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Genetic risk scores based on risk-associated single nucleotide polymorphisms can reveal inherited risk of bladder cancer in Chinese population

Chenyang Xu, MD[a,b], Xiaoling Lin, MD, PhD[b], Wei Qian, MD[a], Rong Na, MD[d], Hongjie Yu, MD, PhD[c], Haifei Jia, MD[a,b], Haowen Jiang, MD[a,b], Zujun Fang, MD[a,b], S. Lilly Zheng, MD, PhD[c], Qiang Ding, MD[a,b], Yishuo Wu, MD[a,b,c,*], Jie Zheng, MD[a,b,*], Jianfeng Xu, MD, PhD[b,c,*]

Abstract

Genome-wide association studies have identified single nucleotide polymorphisms (SNPs) associated with bladder cancer (BCa) risk in Caucasian and East Asian population. The objective of this study was to validate these SNPs in Chinese population and evaluate whether these SNPs could differentiate the individual inherited risk for BCa.

A case-control study including 581 BCa cases and 1561 healthy controls was performed. Germline DNA samples from all individuals were genotyped for eight SNPs. Genetic risk score (GRS) was calculated for each individual based on the odds ratios and risk allele frequencies of five risk-associated SNPs.

Among eight SNPs evaluated in this study, rs798766 at 4p16.3 [OR = 1.39 (1.15–1.67), $P < .001$], rs9642880 [OR = 1.17 (1.06–1.30), $P < .001$] and rs4813953 at 20p12.2 [OR = 1.09 (1.02–1.17), $P = .016$] were found associated with BCa risk in Chinese population. A genetic risk score was established based on five SNPs (including the above three SNPs and two other SNPs which have the consistent direction with previous reported genome-wide association study). The mean GRS was significantly higher in BCa cases than controls (1.22 vs. 1.01, $P < .001$). When subjects were categorized into low- (<0.8), average- (0.8–1.2), and high-risk (>1.2) groups, the likelihoods of BCa were 25.2%, 33.7% and 55.0%, respectively (P-trend $< 2.2 \times 10^{-16}$). In subgroup analyses, no significant difference was observed in mean GRS among BCa patients with different stages or grades.

In conclusion, two SNPs derived from East Asian and one SNP from Caucasian were associated with BCa risk in Chinese population. These results provided additional information of genetic risks for BCa in Chinese population. Genetic risk score based on these SNPs can reveal inherited risk of BCa, and may have potential for modifying personalized cancer screening strategy.

Abbreviations: AUC = area under curve, BCa = bladder cancer, GRS = genetic risk score, GWAS = genome-wide association study, OR = odds ratio, SNP = single nucleotide polymorphisms.

Keywords: bladder cancer, Chinese, genetic risk, single nucleotide polymorphisms

1. Introduction

Bladder cancer (BCa) is one of the top ten common malignancies all over the world.[1] In China, the incidence and mortality of BCa ranked first among all genitourinary neoplasms during recent years, which accounted for 80,500 new cases and 32,900 deaths annually.[2] Epidemiologic studies have identified that both tobacco smoking and occupational exposures to industrial

Editor: Lishuang Shen.

CX, XL, and WQ these authors contributed equally to this study.

This work was supported by the Scientific Research project supported by Huashan Hospital, Fudan University to Yishuo Wu (2016QD079).

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

[a] Department of Urology, [b] Fudan Institute of Urology, Huashan Hospital, Fudan University, Shanghai, PR China, [c] Program for Personalized Cancer Care, NorthShore University HealthSystem, Evanston, Illinois, USA, [d] Department of Urology, Ruijin Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, PR China.

[*] Correspondence: Yishuo Wu, M.D. Department of Urology, Huashan Hospital, Fudan University, 12 Mid-Wulumuqi Road, Shanghai, China (e-mail: ys_wu1@126.com), Jie Zheng M.D. Department of Urology, Huashan Hospital, Fudan University, 12 Mid-Wulumuqi Road, Shanghai, China (e-mail: atlantica@163.com), Jianfeng Xu, Dr.PH 1001 University Place, Evanston, IL 60201, U.S.A (e-mail: jxu@northshore.org).

