HHS Public Access

Author manuscript

Curr Opin Urol. Author manuscript; available in PMC 2024 September 09.

Published in final edited form as:

Curr Opin Urol. 2023 November 01; 33(6): 414–420. doi:10.1097/MOU.0000000000001126.

Use of genomic markers to improve epidemiologic and clinical research in urology

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Abstract

Purpose of review—Urologic cancers result from the appearance of genomic alterations in the target organ due to the combination of genetic and environmental factors. Knowledge of the genomic markers involved in their etiology and mechanisms for their development continue to progress. This reviewed provides an update on recent genomic studies that have informed epidemiologic and clinical research in urology.

Recent findings—Inherited variations are an established risk factor for urologic cancers with significant estimates of heritability for prostate, kidney, and bladder cancer. The roles of both rare germline variants, identified from family-based studies, and common variants, identified from genome-wide association studies, have provided important information about the genetic architecture for urologic cancers. Large-scale analyses of tumors have generated genomic, epigenomic, transcriptomic, and proteomic data that have also provided novel insights into etiology and mechanisms. These tumors characteristics, along with the associated tumor microenvironment, have attempted to provide more accurate risk stratification, prognosis of disease and therapeutic management.

Summary—Genomic studies of inherited and acquired variation are changing the landscape of our understanding of the causes of urologic cancers and providing important translational insights for their management. Their use in epidemiologic and clinical studies is thus essential.

Keywords

genomics; germline variants; somatic mutations; urologic cancer

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Conflicts of interest

The authors declare no conflicts of interest.

INTRODUCTION

In 2020, the worldwide incidence of the major urologic cancers (prostate, bladder and kidney) was estimated at 2.4 million cases (12.5% of all cancers) [1]. Approximately 267 000 patients died from one of these malignancies [1] and the burden associated with care can be costly [2]. Like all cancers, they result from the appearance of genomic alterations in the target organ, and their risk of development is linked to the combination of lifestyle, environmental and genetic factors [3]. In recent years, knowledge of both inherited germline variation and acquired alterations in tumors has continued to progress, and their use in epidemiological and clinical studies has made it possible to better characterize these diseases and improve their screening and management.

Germline variants

Germline variants are DNA sequence changes that affect all cells in the body, including germ cells. They can therefore be transmitted to their descendants. Family-based studies have described the familial aggregation for urologic cancers, with significant estimates of heritability (the proportion of variability in disease risk in a population due to underlying genetic factors) for prostate cancer (57%), kidney cancer (38%), and bladder cancer (30%) [4]. As a result, the role of uncommon germline variants (typically with minor allele frequency less than 1%) as well as common germline variants (those with a frequency greater than 1%) and risk for these cancers have been described. New approaches using germline variants from large publicly available databases have also been used to further investigate risk factors for urologic cancer.

Rare germline variants

The role of genetic factors in cancer was first suggested by the identification of families with multiple cases of the same cancer or of different cancers. These families constitute hereditary forms of cancer in which the transmission of the disease is compatible with Mendelian inheritance. In these rare forms, the disease results from the mutation of a specific gene which is transmitted in the family. Using different methods, some of these genes have been identified for urologic cancers. For example, mutations in the Von Hippel-Lindau (*VHL*) gene, observed in patients with von Hippel-Lindau disease, are associated with an increased risk of developing clear cell renal carcinoma [5]. It is therefore important to refine the criteria for selecting patients for whom the screening for mutations in these genes is necessary, like the clinical consensus described for renal cell carcinoma [6].

To try to identify factors associated with aggressive prostate cancer, Darst *et al.* investigated whether rare pathogenic, likely pathogenic, or deleterious germline variants in DNA repair genes were associated with aggressive prostate cancer risk in a study of 5545 men of European ancestry. This study found significant associations between rare variants in *BRCA2*, *PALB2*, and *ATM* [7]. The contribution of rare variants to prostate cancer risk in men of African ancestry showed a similar overlap in implicated genes, with the highest risk for aggressive disease observed in men with pathogenic variants in *ATM*, *BRCA2*, *PALB2* and *NBN* genes [8]. With the increased value of characterizing rare variants, the evaluation

of barriers that exist in access and translation of results will be needed to ensure equitable care for all men [9].

