatment of both conditions.

Advances in the Application of MR in Bladder Cancer

Many researchers have used MR studies to infer causal relationships between bladder cancer and behavioral habits and other diseases, providing insights into the pathogenesis of bladder cancer and serving as a reference for diagnosis, treatment, and lifestyle guidance.

The development of bladder cancer is a complex process involving multiple factors, with behavioral habits playing an important role. To assess the correlation between obesity and the risk of bladder cancer more accurately, Wan et al. used the MR method to investigate the causal

relationship between body fat and bladder cancer risk[47]. The results showed that an increase of one standard deviation in body fat index (total body fat and fat mass in the right leg, left leg, right arm, left arm, and trunk) may increase the risk of bladder cancer by 51.8%, 77.9%, 75.1%, 67.2%, 59.7%, and 36.6%, respectively. This provides a reference for the development of early prevention strategies for bladder cancer . Smoking and alcohol consumption have long been considered risk factors for cancer. To explore whether this relationship is causally associated, Xiong et al. conducted a univariable and multivariable MR study[48]. The results showed that an increase of one standard deviation in daily smoking quantity, lifetime smoking index, and age of smoking initiation led to a 1.79-fold (95% CI: 1.31-2.45), 2.38-fold (95% CI: 1.45-3.88), and 1.91-fold (95% CI: 1.46-2.50) increase in the risk of bladder cancer, respectively. However, the causal association between alcohol consumption and bladder cancer was not significant. These findings suggest that reducing body fat, reducing smoking, or quitting smoking may be important preventive measures for bladder cancer, while the protective effect of controlling alcohol consumption needs further research for validation.

Numerous MR studies have been applied to explore the causal relationships between bladder cancer and other diseases, which have significant implications for improving the prevention and treatment strategies for complications associated with bladder cancer. Human papillomavirus (HPV) infection has long been recognized as a significant risk factor for cervical cancer, but its relationship with bladder cancer risk has been controversial[49,50]. Therefore, Sun et al. conducted a meta-analysis combined with a two-sample MR analysis to explore the relationship between HPV and bladder cancer[51]. The meta-analysis results showed a significant association between HPV infection and the risk of bladder cancer (OR = 3.35) and the prognosis of bladder cancer patients (RR = 1.73). The two-sample MR analysis further confirmed the causal relationship

between HPV E7 protein exposure and bladder cancer, suggesting that HPV infection may significantly increase the risk of bladder cancer incidence, recurrence, and mortality . The relationship between blood pressure and cancer has been a subject of considerable attention, but due to confounding factors such as smoking, observational studies have shown inconsistent views on the relationship between blood pressure and bladder cancer[52,53]. Stanley et al. conducted an MR study on 27,107 men from cohorts in the UK and Sweden and found a positive association between systolic blood pressure and the risk of bladder cancer in the Swedish cohort, but the correlation was not significant in the UK cohort[54]. To explore the bidirectional causal relationship between benign prostatic hyperplasia (BPH) and bladder cancer, Du et al. conducted a two-way MR study[55]. The results showed that BPH may increase the risk of bladder cancer (OR = 1.095, 95% CI = 1.030-1.165), and bladder cancer also plays a crucial role in the development of BPH . These findings indicate that early HPV vaccination, blood pressure control, and integrated prevention and treatment of BPH may prevent the occurrence of bladder cancer and control its progression.

Advances in the Application of MR in Prostate Cancer

Prostate cancer is the second most common cancer and the fifth leading cause of cancer-related deaths among men worldwide. Investigating its risk factors and potential etiology is crucial for identifying high-risk populations and early prevention efforts[55]. Contemporary scholars have extensively utilized MR studies to determine the causal associations of traditional risk factors, other diseases, serum ion concentrations, and novel biomarkers with prostate cancer progression. These studies provide valuable insights into the underlying mechanisms of the disease and serve as important reference points for cancer diagnosis and treatment.

Previous research has identified several risk factors for prostate cancer, such as smoking, high body mass index (BMI), and occupational exposure[56]. To further confirm the causal relationship between exogenous exposure factors and prostate cancer risk, Gu et al. conducted a meta-analysis and a comprehensive MR study based on existing reports and patient information from European cohorts[57]. They considered data on 13 risk factors and 17 protective factors, which were subsequently validated through two-sample MR analysis. The results of their study suggested that IGFBP-3 may increase the risk of prostate cancer, while high concentrations of docosahexaenoic acid (DHA), higher BMI, and systemic lupus erythematosus may have a protective effect against prostate cancer. Similarly, Kazmi et al. assessed the risk factors reported in observational epidemiological studies using a large-sample two-sample MR study (n > 140,000) and found that higher BMI may decrease the risk of prostate cancer, while taller height may be closely related to aggressive prostate cancer[58]. Bryony et al. conducted an MR study using the UK Biobank to investigate the role of chronotype and sex hormones in cancer progression, and the results indicated that morning preference and testosterone levels are protective factors for both prostate and breast cancer, although further research is needed to explore the underlying factors linking mental disorders and prostate cancer risk[59].

