Medical Research Archives

European Society of Medicine

OPEN ACCESS

Published: August 31, 2023

Citation: Gao L, Shi X, et al., 2023. The Association between IL10 rs1800896 A/G and rs1800871 T/C Polymorphisms and Cancer Susceptibility, Medical Research Archives, [online] 11(8). https://doi.org/10.18103/mra.v11i8.4243

DOI
https://doi.org/10.18103/mra.v11i8.4243

ISSN: 2375-1924

RESEARCH ARTICLE

The Association between IL10 rs1800896 A/G and rs1800871 T/C Polymorphisms and Cancer Susceptibility

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ABSTRACT

Background: The significance of interleukin-10(IL-10) on the susceptibility of malignant tumor is one of the hot spots of current research. 1082A > G (rs1800896) and -819C > T (rs1800871) are two genetic variants of IL-10, and their effects on malignancy need to be further explored. Therefore, in order to further explore the relationship between IL-10 polymorphisms and cancer susceptibility and the role of IL-10 in the occurrence and development of malignant tumors, in this paper, we use of odds ratios (ORs), corresponding 95% confidence intervals (CIs), and in silico tools. analysis to study the relationship between the two. Furthermore, GSEA was used to analyze the expression of IL-10 in renal cell carcinoma, bladder cancer and prostate cancer. We conducted a systematic analysis of 50 controlled trials involving 15,418 cancer patients and 18,597 controls. The analysis showed that the -1082A>G (rs1800896) and -819C>T (rs1800871) polymorphism were associated with the risk of bladder cancer. GSEA showed that IL-10 was highly expressed through the Cytokine-Cytokine-receptor-interaction pathway, JSK-STAT-signaling pathway, Natural killer cell mediated cytotoxicity pathway and Leukocyte transendothelial migration pathway.

Keywords: IL-10, Cancer, susceptibility, SNP.

1. Introduction

Cancer is a major problem and challenge facing global public health threat. Over the decades, with the continuous improvement of human health, the increasing average lifespan, and the continuous changes in lifestyle and diet, the incidence and mortality rates of cancer have continued to rise.. In 2020, there were approximately 19.3 million new cancer cases and 10 million cancer-related deaths worldwide (excluding non-melanoma skin cancer)[1]. The occurrence and development of malignant tumors is a complex process, in which various internal and external factors interact with each other. Internal factors such as immune status, endocrine changes, and gene mutations in important signal transduction pathways are the main influencing factors, external factors include environmental pollution, radiation, chemical substances, etc.[2,3].

T cells, monocytes, macrophages, certain subsets of dendritic cells, and B cells are primary producers of IL-10, a multifunctional cytokine with anti-inflammatory properties. Apart from these, IL-10 is also produced by non-immune cells, such as keratinocytes, epithelial cells, and certain types of tumor cells. Five exons make up the human IL-10 gene, located on chromosome 1q32.1[4]. IL 10 plays an irreplaceable role in the immune and inflammatory responses involved in the pathogenesis of cancer[5]. The expression of IL-10 gene may be influenced by several single-nucleotide
polymorphisms (SNPs) contained in the IL-10 promoter[6]. The genetic variations -1082A>G (rs1800896) and -819C>T (rs1800871) have been extensively studied in various types of cancers, including breast cancer, lung cancer, stomach cancer and bladder cancers[7,8,9,10]. Due to the fact that IL-10 has both immunosuppressive and anti-angiogenic properties, there has been a long-standing controversy over whether the polymorphism of IL-10 can promote or inhibit the occurrence and development of malignant tumors[11]. Although a large amount of research has been conducted to elucidate the impact of IL-10 gene polymorphisms on cancer susceptibility, the relationship between tumor progression and IL-10 in cancer susceptibility remains unclear[12,13]. The results of these studies have generated different conclusions, possibly due to limited sample sizes or other factors such as racial background, eexperimental methods, etc. Therefore, in order to investigate the relationship between these two IL-10 gene polymorphisms and cancer susceptibility, a meta-analysis was conducted in this study.

2. Method

2.1 Eligibility criteria for studies

Two researchers independently conducted preliminary searches using specific keywords in multiple databases such as Pubmed, EMBASE, and the Chinese National Knowledge Infrastructure (CNKI) with a cut-off date of December 30, 2022. The keywords used were ("IL 10 or Interleukin-10 or rs1800896 or rs1800871") AND ("cancer" OR "tumor" OR "carcinoma") AND ("mutant" OR "variant" OR "variation"). The titles and abstracts of the retrieved literature were manually screened for further evaluation of their accuracy.

2.2 Criteria for acceptance and exclusion

It is necessary for the literature content to meet the following criteria in order to be included in this meta-analysis: (I) In order to investigate IL-10 polymorphism's relationship with cancer, case-control studies are required; (II) they must be available genotype and allele data; and (III) the control group must conform to the Hardy-Weinberg equilibrium principle. It will not include studies in which IL 10 polymorphisms research has not been conducted or in which enough data have not been collected to calculate odds ratios (ORs) and 95% confidence intervals (CIs). Multiple studies can use the same data set, but only the study with the largest sample size will be included in the analyses.

2.3 Data extraction

All eligible research data were independently collected by two researchers, and the data were exchange and verified by the two researchers. We rechecked the original data to resolve any discrepancies. In the collection of information, we included details such as the first author of the article, the country of origin of the included cases, the year of publication, country of origin, type of malignancy, source of cases (either by hospital or by population), the racial composition of the study, genotyping method, number of cases and controls, and the distribution of genotypecases and controls.

2.4 Statistics analysis

Each study in the control groups was evaluate for HWE using chi-square goodness-of-fit tests. HWE was considered significantly deviated when $P<0.05$. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of association between IL 10 polymorphisms and malignant tumors. We employed five genetic models: allelic model (A versus G or T versus C), homozygote model (AA versus GG or TT versus CC), heterozygote model (AG versus GG or TC versus CC), dominant model (AA+ AG versus GG or TT + TC versus CC), and recessive model (AA versus AG+GG or TT versus TC + CC). The minor alleles were represented by T and A, while the major alleles were represented by C and G. Heterogeneity was tested using the I2 test and the Q test. In studies lacking heterogeneity, a fixed-effects model was used to calculate the pooled OR ; otherwise, a random-effects model was used. In order to perform the sensitivity analysis, we removed one study at a time and analyzing the remaining studies in a combined manner. The HWE of control genotype distribution was assessed using the $\chi 2$ test, and a p-value of <0.05 was considered inequivalent. Publication bias was assessed using funnel plots and Egger's test. STATA 11.0 was used for all data analyses.

3. Results

3.1. Characteristics of Eligible Studies.

15,418 cancer patients and 18,597 controls were included recruited for the pooled analysis, which included 50 case-control studies (Table 1). The rs1800896 variation was analyzed in 27 studies that included 9,551 cancer patients and 10,899 control subjects. 2 studies on bladder cancer, 4 studies on renal cancer, 21 studies on prostate cancer were included in the stratified analysis by cancer type. Among the studies analyzed as control source, 15 were hospital-based, while 12 were population-based. Based on stratified analysis by ethnicity, 6 studies focused on Asians, 13 on Caucasion, 4 on African and 4 on mixed. In subgroup analysis by a genotype method, 10 studies zed TaqMan assay,1 study used PCR-RFLP, 5 studies used ARMS-PCR, 6 studies used PCR, 2 studies used real-time PCR and 3 studies performed MassARRAY. 27 studies with 5,867 cancer patients and 7,708 controls were included in the study of the rs1800871 variant. 2 of these studies involved bladder cancer, 4 involved renal cancer and 17 involved prostate cancer. Stratified analysis of control source included 11 population-based studies and 12 hospital-based studies. Asians dominated 11 studies, Caucasion dominated 7, African dominated 2 and mixed dominated 3. Among these studies that used the classical genotyping method,10 studies used TaqMan assay, 10 studies used PCR-RFLP, 4 studies used ARMS-PCR and 3 studies used PCR.

Analyzing IL 10 at rs1800896 and rs1800871 polymorphisms in different ethnicities, we calculated minor allele frequencies (MAFs).. The MAFs of the rs1800896 variant were as follows: global population, 0.3968; Africans, 0.0915; East Asians, 0.6577; Europeans, 0.4930; South Asian, 0.4090; and Americans, 0.4420. The MAFs of rs1800871 were as follows: global population, 0.4347; Africans, 0.4357; East Asians, 0.6756; Europeans, 0.2396; South Asian, 0.4580; and Americans, 0.3330 (Figure 1).