How to cite this article: Xu C, Lin X, Qian W, Na R, Yu H, Jia H, Jiang H, Fang Z, Zheng SL, Ding Q, Wu Y, Zheng J, Xu J. Genetic risk scores based on risk-associated single nucleotide polymorphisms (SNPs) can reveal inherited risk of bladder cancer in Chinese population. Medicine 2020;99:19(e19980).

Received: 14 December 2019 / Received in final form: 10 March 2020 / Accepted: 21 March 2020

http://dx.doi.org/10.1097/MD.0000000000019980

chemicals contributed to the risk of BCa, which may account for 50% and 6% of BCa cases, respectively.[3] Besides smoking and occupational exposures, studies have also reported familial aggregated BCa[4,5] and an estimated familial risk of 30% was revealed,[6] indicating the importance of genetic factors in the development of BCa. Although family history may reflect inherited risk, this can be affected by the size of family and lack of information. In addition, family history may not be informative in evaluating the inherited risk for most people due to the low incidence of family aggregated BCa.[4–7]

Recently, genome-wide association studies (GWAS) have identified multiple single nucleotide polymorphisms (SNPs) associated with the inherited risk of BCa.[8–11] These SNPs have a low to moderate effect on BCa risk, with OR ranging from 1.1 to 1.6. Genetic risk score (GRS) based on SNPs is considered as a useful and generally applicable tool to evaluate the inherited risk for each individual. For individuals who carry more than one risk alleles, GRS could calculate the cumulative effect of all genetic variants.[12] In terms, the result of GRS value is one's relative risk to the general population, which makes it easy to implement for individual risk assessment.

In this study, we aimed to validate eight previously reported risk-associated SNPs of BCa in Chinese population and then evaluate whether GRS based on these SNPs could reflect the risk of BCa for each individual.

2. Methods

2.1. Study cohort

581 BCa patients were recruited from Huashan Hospital, Fudan University, Shanghai, China between 2010 and 2017. All cases were diagnosed as BCa based on pathologic diagnosis. The control group consisted of healthy subjects who had undergone routine physical examination either at Huashan Hospital or in local communities in Shanghai (n = 1561).

2.2. DNA sampling, SNP selection and genotyping

(1) A blood sample was obtained from each participant for DNA extraction at the time of recruitment. Genomic DNA was extracted from leucocytes of peripheral blood using QIAamp DNA Blood Mini Kit (QIAGEN, Germany) according to the standard protocol. Candidate SNPs were identified referring to previous GWAS or meta-analysis of GWAS based on either East Asian population or Caucasian population. Criteria were as follows: (1) all SNPs were discovered by GWAS, all of which exceeded a genome-wide significance level ($P < 5.0 \times 10^{-8}$) in a single ethnicity;
(2) all SNPs were confirmed in independent sets of case-control studies with same direction of effect;
(3) the sample size of the original study is larger than 500 cases vs 500 controls.

Taken together, 17 SNPs from either East Asian population or Caucasian population were identified according to the above criteria, and we were able to genotype eight of them in the current study. Genotyping was performed using the MassARRAY iPLEX (Sequenom, Inc., San Diego, CA) and experiments were carried out according to the manufacturer's protocol. Primers were designed using MassARRAY Assay Design 3.1 software (Sequenom, Inc., San Diego, CA). The reactions were performed in 384-well plates. Each plate contained four duplicate subjects selected at random, as well as 4 negative controls in which water was substituted for DNA. The average concordance rate was 100%.