The identification of rare germline mutations to orientate towards specific targeted therapies has also been of great interest. Belzutifan, a highly specific-HIF2α inhibitor, was developed based on the role of *VHL* in the regulation of the expression of the α-subunit of the transcription factor hypoxia-inducible factor (HIF) and received FDA approval for the treatment of nonmetastatic renal cell carcinomas tumors from patients who carry *VHL* germline mutations [10]. Similarly, inhibitors of poly (ADP-ribose) polymerase (PARP) have been approved for metastatic castration-resistant prostate cancer who carry either germline or somatic mutations of *BRCA1* or *BRCA2* genes [11], as tumor cells with these mutations cannot efficiently repair the double stranded breaks caused by PARP inhibition.

Common germline variants

In addition to the rare variants identified for various sites, many common inherited genetic variants (those with >1% prevalence) have been uncovered from genome-wide association studies (GWAS). A recent GWAS of bladder cancer identified several new susceptibility variants bring the total number of independent markers to 24 [12▪▪]. Large, trans-ancestry analyses of prostate cancer have now identified a total of 269 germline variants for this common malignancy [13]. These studies have provided novel biological insights into these cancers by identifying key links between genetic susceptibility (*PAG1*, *MTAP-CDKN2A*) and smoking (the leading risk factor) in bladder cancer [12▪▪] and genetic susceptibility and key elements of the androgen signaling pathway (*AR*, *FOXA1* and *HOXB13*) [13] for prostate cancer. In GWAS of prostate cancer the inclusion of non-European ancestry samples, especially those of African ancestry, has improved the identification of signals and allowed for an exploration of risk across populations [13,14]. In the future, as samples sizes for GWAS grow, additional trans-ancestry analyses are also needed to inform risks in all ancestral populations for other urologic cancers.

Because the risks associated with many common variants are small, the aggregation of variants into a polygenic risk score (PRS) is being increasingly considered as a tool to stratify patients into high-risk vs. low-risk groups to aide with decisions about clinical management. For prostate cancer, the identification of men with aggressive disease with the potential to be fatal is still a clinical challenge. Thus far, however, the 269-marker prostate cancer PRS has not been shown to aide in the prediction of risk for aggressive or lethal disease [13,15,16]. For prostate cancer, different approaches using genetic variants that predict prostate-specific antigen (PSA) levels [17▪▪] and other methods for PRS development [18] are being explored to help improve risk discrimination. Tools that incorporate other risk factors along with the PRS can also inform which patients may be at higher or lower risk of developing disease. For bladder cancer, 50% of newly diagnosed cases can be attributed to cigarette smoking [19]. Incorporating this information into a risk model that also included a 24-marker PRS was recently described in a GWAS of bladder cancer. Projections for the average lifetime absolute risk of bladder cancer for never/former/current smokers showed an approximately 4-fold difference depending on the deciles of the PRS (Fig. 1) [12▪▪]. These projections highlight how such a risk model could be used,

in the future, to identify patients for increased surveillance under high-risk scenarios for bladder cancer (hematuria or recurrent urinary tract infections). Ultimately the utility of risk models to predict and prevent urologic cancers will need more exploration and prospective validation to determine their clinical utility [20,21].

Genetic tools for risk factor identification

The involvement of environmental factors in the risk of developing urologic cancers is well known. However, some traditional observational epidemiological studies may be subject to unmeasured confounding and biases that can hamper the identification of novel risk factors. Mendelian randomization (MR) is an epidemiological method that uses germline genetic markers as instrumental variables (IV) or 'proxies' to determine the causal effect of an exposure (Fig. 2) [22,23]. The advantage of using germline genetic markers is that they are fixed at conception and thus not subject to reverse causality and bias due to measurement error. Therefore, MR studies have been used as a tool to understand environmental determinants of disease [24].