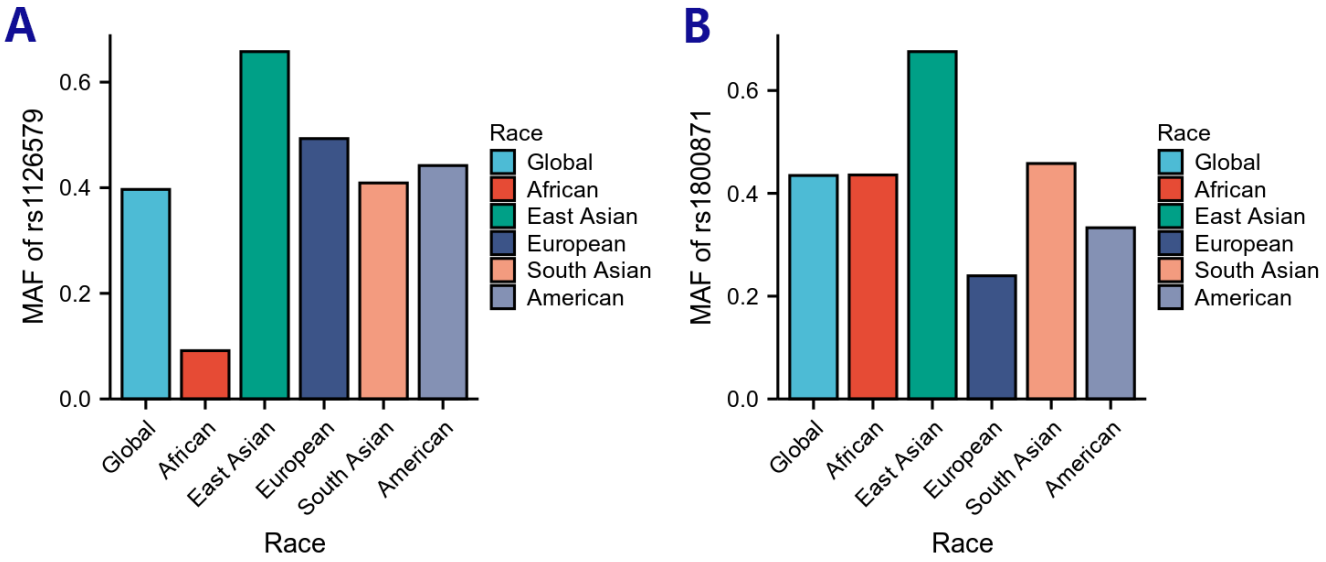


Figure 1. Minor allele frequencies of IL 10 rs1800896 (A) and rs1800871 (B) variants in various races.

3.2. Overall and Stratified Analyses.

As shown in Table 2, IL 10 rs1800896 or rs1800871 have a strength association with cancer susceptibility. In the pooled data, SNP rs1800896 is significantly associated with cancer risk. Individuals with G-allele had an 16% higher risk of developing cancer compared to those with the A-allele (95%CI = 1.03-1.29, P = 0.003, Figure 2(A)). When subgroup analysis was performed by cancer type, there was a 36.4% increase in bladder cancer risk for those carrying the A-allele in comparison to those carrying the G-allele (95%CI = 1.097-1.696, P = 0.005). An identical result was observed in homozygote contrast (95%CI = 1.126-3.547, P =0.018), heterozygote models (95%CI = 1.157-3.548, P =0.014) and dominant models (95%CI = 1.193-3.516, P = 0.009). For prostate cancer, similar results were observed in the heterozygote model (95%CI = 1.001-1.257, P =0.048) and dominant model (95%CI =1.005-1.283, P = 0.042). In stratified analysis by ethnicity, Caucasion individuals with the A-allele had an 13.9% higher risk of developing cancer compared to those with the G-allele (95%CI = 1.024-1.267, P = 0.016). Similar pattern of findings was observed in studies based on population, high quality studies and studies that used MassARRAY method. For the 1800871, individuals with C-allele had an 2% higher risk of cancer compared to those with the T-allele (95%CI = 0.95-1.10, P = 0.000, Figure 2(B)). In subgroup analysis by cancer type, a significant correlation with bladder cancer susceptibility were observed in the allelic (95%CI = 1.191-1.631, P = 0.000), homozygote models (95%CI = 1.282-2.418, P = 0.000), heterozygote models (95%CI = 1.043-1.927, P = 0.026), dominant models (95%CI = 1.192-2.112, P = 0.002), and recessive models (95%CI = 1.166-1.816, P = 0.001). An identical result was observed in the Asian (allelic contrast, 95 %CI = 1.040-1.425, P = 0.014; homozygote model, 95 %CI = 1.027-1.79, P = 0.032; recessive model, 95% CI = 1.098-1.436, P = 0.001) and Caucasion (allelic contrast, 95 %CI = 1.018-1.252, P = 0.022; homozygote model, 95 %CI = 1.026-1.717, P = 0.031). In addition, PCR, ARMS-PCR and low quality studies also yielded similar results.

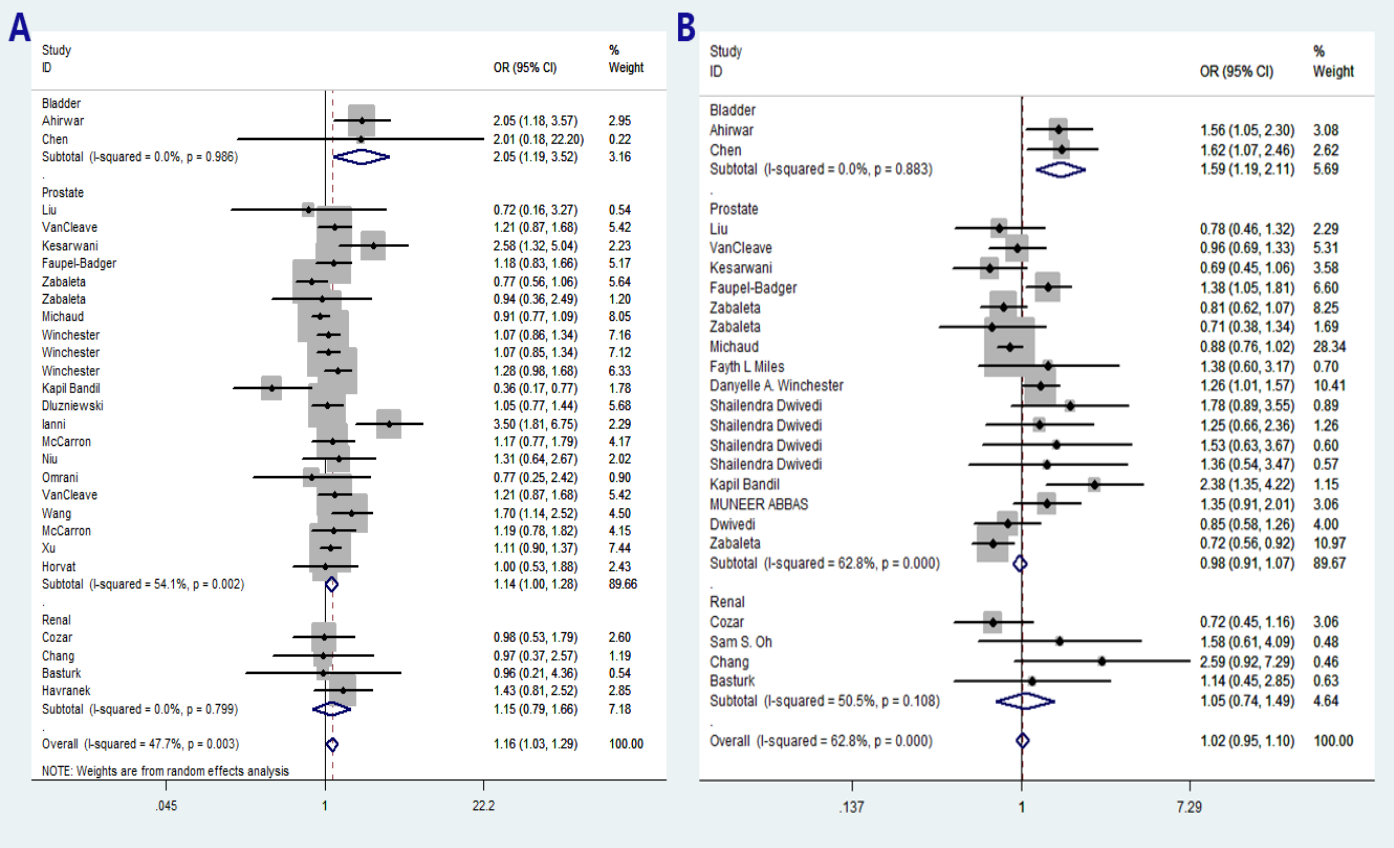


Figure 2. Forest plot of ORs for the relationship between IL 10 variants rs1800896（A: Dominant model or rs1800871 B: Dominant model） and risk of cancer in stratification analysis by type of cancer.