2.3. Statistical analyses

All the SNPs were evaluated for Hardy-Weinberg equilibrium using a goodness-of-fit χ^2 test. The genetic association between SNPs and BCa were analyzed by comparing allelic frequencies of these SNPs between cases and controls. A genetic score was calculated for each individual based on personal genotype of five SNPs (3 SNPs are significantly associated with BCa risk, two SNPs have the same effect with reported GWAS although not significant). The genetic score of each individual was weighted by odd ratios (ORs):

(1) the allelic OR for each SNP was obtained from external studies;
(2) the genotypic OR was calculated assuming a multiplicative model of allelic OR;
(3) the relative risk to average risk level in Chinese population was calculated based on genotypic OR and genotype frequency (HapMap CHB population data);
(4) the final genetic score of each individual was calculated by multiplying relative risk of each SNP.

A student *t*-test was applied in comparing continuous variables and a chi-square test was used in analyzing categorical data. A Cochran-Armitage trend test was used to evaluate the increasing likelihood of BCa with different GRS ranges in the study population. All the statistical analyses above were performed using SPSS 19.0 (Statistical Product and Service Solutions, IBM Corporation, Armonk, NY) and R version 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria). A 2-tailed *P*-value of less than .05 was considered the threshold for statistical significance.

2.4. Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board of Huashan Hospital, Fudan University, Shanghai, China (KY2011-009) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Written Informed consent was obtained from all individual participants included in the study.

3. Results

Baseline characteristics of 581 BCa cases and 1561 healthy controls were summarized in Table 1. The average age was similar between BCa patients and healthy controls (64.0 vs 62.7, $P = .06$). Since the healthy physical examination and survey was focusing on males, so 99.9% of subjects in the control cohort were males. Among 581 BCa cases, we were able to acquire the smoking history from 490 subjects. 119 (20.5%) BCa patients had a heavy smoking history (a smoking history $\geq$ 20 years with daily consumption of $\geq$ 20 cigarettes), while 355 out of 1561 (22.7%) control subjects had a heavy smoking history ($P = .29$, Table 1). Over half of the BCa cases were low grade carcinoma or Papillary urothelial neoplasm of low malignant potential

Table 1

Characteristics of study subjects.

	Case	Control	
	N = 581	N = 1561	*P*
Age Mean (SD)	64.0 (13.4)	62.7 (9.3)	.061
Gender, N (%)	509 (87.6%)	1559 (99.9%)	<.001
Heavy smoker, N (%)*	119 (20.5%)	355 (22.7%)	.29
Positive family history of BCa, N(%)†	5 (1.02%)	4 (0.30%)	.067
Grade of tumor, N (%)			
PUNLMP‡	37 (6.4%)	/	
Low grade	268 (46.1%)	/	
High grade	162 (27.9%)	/	
missing	114 (19.6%)	/	
Tumor invasion, N (%)			
NMIBC§	350 (60.3%)	/	
MIBC‖	117 (20.1%)	/	
missing	114 (19.6%)	/	
Genetic risk score			
Mean (SD)	1.22 (0.35)	1.01 (0.26)	<.001

* heavy smoker: having smoking history >20 yr with daily consumption of ≥20 cigarettes.
† BCa = bladder cancer.
‡ PUNLMP = Papillary urothelial neoplasm of low malignant potential.
§ NMIBC = non-muscle invasive bladder cancer.
‖ MIBC = muscle invasive bladder cancer.

(PUNLMP) (52.5%), and 60.3% of the cases were non-muscle invasive BCa (NMIBC).