Existing literature suggests that mental illnesses such as schizophrenia and bipolar disorder may lead to complex physiological changes and increase the risk of cancer[60,61]. Ge et al. explored the relationship between schizophrenia and prostate cancer and found a decreased risk of prostate cancer in patients with schizophrenia based on meta-analysis, while MR analysis indicated that there may not be a clear causal association between the two[19]. Chen et al. used two-sample MR methods to study the potential causal relationship between depression and prostate cancer and found no causal relationship between depression and prostate cancer risk[62]. MR results that are

inconsistent with epidemiological data should be interpreted with caution, and further investigation is required to identify potential factors linking mental disorders and prostate cancer risk.

Epidemiological studies have suggested a negative correlation between serum vitamin D (VD) levels and prostate cancer[63,64]. However, these results may be influenced by confounding factors such as obesity, physical activity, smoking, alcohol consumption, and dietary patterns. To further validate the causal relationship between VD and prostate cancer, Jiang et al. conducted a two-sample MR study[65]. However, their research found no causal association between serum vitamin D and a reduced risk of prostate cancer. This result suggests that vitamin D supplementation may not have a significant effect on preventing the occurrence of prostate cancer. Lv et al. performed a meta-analysis combined with MR studies and found that high serum phosphorus concentration may increase the risk of prostate cancer by 7-8%, indicating a causal relationship between the two[66]. Therefore, the role of early nutrient supplementation as one of the means to prevent cancer should be thoroughly evaluated.

Despite the wide application of the classical biomarker prostate-specific antigen (PSA), the search for novel biomarkers remains of significant importance for early prevention, prognosis assessment, and treatment guidance in prostate cancer. Insulin-like growth factors (IGFs) are essential growth peptides, and previous studieshave reported associations between IGF-I, IGF-II, IGFBP-2, IGFBP-3, and overall prostate cancer risk[67]. Watts et al. utilized MR studies to demonstrate a causal relationship between higher IGF-I levels and increased risks of overall and aggressive prostate cancer, further confirming the significant role of IGF in prostate cancer. Microseminoprotein-beta (MSP) is a protein secreted by the prostate epithelium into semen, and prospective studies have shown that a 1 ng/ml increase in serum MSP concentration is associated

with a 2% decrease in prostate cancer risk[68]. The latest MR studies suggest that elevated serum MSP levels may reduce the risk of prostate cancer, indicating a causal protective effect[69].

DISCUSSION

MR is a growing method in research that offers distinct benefits for figuring out cause-and-effect relationships. Genetic variations, untouched by confounding factors, enable better control over biases. A clear time sequence between genotypes and diseases rules out reverse causality problems. But, MR isn't free from challenges: finding suitable genetic variations, needing large sample sizes for statistical strength, proving associations between genetic variations and exposures, and multiple validations for solid conclusions all pose difficulties.

In the field of urogenital system tumors, MR's worth is clear. Unlike prospective studies, it may lead to new insights, encouraging researchers to reassess old work and scrutinize confounding factors' impact. Bidirectional MR sheds light on disease connections, aiding prevention and management. In disputed areas, MR clears away confusion to reach trustworthy conclusions, enriching clinical knowledge. Overall, MR stands as a practical and robust tool in urogenital system tumor research, though it needs careful handling to overcome its limitations and make results more dependable.

In summary, MR has a broad prospect in the field of medical research, particularly in urogenital system tumor studies, with great potential. Methodologically, combining other analytical approaches such as meta-analysis and nested case-control studies is a future trend that can provide comprehensive result interpretation and explore underlying mechanisms in greater depth. Moreover, while current MR research relies mainly on public databases from European cohorts, leveraging multiple databases such as the U.S. National Health and Nutrition Examination Survey（NHANES） and the FinnGen consortium could enhance the persuasiveness and

applicability of research. Additionally, as patient data is currently predominantly focused on individuals of European descent, the applicability of research results in Asian populations may be limited. Therefore, conducting research targeting Chinese and Asian patients and constructing databases could become future research directions. In terms of research content, apart from focusing on the causal associations between risk factors and cancer risk, more MR studies should concentrate on investigating disease progression and patient prognosis, which are crucial for delving into disease mechanisms. Furthermore, in the context of renal cell carcinoma and bladder cancer, there is a lack of large-scale MR studies examining the role of traditional risk factors, which also represents an important direction for future in-depth investigations.

CONCLUSION

Mendelian Randomization (MR) is increasingly recognized as a valuable tool in urological tumor research for establishing causality and managing biases. Despite challenges like identifying genetic variants and needing large sample sizes, MR offers new perspectives, particularly in understanding disease progression and patient prognosis. Future research should integrate MR with other analytical methods and diversify data sources beyond European cohorts to include global populations, thereby enhancing the applicability and depth of findings in urological oncology.

REGISTRATION AND PROTOCOL

This study has undergone submission to the PROSPERO database, an international prospective register of systematic reviews, and has been assigned the identification number 494347. Our research is titled "Unveiling the Etiology of Urologic Tumors: A Systematic Review of Mendelian Randomization Applications in Renal Cell Carcinoma, Bladder Cancer, and Prostate Cancer." Presently, the study is in the pre-registration phase, awaiting formal registration and confirmation. This step is integral to ensuring transparency and methodological rigor in our systematic review process, aligning with best practices in research reporting and review management.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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Figure legends

Figure 1. Flow of information through the different phases of the review.