3.3 In Silico and ELISA analysis of IL 10 expression

To investigate the expression of IL 10, we use computational tools to analyze the impact of sample types and the race of patients. According to Figure 3, the expression of IL 10 was increased in BLCA and PRAD, while it was decreased in KIRC. However, tthe differences in IL 10 expression among these three tumors were not statistically significant, as were the difference in OS and DFS. Moreover, we used an online database to evaluate the expression of IL 10 in in different genotype. As described in Figure 4, for the rs1800896 variant, IL 10 expression in individuals with CC genotypes was statistically higher than in those with TT+CC genotypes (Figure 4A, p =0.0049). For rs1800871, IL 10 expression was upregulated individuals with the GG genotype (Figure 4B, p =0.0142). The expression of IL 10 gene in different stages of bladder cancer and kidney cancer is shown in figure 5, with significant differences in IL 10 expression observed in different stages of bladder cancer and kidney cancer (figure 5A and 5B).

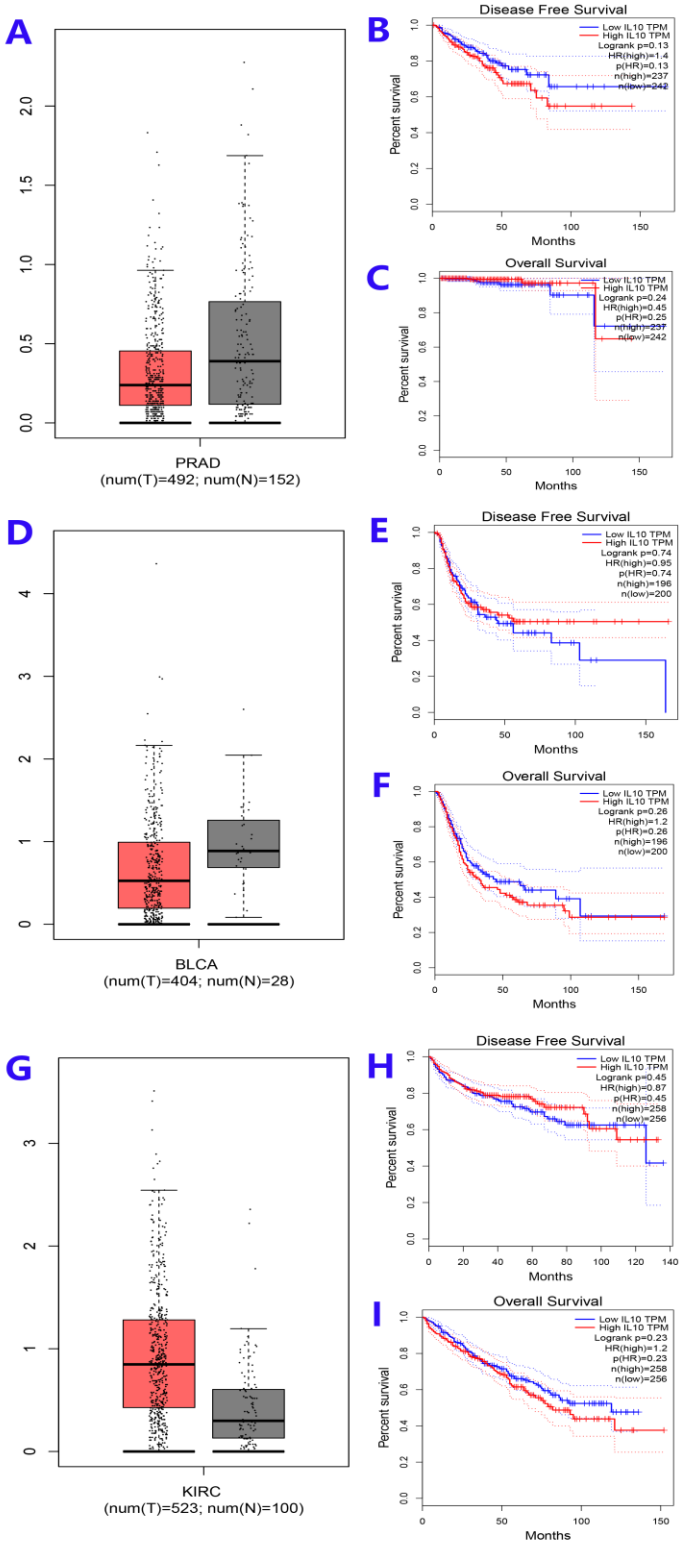


Figure 3. In silico analysis of IL 10 expression based on sample types. The expression of IL 10 in prostate cancer (PRAD) is described in (A). Effect of IL 10 level on PRAD patients' DFS (disease free survival) is shown in (B) and OS (overall survival) is shown in (C). The expression of IL 10 in bladder cancer (BLCA) is shown in (D). Effect of IL 10 level on BLCA patients' DFS is shown in (E) and OS is shown in (F). Expression in kidney renal clear cell carcinoma (KIRC) was shown in (G). Effect of IL 10 level on KIRC patients' DFS is shown in (H) and OS is shown in (I).

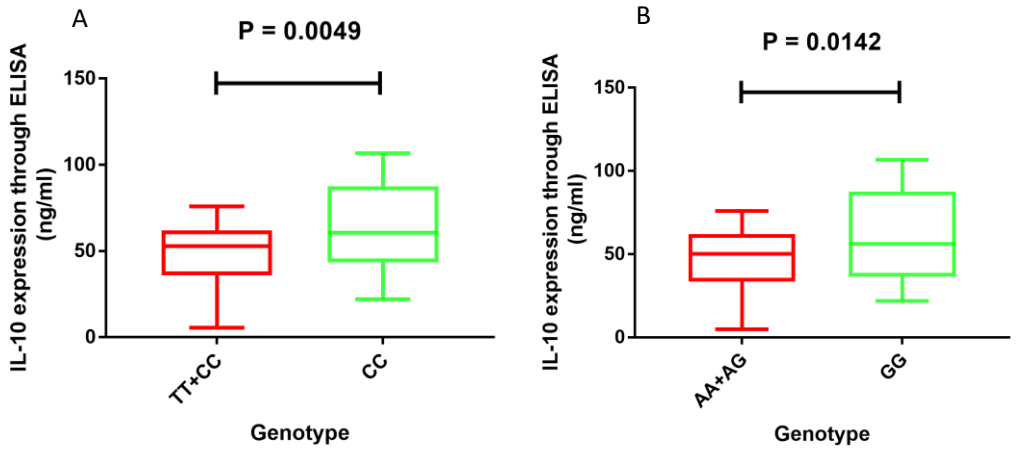


Figure 4. Analysis of serum IL 10 levels in rs1800896 (A) and rs1800871 (B). For rs1800896 variant, IL 10 expression subjects with CC genotypes was statistically higher than in those with TT+CC genotypes (A). For rs1800871 polymorphism, the expression of IL 10 is upregulated in GG genotype (B).

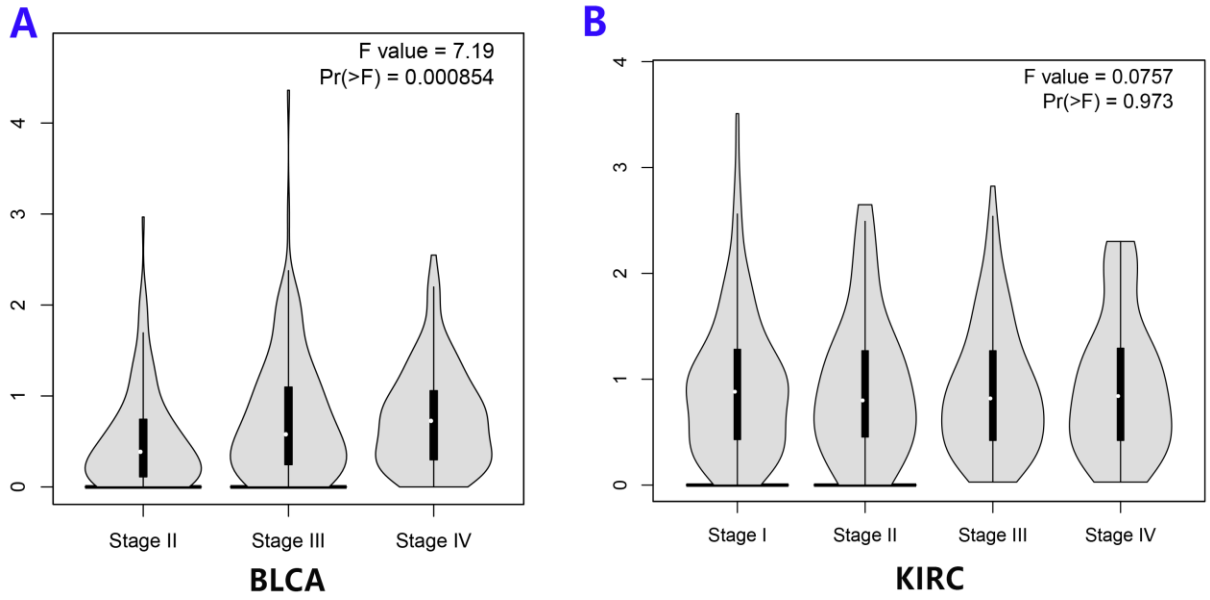


Figure5. IL 10 expression in different stages of BLCA and KIRC cancers.