MR benefits from the accessibility of data from the large number of GWAS performed to date, with over 55 000 genetic markers for nearly 5000 diseases and traits [25], and from biobanks which include clinical, biological and genetic data [26]. For example, several factors related to obesity have been associated with kidney cancer in traditional epidemiologic studies but the individual contributions of associated factors have not been disentangled. Using genetic markers as IVs, Johansson *et al.*[27] evaluated the association between 13 relevant risk factors and confirmed associations between obesity and body shape (increasing body mass index, waist-to-hip ratio or percentage body fat), diastolic (but not systolic) blood pressure and fasting insulin as risk factors for kidney cancer. In another study, Mariosa *et al.* used genetic instruments for early life (age 10) and adult body size to further assess the relationship between kidney cancer and obesity in early life; they found that larger body size at age 10 years (OR = 1.40, 95% confidence interval [CI] = 1.09 to 1.80) and in adulthood (OR = 1.74, 95% CI = 1.43 to 2.11) were associated with higher kidney cancer risk [28▪]. We would note, however, that MR may not work well for some risk factors, like occupational and environmental exposures (that are known and suspected risk factors for urologic cancer), because of a lack of identified genetic determinants. In these cases, traditional epidemiologic studies that are enhanced by state-of-the-art exposure assessment methods, have successfully and unequivocally identified many important risk factors for urologic tumors [19].

MR is also being considered as an approach to identify novel drug targets [29,30]. For example, Fang *et al.* found a significant inverse association between genetic instruments that proxied proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, drugs that lower low-density lipoprotein cholesterol levels and risk of total and early-onset prostate cancer and [31▪▪]. MR has great potential to guide the efficacy and safety of targets for drug discovery and therapeutic interventions as long as its underlying assumptions are met, however, randomized controlled trials still represent the gold standard for guiding clinical practice.

Somatic (tumor) alterations

Large-scale analyses of tumors have generated genomic, epigenomic, transcriptomic, and proteomic data that have provided novel insights into the etiology and mechanism of carcinogenesis involved in urologic cancer [32–35]. These tumors characteristics, along with the associated tumor microenvironment [36], have provided more accurate stratification and prognosis of disease and new clues for therapeutic management.

Somatic mutations and mutational signatures

Somatic mutations are present in normal cells and accumulate with age in response to endogenous and exogenous mutational processes. In some cases, the accumulation of these somatic mutations leads to the development of cancer. Several studies have now characterized the somatic mutational landscape of urologic cancer describing major mutational events like fusions involving ETS family genes in prostate cancer [37], mutations in chromatin-modifying or -regulatory genes (*KDM6A*, *KMT2A*, *KMT2C*, *ARID1A*) in bladder cancer [38], and shared *TP53* and *PTEN* mutations across all kidney cancer histologic subtypes [39].

Mutational processes that are active during cancer development leave characteristic mutational patterns on the genome called mutational signatures [32]. These mutational signatures have provided novel etiologic insights into the development of several cancers. Mutational signatures associated with tobacco smoking have been described in bladder cancer (APOBEC Signature, single base substitution signature 13 (SBS13) and SBS5) and in kidney cancer (SBS5) [40]. Interestingly, both signatures are not thought to be attributed to direct DNA damage (by tobacco carcinogens) but rather to other endogenous processes possibly related to the inflammatory response induced by smoking. Signature analyses have also confirmed a causal role for exposures with previously limited evidence in the etiology of urologic cancers including the identification of unique signatures associated with exposure to aristolochic acid (in upper tract urothelial carcinoma [41,42]) and vinylidene chloride exposure (in kidney cancer) [43]. Future genomic analysis of tumor samples with carefully characterized exposure information will be needed [44] to uncover more about the etiology and mechanisms associated with exogenous exposures [45] in urologic cancers, particularly given that some known or suspected human carcinogens do not appear to generate distinct mutational signatures [43,46].

Recent studies have shown that mutational signatures can also help guide therapeutic and prognosis of cancer. Tumors that show signatures of homologous recombination deficiency (HRD) have been observed to have a more favorable clinical outcome with PARP inhibitor treatment, for example [47]. Similarly, tumor signatures of mismatch repair (MMR) deficiency in patients with Lynch-associated upper tract urothelial carcinoma are being considered for therapy with immune checkpoint inhibitors [48], based on the success observed for other Lynch/high microsatellite instability (MSI)–associated tumors. Larger studies, however, are needed to confirm the predictive role of these signatures in therapeutic response.

Transcriptome analysis of tumors is also being used to predict recurrence, progression and survival in urologic cancers. In bladder cancer, six mRNA molecular subtypes have been described in muscle-invasive (MI) tumors [49] and four separate subtypes have been identified in nonmuscle invasive (NMI) tumors [50]. These efforts have provided important prognostic information compared to clinical characteristics. This approach was recently extended in a study of patients with high-risk NMI treated with Bacillus Calmette-Guérin (BCG) to define three molecular subtypes that were predictive of BCG treatment response [51]. In MI bladder cancer, tumor profiling is also being evaluated to guide the selection of individualized neoadjuvant or adjuvant chemo- or immunotherapy [52■■]. Identifying a subset of patients that could be treated earlier with radical cystectomy (in high-risk NMI disease) or with therapeutic alternatives highlights the utility of transcriptomic profiling of tumors to improve outcomes in bladder cancer.