All candidate SNPs passed Hardy-Weinberg equilibrium test in control group. The association of eight SNPs and BCa risk is presented in Table 2 (including both allelic and genotypic results). Among eight SNPs, in terms of allelic tests, rs798766 at 4p16.3 (OR = 1.39, $P < .001$), rs9642880 (OR = 1.17, $P < .001$) and rs4813953 at 20p12.2 (OR = 1.09, $P < .001$) were significantly associated with increased risk of BCa (Table 2). For genotypic tests, significant associations were found for rs798766 in all 3 genetic models, and for rs4813953 in recessive and additive model, respectively. Meanwhile, 2 other SNPs (rs401681 at 5p15.33 and rs1014971 at 22q13.1) demonstrated the same magnitude of effect for BCa risk, yet not statistically significant (Table 2). Since rs401681 and rs1014971 were proved to be associated with BCa risk in East Asian in previous study,[13] all these 5 SNPs mentioned above were used to calculate GRS (Table 3). In addition, false positive report probabilities [14] were calculated for each SNP to validate the results (Supplementary Table 1, http://links.lww.com/MD/E205). We found that false positive report probabilities values of rs798766 and rs9642880 remained below 0.5 in the estimated prior probability range (0.01–0.25), indicating a strong correlation between these 2 SNPs and BCa risk. Yet a similar but weaker result was found for rs4813953.

Overall, the mean GRS was significantly higher in BCa cases than in controls (1.22 vs 1.01, $P < .001$, Table 1). To further evaluate the utility of the GRS, all subjects were stratified into 3 groups according to their GRS distribution, and the likelihoods of BCa were revealed in Figure 1A. The likelihoods of BCa in subjects with low (<0.8), medium (0.8–1.2) and high (>1.2) GRS was 25.2%, 33.7%, 55.0% respectively (P-trend $< 2.2 \times 10^{-16}$). The study population was then stratified into 4 groups based on the quartiles of the GRS (Fig. 1B). The likelihoods of BCa for individuals with low (0–25% percentile), medium-low (25%-50% percentile), medium-high (50%-75% percentile) and high (75%-100% percentile) GRS would be 19.5%, 35.9%, 40.7% and 60.4% (P-trend $< 2.2 \times 10^{-16}$). While evaluating the predictive performance for BCa risk, the area under curve (AUC) of GRS was 0.679 (95% CI: 0.650 - 0.705) (Fig. 2).

In addition, we performed subgroup analyses of GRS in BCa patients with different grades and stages (Table 4). No significant difference was seen in the mean GRS between patients with low grade BCa (including PUNLMP and low grade disease) and high grade BCa (1.22 vs 1.20, $P = .71$). Similar result was also observed between NMIBC and muscle invasive bladder cancer (MIBC) cases.

Table 2

Association analysis results of 8 single nucleotide polymorphisms for bladder cancer in Chinese population.

				Risk	RAF	RAF	Allelic test		Genotypic test (*P* value)			HWE*	
SNP ID	Region	Gene	Alleles	alleles	in cases	in controls	OR (95%CI)	*P*	Dominant	Recessive	Additive		Origin of GWAS
rs798766	4p16.3	TACC3	C/T	T	0.152	0.11	1.39 (1.15–1.67)	<.001	.001	.016	.01	.74	EAS
rs401681	5p15.33	CLPTM1L	C/T	C	0.689	0.684	1.01 (0.96–1.06)	.76	.80	.52	.68	.05	EAS
rs9642880	8q24.21	CASC11	C/T	T	0.349	0.297	1.17 (1.06–1.30)	<.001	.056	.40	.17	.02	EAS
rs4907479	13q34	MCF2L	A/G	G	0.683	0.694	0.98 (0.93–1.04)	.55	.85	.37	.92	.73	European
rs17674580	18q12.3	SLC14A1	C/T	C	0.911	0.93	0.98 (0.96–1.00)	.051	.60	.061	.64	.81	EAS
rs4813953	20p12.2	LOC339593	C/T	T	0.623	0.572	1.09 (1.02–1.17)	.016	.08	.035	.024	.68	European
rs6104690	20p12.2	C20orf187	A/G	G	0.344	0.365	0.94 (0.84–1.06)	.31	.62	.18	.20	.30	European
rs1014971	22q13.1	APOBEC3A	C/T	A	0.274	0.269	1.02 (0.90–1.15)	.77	.79	.40	.49	.09	EAS

CI = confidence interval, EAS = East Asian, GWAS = genome-wide association study, OR = odds ratio, RAF = risk allele frequency, SNP = single nucleotide polymorphism.
* Hardy–Weinberg equilibrium (HWE) test.