In addition, we explored the correlation between IL 10 and related immune cells and their related markers. As shown in Figure 6A, IL 10 was closely related to Purity, CD8 + T Cell, CD4 + T Cell, Macrophage, Neutrophil and Dendritic Cell (Figure 6A). In Macrophage M1 cells, IL 10 was related to NOS2 and PTGS2 (Figure 6B); In Macrophage M2 cells, IL 10 was closely related to MRC1 and MS4A4A (Figure 6C).; In Neutrophil cells, FUT4 and ITGAM are significantly associated with IL 10 (Figure 6D); and in dendritic cells, CD1C, ITGAX and THBD were significantly correlated with IL-10 (Figure 6E).

STRING analysis showed that at least 20 proteins were related to IL 10 gene expression (Figure 7 A), with the most relevant being IL 10RA, IL 6, TNF, IL 1B, CXCL8, CCL2, STAT3, CSF2, CCL5 and CD80 (Figure 7 B). Subsequently, gene set enrichment analysis (GSEA) was performed to further investigate functional enrichment using the Kyoto Encyclopedia of Genes and Genomes (KEGG). Figure 8A displays the correlation map

between the heat map and gene list. GSEA suggested that IL-10 was significantly enriched in the Cytokine-Cytokine-receptor-interaction pathway (Figure 8B), JSK-STAT-signaling pathway (Figure 8C), Natural killer cell mediated cytotoxicity pathway (Figure 8D) and Leukocyte transendothelial migration pathway (Figure 8E).

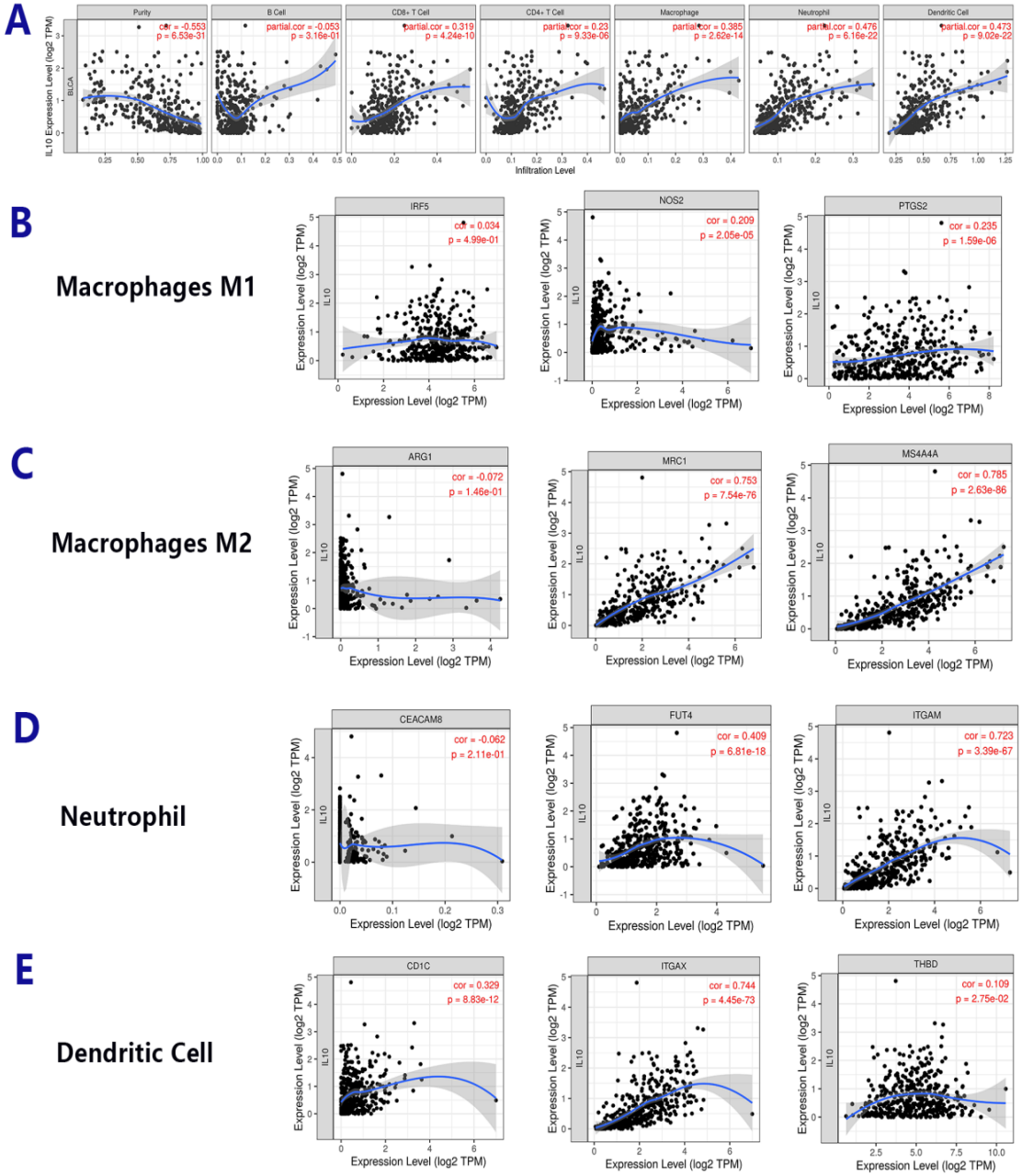


Figure 6 The correlation between IL 10 and related immune cells (A) and their related markers(B-E).

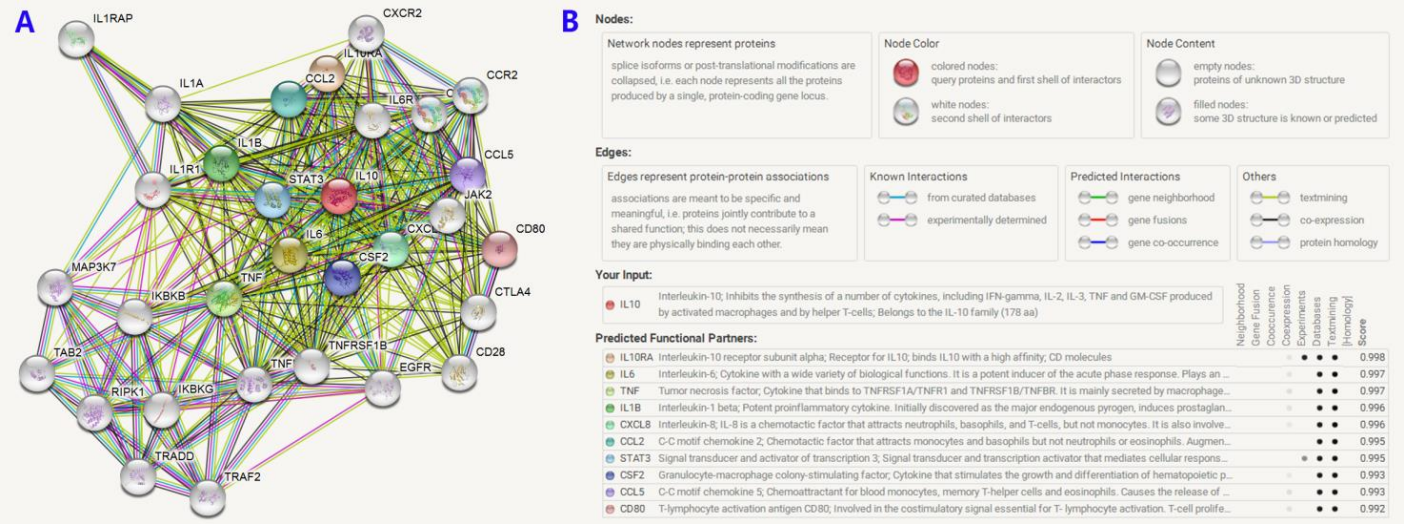


Figure 7. The relationship of IL 10 protein assessed by the STRING tools. At least 20 proteins can participate in the interaction with IL 10 (A). The most relevant are IL 10RA (Interleukin-10 receptor subunit alpha), IL 6 (Interleukin-6), TNF (Tumor necrosis factor), IL 1B (Interleukin-1 beta), CXCL8 (Interleukin-8), CCL2(C-C motif chemokine 2), STAT3 (Signal transducer and activator of transcription 3), CSF2 (Granulocyte-macrophage colony-stimulating factor),CCL5 (C-C motif chemokine 5) and CD80 (T-lymphocyte activation antigen CD80) (B).