The characterization of circulating tumor DNA (ctDNA) in blood has received recent attention because of the potential to inform early cancer diagnoses, treatment selection and disease monitoring. ctDNA is currently being evaluated as a tool to monitor minimal residual disease, recurrence, and response to treatment in bladder cancer [53]. Further, an analysis of ctDNA from patients with metastatic castration-resistant prostate cancer has revealed novel genomic and transcriptomic mechanisms of treatment resistance [54■■]. Other next generation sequencing technologies are also being applied to cell-free DNA for early cancer diagnosis, including multicancer early detection tests that screen for methylation-based markers [55]. Although the specificity of these tests has been shown to be quite high, the overall sensitivity appears to be limited for urologic cancers: 11.2% for prostate cancer, 18.2% for kidney cancer, and 34.8% for bladder cancer [55]. As a result, other biomarkers, including urinary microRNAs, are increasingly being evaluated or the detection of urologic cancers because of their proximity to the target organ [56–58]. Ultimately, large scale testing of these novel technologies will still be needed before their application in the general population.

CONCLUSION

Genomic studies of inherited and acquired alterations are changing the landscape of our understanding of the causes of urologic cancers. Large-scale analyses of tumors have added to this knowledge and have the potential to provide more accurate stratification, prognosis of disease, and therapeutic management. Future work should aim to integrate information on lifetime exposure/risk-factors, germline genetic variation, and tumor characteristics to further our understanding of the etiology and mechanisms for urologic cancers.

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KEY POINTS

- Both genetic and environmental factors are involved in risk of developing urologic cancers
- Risk models incorporating genetic markers and environmental factors are being developed to predict the risk of urologic cancers in the future
- Somatic mutational analyses can be used to identify/confirm environmental factors involved in the risk of urologic cancers
- Exploration of several genomic markers show promise to determine disease staging, predict outcome, monitor recurrence, progression, and for therapeutic management