Table 3

Summarization of 5 single nucleotide polymorphisms for calculation of genetic risk scores.

SNP ID	Risk allele	OR (95%CI) in original GWAS	OR in this study	References
rs401681	C	1.22 (1.01–1.48)	1.01	Wang M et al (2011)
rs798766	T	1.32 (1.09–1.59)	1.39	Wang M et al (2014)
rs1014971	A	1.14 (1.00–1.28)	1.02	Wang M et al (2014)
rs9642880	T	1.24 (1.09–1.30)	1.17	Wang M et al (2014)
rs4813953	T	1.19 (1.13–1.26)	1.09	Rafnar T et al (2014)

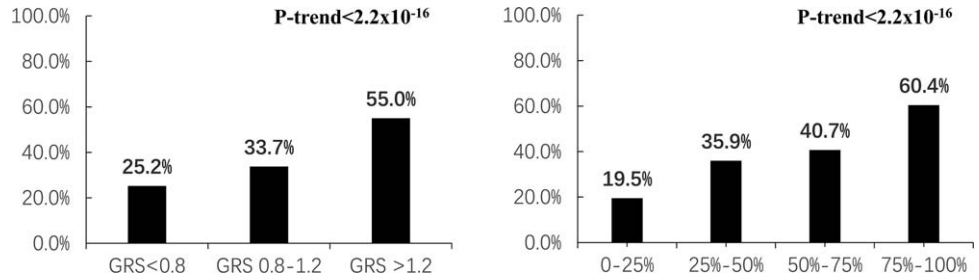

Figure 1. Bladder cancer incidence in different genetic risk scores group in the study population. A) The likelihood of BCa in 3 groups with low (<0.8), medium (0.8–1.2) and high (>1.2) genetic risk score. B) The likelihood of BCa in four quartiles according to each individual's genetic risk score.

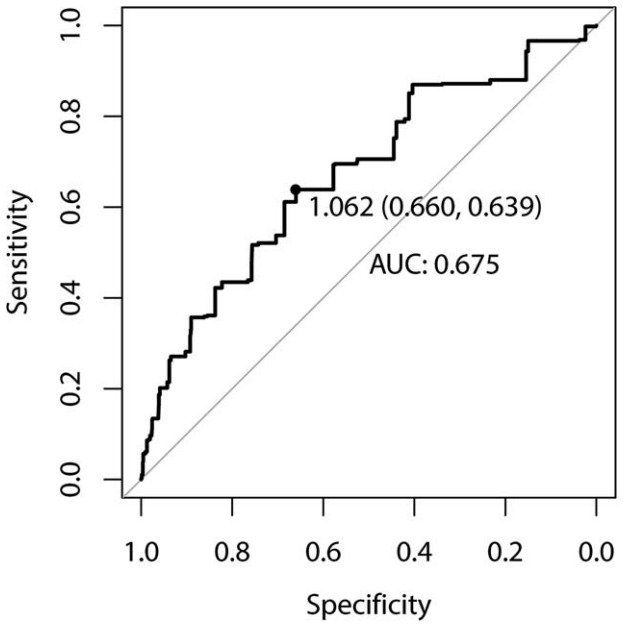

Figure 2. ROC curve of the genetic risk score model.

4. Discussion

Genetic risk score has the potential for personal risk predication in several diseases, such as diabetes mellitus,[15,16] coronary heart diseases[17,18] and cancers.[19–21] In the current study, our objective was to evaluate whether GRS could reflect the inherited risk of BCa. Here we calculated GRS for each individual based on results of association analysis, and we found GRS could reveal the personal risk for BCa in Chinese population.