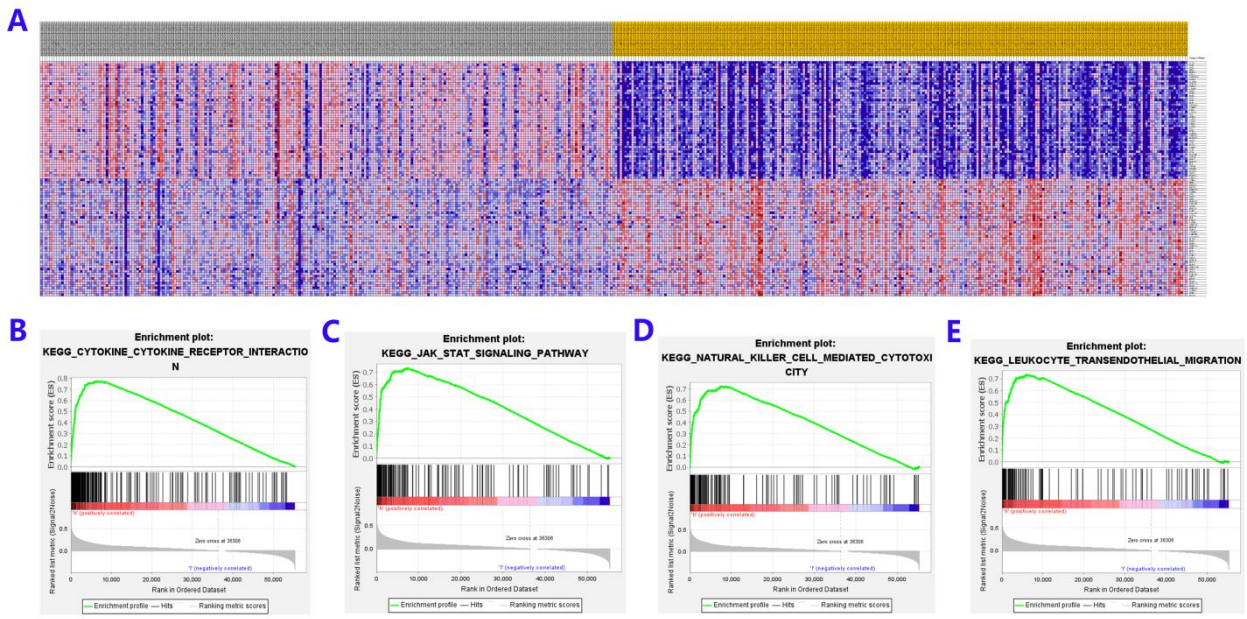
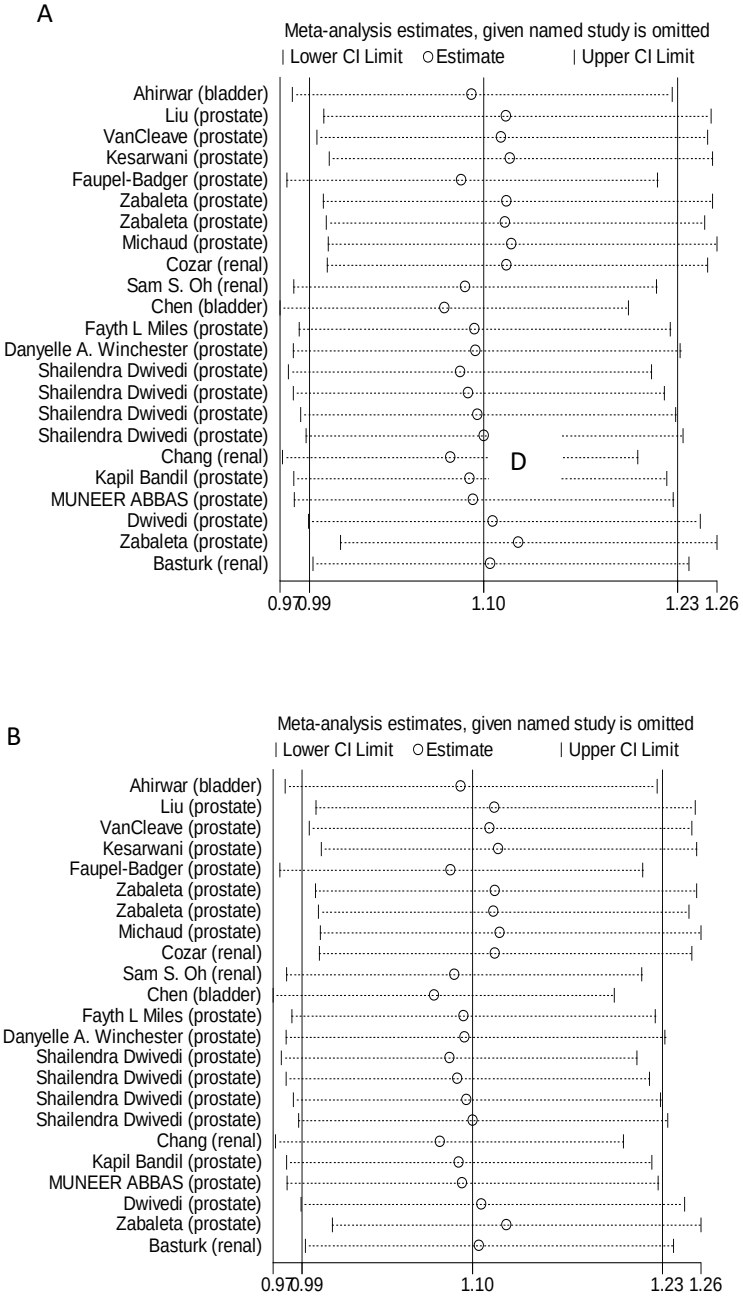


Figure 8. GSEA analysis of samples with high expression of IL 10. Heat map and gene list association profiles are described in (A). GSEA revealed that the Cytokine-Cytokine-receptor-interaction pathway (B), JSK-STAT-signaling pathway (C),Natural killer cell mediated cytotoxicity pathway (D) and Leukocyte transendothelial migration pathway (E) were enriched in IL 10 high-expression group.

3.4. Sensitivity Analysis and Publication Bias.

In this study, a sensitivity analysis was performed by excluding each individual study to evaluate how it impacted the overall odds ratios (ORs). The significance of the ORs for the IL10 variants rs1800896 and rs1800871 ($P < 0.05$) was

not significantly influenced by any individual study, as shown in Figures 9(A) and 9(B). Furthermore, the assessment of publication bias through the using of Begg's funnel plots revealed no substantial publication bias for any of the five genetic models of rs1800896 (Figure 9(C), P > 0.05) or rs1800871 variants (Figure 9(D), P > 0.05).



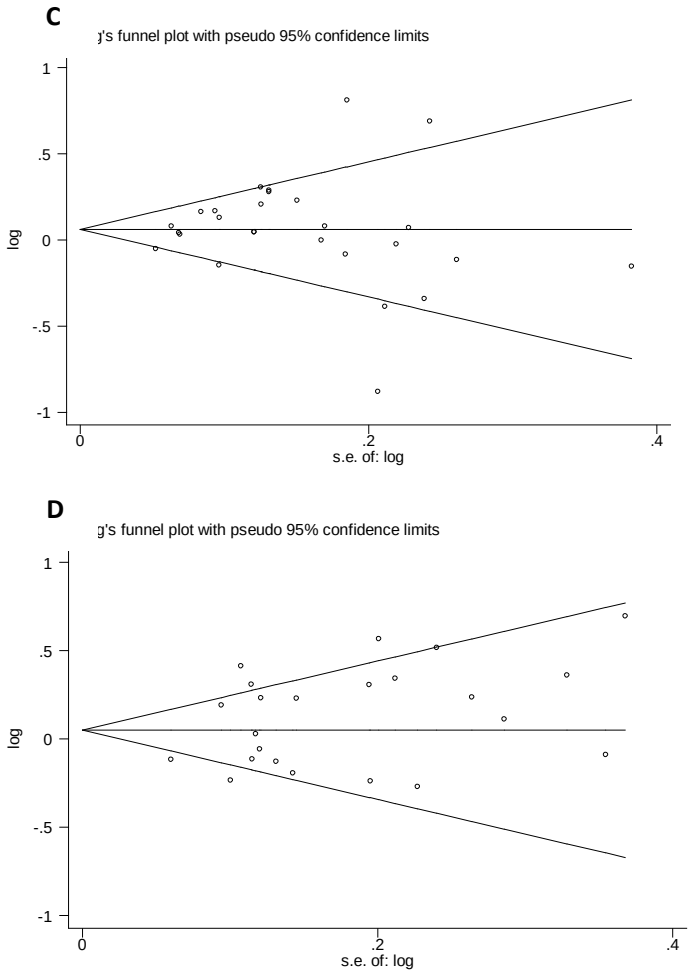


Figure 9: Sensitivity analysis and Begg's funnel plot of IL 10 variants. Sensitivity analysis of IL 10 variant rs1800896 (A) and rs1800871 (B) indicated that a single study could not influence the significance of ORs. Begg's funnel plot analysis of rs1800896 (C) and rs1800871 (D) polymorphisms under heterozygous comparison model revealed no evidence of publication bias.