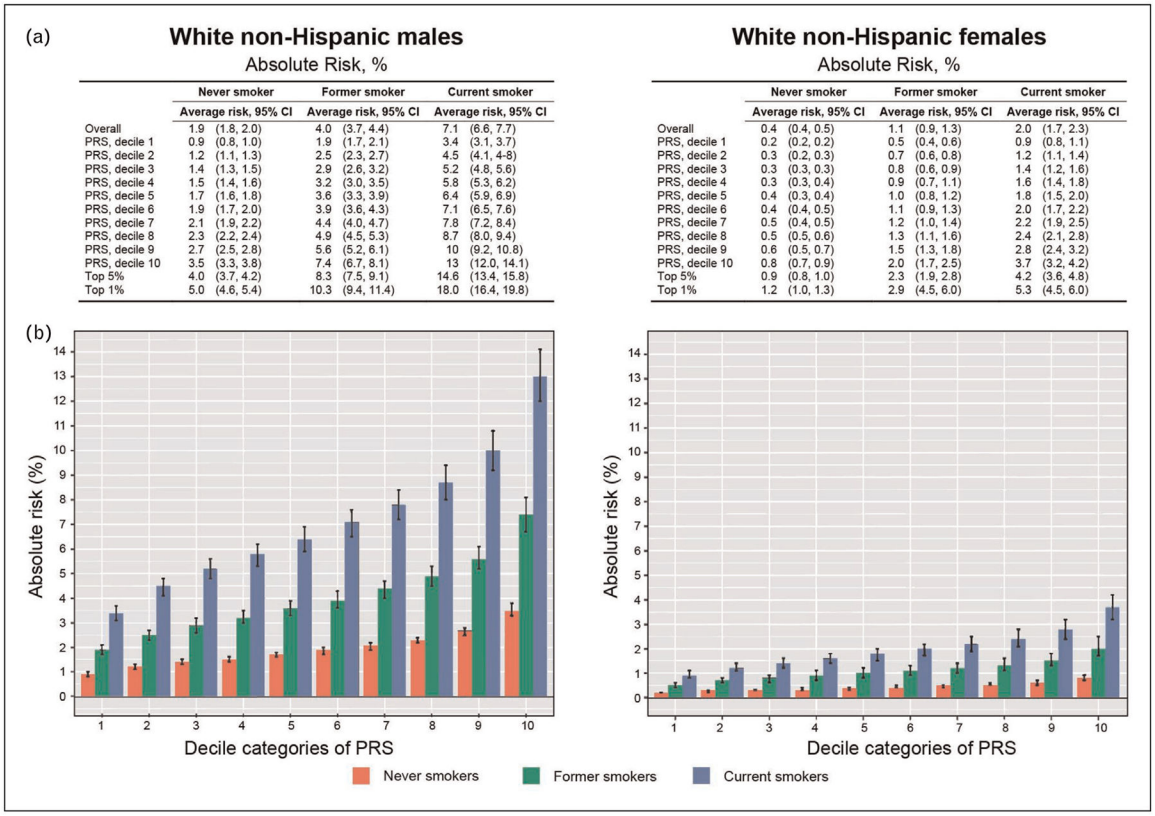

FIGURE 1.

Estimates of absolute risk of bladder cancer for White non-Hispanic males and females based on genetic polygenic risk score and smoking status, from Koutros et al. Eur Urol. 2023;84(1):127–137. a. Average and top (5% and 1%) absolute risks and 95% confidence intervals (CI) for never, former and current smokers by deciles of the polygenic risk score (PRS) for White non-Hispanic males and females (age interval 50–80 years). b. Bar graph of average absolute risk for never (red), former (green), and current (blue) smokers showing risk difference increasing with higher PRS deciles.

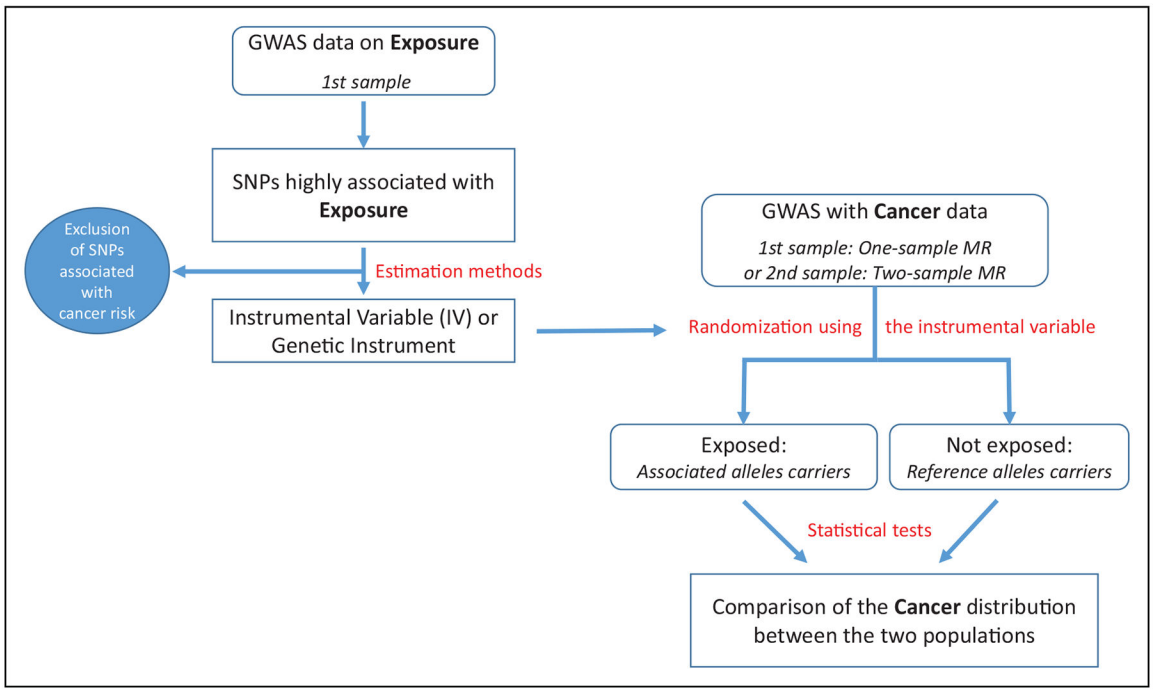

FIGURE 2.
Flow chart of a mendelian randomization study.