Hereditary traits have been considered essential in the development of BCa. Case-control study in Italy confirmed a two-fold increased BCa risk for individuals with positive family history of BCa.[7] In a large population-based study, individuals with first- or second-degree relatives diagnosed of BCa had an increased risk of developing urothelial cancer.[22] However, only 2% to 3% of the subjects had a positive family history of BCa,[7] which made it difficult to evaluate inherited risk for the majority of population by family history. Moreover, family history is uninformative in China due to the relatively poor public healthcare and birth control policy during past decades. The prevalence was even lower in the current study, 490 out of 581 BCa cases provided their family history, among which only five patients (1.02%) had a positive family history of BCa (three subjects had first-degree relatives with BCa). Such low prevalence may be caused by the unawareness of disease for family members when providing the family history information. An advantage of GRS over family history is the objective measurement of disease risk, not susceptible to various issues during the collection of family history and other recall bias.

In current study, we performed an external validation of the associations between eight SNPs and BCa in Chinese population. For all validated variants, the minor allele frequencies of all SNPs were over .05, indicating they are not rare variants in Chinese population (Table 2). Meanwhile, the risk allele frequency in the control group share similar frequencies with previous studies in East Asian.[9,10,23,24] GRS was calculated based on five SNPs (rs798766, rs9642880, rs4813953, rs401681 and rs1014971) which had consistent direction with reported GWAS of BCa (OR > 1) (Table 3). GRS was calculated based on these five SNPs which had consistent direction with reported GWAS of BCa (OR > 1). The SNP rs798766 is associated with BCa risk in both European and East Asian populations.[11,25] It is located in an intron of *TACC3*. Although no direct association of BCa risk between rs798766 and the expression of *TACC3* was observed. A significant association between rs798766 and *FGFR3* expression was observed for BCa risk, so it is biologically plausible that rs798766 may influence *FGFR3* expression by altering distant regulatory elements.[11]*FGFR3* somatic mutation is common in NMIBC patients and may predict a good prognosis.[26,27] Rs9642880 has also been identified and verified in both

Table 4

Genetic score in bladder cancer cases with different grades and stages.

Tumor grade and stage	PUNLMP & low grade (N = 305)	High grade (N = 162)	*P*	NMIBC (N = 350)	MIBC (N = 117)	*P*
GRS, Mean (SD)	1.22 (0.36)	1.20 (0.35	.71	1.22 (0.36)	1.19 (0.35)	.38

[a]PUNLMP = papillary urothelial neoplasm of low malignant potential.
[b]NMIBC = non-muscle invasive bladder cancer.
[c]MIBC = muscle invasive bladder cancer.

Caucasian and Chinese population.[9,23,27] It is located 30 kb upstream of c-MYC oncogene, which mediates cell growth regulation, differentiation and apoptosis. Rs4813953 was found associated with BCa risk from an Icelandic GWAS and then validated by a multi-ethnic meta-analysis of 17 studies.[10] Two other SNPs (rs1014971 and rs401681) were also correlated with increased BCa risk in Chinese population in previous report.[11] The etiologic mechanism is largely unknown.

It is well recognized that a genetic score based on risk-associated SNPs could be a supplementary tool to family history, and could provide more precise predication for personal cancer risk.[19–21] GRS is multiplied by all SNPs and each SNP is population-standardized, the mean GRS in the general population is expected to be 1.0.[10,12] In the current study, the mean GRS was 1.01 in the healthy controls, which was expected to be a sample from the general population. In comparison, the mean GRS was 1.22 in BCa cases, which was significantly higher than in the healthy controls. For individuals with high GRS (> 1.2), the risk of BCa would be 1.6- folds and 2.1- folds higher compared to those who have medium GRS (0.8–1.2) and low GRS (<0.8). In contrast to subjects with GRS in the lowest quantile, those with GRS in the highest quantile had an OR of 3.10 (Fig. 1B). In addition, while evaluating the cancer predictive performance of GRS, it yielded an AUC of 0.679, indicating it could predict the risk of BCa. The AUC was not high, this might be attributed to the nature of GRS was a predictive model rather than a diagnostic test. These results indicated GRS was useful to evaluate inherited risk of developing sporadic BCa. Therefore, GRS may have the potential to inform susceptible population for early regular examination of BCa (eg, urine test, molecular biomarkers, and ultrasound).