4. Discussion

This study investigated the impact of two common promoter polymorphisms (-1082A>G and -819C>T) in the IL-10 gene on susceptibility to kidney, bladder, and prostate cancer. The results showed that the -1082 polymorphism of the IL-10 gene is significantly associated with bladder cancer risk in various models, including allele contrast (95%CI = 1.097-1.696, P = 0.005), homozygote model (95%CI = 1.126-3.547, P = 0.018), heterozygote model (95%CI = 1.157-3.548, P = 0.014), and dominant model (95%CI = 1.193-3.516, P = 0.009). Additionally, the -819 polymorphism was found to have a strong correlation with bladder cancer. However, no significant association has been found between the above two polymorphisms and kidney or prostate cancer.

IL-10 cytokine exhibits anti-inflammatory properties, which may lead to immune escape of cancer cells, indicating a possible role in tumorigenesis. On the other hand, it also demonstrates anti-angiogenic characteristics and can reduce tumor growth and angiogenesis in animals and in vitro experiments[14]. The expression of IL-10 cytokine is further constrained by promoter polymorphisms (-1082A>G, -819C>T), and studies has been suggested that the presence of IL-10 -

1082G/-819T haplotype is associated with a decrease in IL-10 levels[15,16].

Some studies have attempted to explore the role of IL-10 gene polymorphisms, but a clear understanding of their mechanisms is still difficult to achieve. This can be attributed to the complex and multifactorial nature of cancer development, which is influenced by various factors including environmental and genetic factors. Isolating a single factor may not provide an accurate conclusion. In addition, the distribution of IL-10 gene polymorphism varies amongst different races and genders, making the analysis results more complex. Therefore, considering all these complex factors, study only IL-10 gene polymorphism may have limitations and affect the accuracy of the results.

In order to increase the relevance of our research, we incorporated two polymorphisms (-1082A>G and -819C>T) in our investigation to study their relationship with kidney, bladder, and prostate cancers. Additionally, we conducted further studies on different dimensions such as race, experimental method, ethnicity, population characteristics, and study quality. By doing so, we aimed to consider as many controllable variables as possible and draw comprehensive conclusions. Our findings revealed that -1082A>G and -819C>T were particularly associated with bladder cancer. Specifically, in Caucasians and in high-quality, the relationship between -1082A>G and tumor risk is closer. In contrast, the association between -819C>T and tumor risk was observed in both Asians and Caucasians, although it was more pronounced in studies of low-quality studies.

Our meta-analysis has several advantages compared to previously published ones. Firstly, we included more studies (50 studies) and large sample sizes compared to others studies of the same type. Secondly, we included two types of polymorphisms (-1082A>G and -819C>T). Thirdly, there was no publication bias in our study. Lastly, we included a more comprehensive range of ethnicities. However, our study also has limitations. Firstly, we only included studies published in English. Secondly, we only considered the impact of genes on tumors, while tumor development is the result of complex multifactorial influences. For renal cancer, its pathological classification is complex and cannot be generalized, and tumors of different stages should also be distinguished.

5. Conclusion

To summarize, this research has compiled all trelevant information concerning the genetic correlation between IL-10 variants rs1800896 and rs1800871 and susceptibility to kidney, bladder and prostate cancers. The findings from our study suggest that the variations in rs1800896 and rs1800871 polymorphisms are linked to an increased risk of bladder cancer, especially among individuals of Caucasion. GSEA Cytokine-Cytokine-receptor-interaction pathway, JSK-STAT-signaling pathway, Natural killer cell mediated cytotoxicity pathway and Leukocyte transendothelial migration pathways were enriched in IL 10 high expression group.

AUTHOR CONTRIBUTIONS

Lifeng Zhang and Shenglin Gao conceived the study design. Lei Gao and Li Zhang were involved in the database searching. Xiaokai Shi and Shenglin Gao carried out the experiments and participated in the statistical analyses. Lei Gao and Lifeng Zhang wrote the draft manuscript. Li Zuo revised the manuscript and provided financial assistance. All authors agreed with the final edition of the manuscript.

FUNDING

The current study was granted by Jiangsu Province 333 High-level Talent Project. "The 14th Five-Year Plan" High-Level Health Talents Training Project (2022CZBJ057). Changzhou Sci&Tech Program (Grant number: CJ20220146) and Jiangsu Province Postdoctoral Research Fundation (Grant number: 2021K588C).

DATA ACCESSIBILITY

It is possible to obtain the raw data of this study from the corresponding authors upon reasonable request.

DECLARATION OF INTEREST

The authors declared no competing interest.

ETHICS APPROVAL

The Ethics Committee of the Changzhou No.2 People's Hospital approved the present study (Approval number: [2020]KY223-01). Experiments with human participants were conducted in compliance with the Declaration of Helsinki, and we obtained informed consent from all patients.

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TABLE 1. Study characteristics of IL10 rs1800896 A/G and rs1800871 T/C variants in the current analysis. HWE: Hardy-Weinberg equilibrium of control. HB: hospital based; PB: population based. PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; ARMS-PCR: amplification refractory mutation system-polymerase chain reaction.

First author					Source of	Case	Control	Case			Control			HWE	
rs1800896 A/G	Year	Origin	Cancer	Ethnicity	control			AA	AG	GG	AA	AG	GG		Method
Ahirwar	2009	India	bladder	Asian	HB	214	385	84	112	18	143	181	61	0.000	ARMS-PCR
Liu	2010	China	prostate	Asian	PB	262	270	222	36	4	240	27	3	0.035	PCR-RFLP
Kesarwani	2009	India	prostate	Asian	HB	159	259	69	78	12	111	103	45	0.027	ARMS-PCR
Faupel-Badger	2008	Finland	prostate	Caucasian	PB	509	382	173	251	85	115	194	73	0.582	TaqMan
Zabaleta	2008	USA	prostate	Caucasian	HB	475	394	110	239	126	102	206	86	0.347	TaqMan
Zabaleta	2008	USA	prostate	African	HB	66	129	21	38	7	42	74	13	0.018	TaqMan
Michaud	2006	USA	prostate	Mixed	PB	1245	1763	356	599	290	523	857	383	0.000	TaqMan
Cozar	2007	Spain	renal	Caucasian	HB	126	175	42	62	22	58	87	30	0.787	TaqMan
Chen	2013	China	bladder	African	HB	400	400	374	25	1	350	48	2	0.799	ARMS-PCR
Winchester	2015	USA	prostate	Caucasian	PB	867	836	218	449	200	204	429	203	0.447	PCR
Winchester	2015	USA	prostate	Mixed	PB	832	836	206	434	192	204	429	203	0.447	PCR
Winchester	2017	USA	prostate	Caucasian	PB	620	528	179	305	136	134	254	140	0.386	MassARRAY
Chang	2016	China	renal	Asian	HB	92	550	71	16	5	414	107	29	0.000	PCR
Kapil Bandil	2017	India	prostate	Asian	HB	105	115	36	45	24	69	35	11	0.049	ARMS-PCR
Dluzniewski	2012	USA	prostate	Mixed	HB	458	458	146	212	100	112	242	104	0.222	MassARRAY
Ianni	2013	Italy	prostate	Caucasian	HB	171	96	79	74	18	25	43	28	0.312	real-time PCR
McCarron	2002	UK	prostate	Caucasian	PB	247	223	78	113	56	46	120	57	0.239	ARMS-PCR
Niu	2011	China	prostate	Asian	HB	98	88	24	56	18	42	26	20	0.001	PCR
Omrani	2009	Iran	prostate	Caucasian	HB	41	103	5	31	5	16	77	10	0.000	TaqMan
VanCleave	2010	USA	prostate	African	PB	192	660	22	95	75	92	280	288	0.074	TaqMan
Wang	2009	USA	prostate	Caucasian	PB	255	257	69	130	56	57	117	83	0.119	TaqMan
Basturk	2005	Turkey	renal	Caucasian	HB	29	50	17	9	3	32	13	5	0.060	PCR
Havranek	2005	UK	renal	Mixed	HB	147	149	65	56	26	69	45	35	0.000	real-time PCR
McCarron	2002	UK	prostate	Caucasian	PB	246	223	78	113	55	46	120	57	0.239	PCR
Xu	2005	Sweden	prostate	Caucasian	PB	1383	780	388	689	306	203	390	187	0.991	MassARRAY
Horvat	2015	Croatia	prostate	Caucasian	HB	120	120	37	59	24	42	54	24	0.385	TaqMan

First author						Case	Control	Case			Control			HWE	
rs1800871 T/C								TT	TC	CC	TT	TC	CC		Method
Ahirwar	2009	India	bladder	Asian	HB	214	385	65	103	46	105	165	115	0.005	ARMS-PCR
Liu	2010	China	prostate	Asian	PB	262	270	120	108	34	132	110	28	0.477	PCR-RFLP
VanCleave	2010	USA	prostate	African	PB	191	635	30	85	76	111	278	246	0.037	TaqMan
Kesarwani	2009	India	prostate	Asian	HB	159	259	39	68	52	69	125	65	0.579	ARMS-PCR
Faupel-Badger	2008	USA	prostate	Caucasian	PB	507	384	40	184	283	18	122	244	0.585	TaqMan
Zabaleta	2008	USA	prostate	Caucasian	HB	462	375	31	149	282	22	143	210	0.717	TaqMan
Zabaleta	2008	USA	prostate	African	HB	64	119	7	31	26	19	61	39	0.548	TaqMan
Michaud	2006	USA	prostate	Mixed	PB	1246	1744	83	447	716	139	659	946	0.109	TaqMan
Cozar	2007	Spain	renal	Caucasian	HB	127	175	9	37	81	14	63	98	0.394	TaqMan
Sam S. Oh	2010	USA	renal	Mixed	PB	19	165	4	5	10	8	52	105	0.636	PCR
Chen	2013	China	bladder	Asian	HB	400	400	218	140	42	168	168	64	0.047	ARMS-PCR
Fayth L Miles	2015	USA	prostate	Caucasian	HB	30	88	4	11	15	6	31	51	0.666	TaqMan
Danyelle A. Winchester	2015	USA	prostate	Caucasian	PB	632	731	35	216	381	34	217	480	0.143	TaqMan
Shailendra Dwivedi	2015	India	prostate	Asian	PB	72	71	22	29	21	13	28	30	0.169	PCR-RFLP
Shailendra Dwivedi	2015	India	prostate	Asian	PB	92	88	28	38	26	16	43	29	0.652	PCR-RFLP
Shailendra	2015	India	prostate	Asian	PB	63	53	17	34	12	12	27	14	0.882	PCR-RFLP
Shailendra	2015	India	prostate	Asian	PB	42	59	12	21	9	17	26	16	0.363	PCR-RFLP
Chang	2016	China	renal	Asian	HB	92	580	62	26	4	310	209	61	0.005	PCR
Kapil Bandil	2017	India	prostate	Asian	HB	105	115	16	62	27	23	40	52	0.006	ARMS-PCR
MUNEER ABBAS	2020	USA	prostate	Caucasian	PB	242	177	36	122	84	20	83	74	0.650	TaqMan
Dwivedi	2015	India	prostate	Asian	HB	291	291	92	131	68	80	151	60	0.466	PCR-RFLP
Zabaleta	2008	USA	prostate	Mixed	HB	526	494	38	180	308	41	204	249	0.931	TaqMan
Basturk	2005	Turkey	renal	Caucasian	HB	29	50	2	14	13	7	19	24	0.320	PCR

TABLE 2. Stratified analysis of IL10 rs1800896 A/G and rs1800871 T/C polymorphisms on cancer susceptibility. Ph: P value of heterogeneity test.

Variables	N	Case/Control	OR(95%CI) Ph P A vs. G	OR(95%CI) Ph P AA vs. GG	OR(95%CI) Ph P AG vs. GG	OR(95%CI) Ph P AA+AG vs. GG	OR(95%CI) Ph P AA vs. AG+GG
1082A/G rs1800896							
	2	9551/10	1.075 （ 0.991-1.166 ）	1.168 （ 1.001-1.364 ）	1.145 （ 1.027-1.277 ）	1.156 （ 1.032-1.295 ）	1.050 （ 0.930-1.185 ）
Total	7	889	0.000 0.080	0.000 0.048	0.027 0.014	0.003 0.013	0.000 0.433
Cancer Type							
			1.364 （ 1.097-1.696 ）	1.999 （ 1.126-3.547 ）	2.026 （ 1.157-3.548 ）	2.048 （ 1.193-3.516 ）	1.460 （ 0.788-2.704 ）
bladder	2	614/785	0.077 0.005	0.955 0.018	0.586 0.014	0.986 0.009	0.040 0.229
			1.031 （ 0.845-1.259 ）	1.092 （ 0.733-1.627 ）	1.203 （ 0.802-1.805 ）	1.147 （ 0.792-1.661 ）	0.983 （ 0.752-1.286 ）
renal	4	394/924	0.943 0.763	0.936 0.664	0.614 0.372	0.799 0.469	0.920 0.902
	2	8543/91	1.058 （ 0.967-1.157 ）	1.149 （ 0.967-1.366 ）	1.122 （ 1.001-1.257 ）	1.135 （ 1.005-1.283 ）	1.028 （ 0.895-1.182 ）
prostate	1	80	0.000 0.221	0.000 0.115	0.022 0.048	0.002 0.042	0.000 0.693
Ethnicity							
		930/166	0.846 （ 0.596-1.202 ）	0.921 （ 0.438-1.938 ）	1.533 （ 0.910-2.583 ）	1.167 （ 0.629-2.167 ）	0.713 （ 0.475-1.069 ）
Asian	6	7	0.000 0.352	0.000 0.828	0.045 0.108	0.003 0.625	0.001 0.102
	1	5089/41	1.139 （ 1.024-1.267 ）	1.298 （ 1.053-1.601 ）	1.098 （ 0.988-1.219 ）	1.174 （ 1.006-1.369 ）	1.188 （ 1.029-1.372 ）
Caucasion	3	67	0.001 0.016	0.003 0.015	0.226 0.082	0.028 0.041	0.026 0.019
		850/184	1.109 （ 0.957-1.285 ）	0.937 （ 0.661-1.328 ）	1.278 （ 1.010-1.618 ）	1.198 （ 0.957-1.500 ）	1.065 （ 0.668-1.698 ）
African	4	9	0.085 0.170	0.927 0.715	0.944 0.041	0.938 0.116	0.024 0.791
		2682/32	1.013 （ 0.941-1.089 ）	1.025 （ 0.886-1.185 ）	0.988 （ 0.867-1.125 ）	0.999 （ 0.884-1.130 ）	1.032 （ 0.920-1.157 ）
Mixed	4	06	0.213 0.737	0.225 0.738	0.286 0.851	0.394 0.994	0.090 0.594
Source of control							
	1	6850/74	1.066 （ 1.016-1.120 ）	1.129 （ 1.023-1.246 ）	1.090 （ 1.001-1.187 ）	1.106 （ 1.020-1.198 ）	1.097 （ 0.973-1.236 ）
PB	2	18	0.055 0.010	0.097 0.016	0.510 0.048	0.391 0.014	0.030 0.131
	1	2701/34	1.040 （ 0.871-1.242 ）	1.112 （ 0.786-1.571 ）	1.261 （ 0.961-1.655 ）	1.188 （ 0.896-1.575 ）	0.976 （ 0.767-1.241 ）
HB	5	71	0.000 0.662	0.000 0.549	0.005 0.095	0.001 0.230	0.000 0.840