There were several limitations of this study. First, the sample size of BCa cases was relatively small, so that several BCa risk-associated SNPs from GWAS in East Asians were not validated with significant results. Studies in larger populations are needed to provide external validation and further evaluation between GRS incorporating more SNPs and BCa. Second, not all BCa risk associated SNPs were included; however, the purpose of this study was to demonstrate the utility of GRS in Chinese population, which was fulfilled. Third, almost all subjects in the control cohort were males, which caused the imbalance of gender distribution between cases and controls. This was due to the previous healthy physical examination and survey process was focusing on males, although such gender distribution imbalance would not influence the genetic study results, it might lead to the higher proportion of heavy smokers in control cohort than in cases (22.7% vs 20.5%, $P = .29$).

5. Conclusions

Among 8 candidate SNPs evaluated in this study, 3 SNPs (rs798766, rs9642880, rs4813953) were significantly associated with increased risk of BCa in Chinese population. GRS based on these SNPs could reveal the inherited risk of BCa.

Acknowledgments

We thank all the subjects who participated in this study. We thank Ruochen Jiang (Department of Statistics, University of California, Los Angeles, United States) for statistical consultation.

Author contributions

Conceptualization: Chenyang Xu, Yishuo Wu, Jie Zheng, Jianfeng Xu.
Data curation: Chenyang Xu, Xiaoling Lin, Wei Qian, Rong Na.
Funding acquisition: Yishuo Wu, Jianfeng Xu.
Investigation: Chenyang Xu, Xiaoling Lin, Wei Qian, Yishuo Wu, Jie Zheng.
Methodology: Yishuo Wu, Hongjie Yu, S.Lilly Zheng, Jianfeng Xu.
Resources: Yishuo Wu, Wei Qian, Jie Zheng, Haowen Jiang, Zujun Fang, Qiang Ding.
Statistical analysis: Chenyang Xu, Yishuo Wu, Rong Na, Hongjie Yu, Haifei Jia.
Supervision: Yishuo Wu, Jie Zheng, Qiang Ding, Jianfeng Xu.
Writing-original draft: Chenyang Xu, Yishuo Wu.
Writing-review and editing: Chenyang Xu, Xiaoling Lin, Wei Qian, Yishuo Wu, Jie Zheng.

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.
[2] Chen W, Zheng R, Zeng H, et al. Annual report on status of cancer in China, 2011. Chin J Cancer Res 2015;27:2–12.
[3] Cumberbatch M, Jubber I, Black PC, et al. Epidemiology of bladder cancer: a systematic review and contemporary update of risk factors in 2018. Eur Urol 2018;74:784–95.
[4] Al-Zalabani AH, Stewart KF, Wesselius A, et al. Modifiable risk factors for the prevention of bladder cancer: a systematic review of meta-analyses. Eur J Epidemiol 2016;31:811–51.
[5] Plna K, Hemminki K. Familial bladder cancer in the National Swedish Family Cancer Database. J Urol 2001;166:2129–33.
[6] Mucci LA, Hjelmborg JB, Harris JR, et al. Familial risk and heritability of cancer among twins in nordic countries. JAMA 2016;315:68–76.
[7] Turati F, Bosetti C, Polesel J, et al. Family history of cancer and the risk of bladder cancer: A case–control study from Italy. Cancer Epidemiol 2017;48:29–35.
[8] Kiemeney LA, Sulem P, Besenbacher S, et al. A sequence variant at 4p16.3 confers susceptibility to urinary bladder cancer. Nat Genet 2010;42:415–9.
[9] Kiemeney LA, Thorlacius S, Sulem P, et al. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. Nat Genet 2008;40: 1307–12.
[10] Rafnar T, Sulem P, Thorleifsson G, et al. Genome-wide association study yields variants at 20p12.2 that associate with urinary bladder cancer. Hum Mol Genet 2014;23:5545–57.
[11] Wang M, Chu H, Yan F, et al. Chromosome 4p16.3 variant modify bladder cancer risk in a Chinese population. Carcinogenesis 2011; 32:872–5.
[12] Shi Z, Yu H, Wu Y, et al. Systematic evaluation of cancer-specific genetic risk score for 11 types of cancer in The Cancer Genome Atlas and Electronic Medical Records and Genomics cohorts. Cancer Med 2019;8:3196–205.
[13] Wang M, Chu H, Lv Q, et al. Cumulative effect of genome-wide association study-identified genetic variants for bladder cancer. Int J Cancer 2014;135:2653–60.
[14] Wacholder S, Chanock S, Garcia-Closas M, et al. Assessing the probability that a positive report is false: an approach for molecular epidemiology studies. J Natl Cancer Inst 2004;96:434–42.
[15] Lall K, Magi R, Morris A, et al. Personalized risk prediction for type 2 diabetes: the potential of genetic risk scores. Genet Med 2017;19:322–9.
[16] Redondo MJ, Oram RA, Steck AK. Genetic risk scores for type 1 diabetes prediction and diagnosis. Curr Diab Rep 2017;17:129.
[17] Christiansen MK, Nyegaard M, Pedersen LN, et al. A 45-SNP genetic risk score is increased in early-onset coronary artery disease but independent of familial disease clustering. Atherosclerosis 2017;257: 172–8.
[18] Kullo IJ, Jouni H, Austin EE, et al. Incorporating a genetic risk score into coronary heart disease risk estimates: effect on low-density lipoprotein

cholesterol levels (the MI-GENES Clinical Trial). Circulation 2016; 133:1181–8.
[19] Helfand BT, Kearns J, Conran C, et al. Clinical validity and utility of genetic risk scores in prostate cancer. Asian J Androl 2016;18:509–14.
[20] Iwasaki M, Tanaka-Mizuno S, Kuchiba A, et al. Inclusion of a genetic risk score into a validated risk prediction model for colorectal cancer in Japanese men improves performance. Cancer Prev Res (Phila) 2017; 10:535–41.
[21] Kuchenbaecker KB, McGuffog L, Barrowdale D, et al. Evaluation of polygenic risk scores for breast and ovarian cancer risk prediction in BRCA1 and BRCA2 mutation carriers. J Natl Cancer Inst 2017;109:
[22] Martin C, Leiser CL, O, Neil B, et al. Familial cancer clustering in urothelial cancer: a population-based case–control study. J Natl Cancer Inst 2018;110:527–33.
[23] Cortessis VK, Yuan JM, Van Den Berg D, et al. Risk of urinary bladder cancer is associated with 8q24 variant rs9642880[T] in multiple racial/ethnic groups: results from the Los Angeles-Shanghai case-control study. Cancer Epidemiol Biomarkers Prev 2010;19:3150–6.
[24] Meng XY, Shi MJ, Chen JF, et al. Association between the TACC3 rs798766 polymorphism and risk of urinary bladder cancer: a synthesis based on current evidence. Dis Markers 2017;2017: 7850708.
[25] Figueroa JD, Ye Y, Siddiq A, et al. Genome-wide association study identifies multiple loci associated with bladder cancer risk. Hum Mol Genet 2014;23:1387–98.
[26] Hernandez S, Lopez-Knowles E, Lloreta J, et al. Prospective study of FGFR3 mutations as a prognostic factor in nonmuscle invasive urothelial bladder carcinomas. J Clin Oncol 2006;24:3664–71.
[27] Burger M, van der Aa MNM, van Oers JMM, et al. Prediction of progression of non–muscle-invasive bladder cancer by WHO 1973 and 2004 grading and by FGFR3 mutation status: a prospective study. Eur Urol 2008;54:835–44.