Method										
			0.710（0.445-1.134） -		0.694（0.154-3.134） --		1.000（0.206-4.845） --		0.725（0.161-3.270） --	0.694（0.418-1.152） --
PCR-RFLP	1	262/270	- 0.152		0.635		1.000		0.675	0.158
	1	3221/46	0.999 （ 0.935-1.067 ）		0.970 （ 0.847-1.110）		1.049 （ 0.934-1.177 ）		1.029 （ 0.923-1.148 ）	0.971 （ 0.872-1.080 ）
TaqMan	0	43	0.225 0.982		0.263 0.658		0.189 0.419		0.129 0.604	0.649 0.586
		1125/13	1.111 （ 0.748-1.651 ）		1.277 （ 0.569-2.863 ）		1.358 （ 0.753-2.451 ）		1.290 （ 0.664-2.509 ）	1.087 （ 0.652-1.812 ）
ARMS-PCR	5	82	0.000 0.601		0.000 0.553		0.013 0.309		0.001 0.453	0.000 0.749
		2164/25	1.045 （ 0.959-1.138 ）		1.105 （ 0.929-1.314 ）		1.084 （ 0.931-1.262 ）		1.088 （ 0.943-1.256 ）	0.984 （ 0.724-1.337 ）
PCR	6	83	0.161 0.315		0.409 0.261		0.508 0.298		0.990 0.249	0.003 0.916
		2461/17	1.129 （ 1.035-1.232 ）		1.265 （ 1.063-1.506 ）		1.081 （ 0.926-1.262 ）		1.144 （ 0.989-1.323 ）	1.203 （ 1.047-1.382 ）
MassARRAY	3	66	0.625 0.006		0.676 0.008		0.395 0.321		0.589 0.070	0.333 0.009
			1.553 （ 0.760-3.175 ）		2.454 （ 0.651-9.254 ）		2.073 （ 1.293-3.323 ）		2.201 （ 0.915-5.294 ）	1.480 （ 0.569-3.850 ）
real-time PCR	2	318/245	0.004 0.228		0.006 0.185		0.334 0.002		0.043 0.078	0.007 0.422
Quality of study										
	1	2904/42	0.909 （ 0.780-1.060 ）		0.932 （ 0.675-1.288 ）		1.214 （ 0.896-1.645 ）		1.066 （ 0.800-1.422 ）	0.817 （ 0.670-0.996 ）
Low	1	05	0.001 0.223		0.002 0.671		0.003 0.211		0.003 0.663	0.008 0.046
	1	6647/66	1.162 （ 1.072-1.261 ）		1.284 （ 1.104-1.493 ）		1.133 （ 1.036-1.239 ）		1.172 （ 1.077-1.276 ）	1.214 （ 1.065-1.383 ）
High	6	84	0.007 0.000		0.041 0.001		0.527 0.006		0.299 0.000	0.007 0.004
Sample size										
	1	2762/45	1.052 （ 0.911-1.215 ）		1.194 （ 0.897-1.590 ）		1.337 （ 1.167-1.532 ）		1.280 （ 1.052-1.557 ）	0.966 （ 0.777-1.200 ）
Small	8	12	0.000 0.488		0.000 0.223		0.095 0.000		0.013 0.013	0.000 0.752
		6789/63	1.065 （ 0.981-1.157 ）		1.073 （ 0.970-1.188 ）		1.015 （ 0.928-1.111 ）		1.036 （ 0.951-1.127 ）	1.112 （ 0.987-1.253 ）
Large	9	77	0.014 0.133		0.151 0.172		0.621 0.743		0.330 0.419	0.038 0.080
			OR(95%CI) Ph P		OR(95%CI) Ph P		OR(95%CI) Ph P		OR(95%CI) Ph P	OR(95%CI) Ph P
Variables			T vs. C		TT vs. CC		TC vs. CC		TT+TC vs. CC	TT vs. TC+CC
819T/C rs1800871										
	2	5867/77	1.104 （ 0.992-1.230 ）		1.205 （ 0.991-1.465 ）		1.047 （ 0.911-1.204 ）		1.097 （ 0.950-1.267 ）	1.161 （ 0.999-1.350 ）
Total	3	80	0.000 0.071		0.002 0.061		0.001 0.516		0.000 0.208	0.013 0.052
Cancer Type										

			1.394 （ 1.191-1.631 ）	1.761 （ 1.282-2.418 ）	1.418 （ 1.043-1.927 ）	1.587 （ 1.192-2.112 ）	1.455 （ 1.166-1.816 ）
bladder	2	614/785	0.260 0.000	0.045 0.000	0.512 0.026	0.883 0.002	0.135 0.001
			1.242 （ 0.759-2.031 ）	1.645 （ 0.597-4.535 ）	0.946 （ 0.648-1.380 ）	1.052 （ 0.744-1.488 ）	1.530 （ 1.053-2.224 ）
renal	4	267/970	0.012 0.388	0.036 0.336	0.338 0.773	0.108 0.774	0.057 0.026
	1	4986/59	1.045 （ 0.940-1.163 ）	1.013 （ 0.884-1.161 ）	1.015 （ 0.868-1.186 ）	1.039 （ 0.891-1.212 ）	1.032 （ 0.914-1.164 ）
prostate	7	53	0.001 0.413	0.060 0.854	0.001 0.853	0.000 0.621	0.249 0.614
Ethnicity							
	1	1792/25	1.218 （ 1.040-1.425 ）	1.359 （ 1.027-1.797 ）	1.208 （ 0.913-1.598 ）	1.293 （ 0.989-1.691 ）	1.256 （ 1.098-1.436 ）
Asian	1	71	0.004 0.014	0.034 0.032	0.009 0.186	0.006 0.060	0.055 0.001
		2020/19	1.129 （ 1.018-1.252 ）	1.328 （ 1.026-1.717 ）	1.097 （ 0.959-1.256 ）	1.109 （ 0.897-1.372 ）	1.272 （ 0.990-1.634 ）
Caucasion	7	80	0.057 0.022	0.474 0.031	0.066 0.176	0.044 0.338	0.659 0.060
			0.899 （ 0.730-1.107 ）	0.801 （ 0.520-1.232 ）	0.934 （ 0.684-1.275 ）	0.898 （ 0.670-1.203 ）	0.830 （ 0.557-1.235 ）
African	2	255/754	0.406 0.316	0.416 0.313	0.494 0.665	0.416 0.471	0.556 0.357
		1791/24	0.913 （ 0.718-1.160 ）	1.016 （ 0.552-1.870 ）	0.847 （ 0.742-0.966 ）	0.842 （ 0.743-0.955 ）	1.098 （ 0.607-1.988 ）
Mixed	3	03	0.045 0.455	0.026 0.959	0.321 0.014	0.173 0.007	0.026 0.756
Source of control							
	1	3368/43	1.153 （ 0.997-1.334 ）	1.315 （ 0.979-1.768 ）	1.054 （ 0.952-1.166 ）	1.151 （ 0.973-1.360 ）	1.209 （ 0.953-1.533 ）
PB	1	77	0.001 0.056	0.009 0.069	0.282 0.313	0.035 0.100	0.029 0.118
	1	2499/33	1.057 （ 0.893-1.253 ）	1.122 （ 0.852-1.478 ）	1.015 （ 0.791-1.301 ）	1.054 （ 0.823-1.349 ）	1.211 （ 1.054-1.391 ）
HB	2	31	0.000 0.519	0.023 0.411	0.000 0.909	0.000 0.678	0.084 0.007
Method							
			1.035 （ 0.975-1.098 ）	1.056 （ 0.957-1.166 ）	0.985 （ 0.910-1.067 ）	1.009 （ 0.961-1.059 ）	1.097 （ 0.961-1.253 ）
PCR-RFLP	6	822/832	0.109 0.261	0.093 0.279	0.551 0.715	0.282 0.727	0.187 0.170
	1	4027/49	0.996 （ 0.904-1.097 ）	0.981 （ 0.852-1.128 ）	0.979 （ 0.894-1.072 ）	0.987 （ 0.905-1.077 ）	0.995 （ 0.861-1.151 ）
TaqMan	0	22	0.001 0.939	0.091 0.783	0.012 0.646	0.002 0.775	0.339 0.951
		878/115	1.084 （ 0.974-1.205 ）	1.119 （ 1.024-1.223 ）	1.122 （ 0.931-1.353 ）	1.079 （ 0.965-1.207 ）	1.155 （ 1.026-1.299 ）
ARMS-PCR	4	9	0.032 0.140	0.147 0.013	0.002 0.226	0.004 0.181	0.102 0.017
			1.150 （ 1.058-1.250 ）	1.420 （ 0.574-3.515 ）	1.116 （ 0.932-1.336 ）	1.085 （ 1.007-1.168 ）	1.478 （ 0.582-3.751 ）
PCR	3	140/795	0.235 0.001	0.038 0.448	0.994 0.232	0.669 0.032	0.043 0.441

Quality of study							
		1002/21	1.310 （ 1.062-1.616 ）	1.134 （ 1.053-1.220 ）	1.136 （ 1.016-1.271 ）	1.080 （ 1.036-1.126 ）	1.175 （ 1.063-1.299 ）
Low	5	15	0.021 0.012	0.0653 0.001	0.042 0.025	0.096 0.000	0.145 0.002
	1	4865/55	1.039 （ 0.928-1.162 ）	1.068 （ 0.935-1.220 ）	0.970 （ 0.927-1.016 ）	1.000 （ 0.947-1.056 ）	1.046 （ 0.949-1.154 ）
High	8	93	0.000 0.509	0.016 0.331	0.055 0.203	0.006 0.994	0.089 0.365
Sample size							
	1	1903/29	1.067 （ 0.999-1.138 ）	1.101 （ 0.987-1.227 ）	1.047 （ 0.966-1.135 ）	1.043 （ 0.989-1.101 ）	1.098 （ 1.002-1.203 ）
Small	6	45	0.009 0.053	0.023 0.084	0.021 0.267	0.009 0.121	0.086 0.045
		3964/47	1.018 （ 0.911-1.139 ）	1.038 （ 0.852-1.264 ）	0.992 （ 0.901-1.092 ）	1.000 （ 0.914-1.095 ）	1.080 （ 0.885-1.320 ）
Large	7	63	0.000 0.749	0.013 0.711	0.004 0.865	0.000 0.998	0.029 0.448