IVYSPRING INTERNATIONAL PUBLISHER

Journal of Cancer

2019; 10(4): 1023-1031. doi: 10.7150/jca.26472

Research Paper

The Role of Polymorphisms in Genes of PI3K/Akt Signaling Pathway on Prostate

Wei Xu[1,2#]; Zhihao Ni[3#]; Meng Zhang[1]; Jinbo Chen[4]; Li Zhang[1]; Song Wu[5]✉; Chaozhao Liang[1]✉

1. Department of Urology, The First Affiliated Hospital of Anhui Medical University, Hefei, 230000, China
2. Department of Blood Transfusion, The First Affiliated Hospital of Anhui Medical University, Hefei, 230000, China;
3. Trauma Department of Orthopedics, The Third Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230000, China;
4. Department of Urology, Xiangya Hospital, Central South University, NO.87 Xiangya Road, Changsha, Hunan, 410008, China
5. Shenzhen Following Precision Medical Institute, Shenzhen Luohu Hospital Group, Shenzhen, 518000, China

# These authors contributed equally to the work.

✉ Corresponding authors: Chaozhao Liang, Department of Urology, the First Affiliated Hospital of Anhui Medical University, Hefei 230022, China. Tel.: +86 55162923440; **Email address:** liang_chaozhao@ahmu.edu.cn and Song Wu, Shenzhen Following Precision Medical Institute, Shenzhen Luohu Hospital Group, Shenzhen 518000, China. Tel.: +86 755 8220 3083; **Email address:** doctor_wusong@126.com

Received: 2018.04.04; Accepted: 2019.01.09; Published: 2019.01.29

Abstract

Background and Objective: Increasing evidence suggested that polymorphisms in genes of PI3K/Akt pathway were closely related to prostate cancer (PCa) risk. Nevertheless, these results are controversial and inconclusive. Here, we conducted a comprehensive updated meta-analysis and systematic review to precisely illustrate the association between polymorphisms in genes of PI3K/Akt signaling pathway and PCa risk.

Materials and Methods: The gene set of PI3K/Akt pathway was referenced from the Kyoto Encyclopedia of Genes and Genomes (KEGG) website. Relevant studies were identified by the systematically researching on PubMed, Web of Science and Google Scholar databases up to October 1, 2017. The odds ratios (ORs) with a corresponding 95% confidential intervals (95%CIs) were applied to test their associations. All the analyses were conducted by using Stata 12.0 (Stata Corporation, USA).

Results: Finally, 38 articles comprising 62 case-control studies were enrolled for 13 polymorphisms in genes of PI3K/Akt pathway. However, overall results failed to present a positive association between polymorphisms in genes of PI3K/Akt pathway and PCa risk. Nevertheless, in the subgroup analysis by ethnicity, we identified that *IL-6*-rs1800795 polymorphism was associated with an increased risk of PCa for Caucasian individuals in dominant model (MM + MW vs. WW: OR = 1.245, 95%CI = 1.176-1.318, $P < 0.001$).

Conclusion: Our work suggests that polymorphisms in genes of PI3K/Akt Signaling Pathway are not risk factor for PCa. Further well-designed studies with larger samples and precise designs are demanded to corroborate our findings.

Key words: PI3K/Akt; polymorphism; prostate cancer

Introduction

For males worldwide, prostate cancer (PCa) has the second highest incidence of all cancers. Each year, approximately 238,590 new cases and 29,720 deaths are reported according to cancer statistics, 2013. In view of the anfractuous pathogenesis of PCa, interconnected cell signaling pathways and transmissions which manipulates the survival, evolution and apoptosis of cells[1-3], would provide us new inspirations of the prevention and treatment of PCa patients.

Among diverse pathways, genes encompassed in phosphoinositide 3-kinase (PI3K)/Akt signaling pathway, such as toll-like receptor-4 (*TLR4*), vascular endothelial growth factor (*VEGF*), interleukin 6 (*IL-6*), insulin receptor substrate 1 (*IRS1*) and insulin-like growth factor 1 (IGF1), appear with more common mutations or amplifications in PCa (**Figure S1** and **Figure S2**). PI3K is a phosphatidylinositol kinase which is encoded by the *PIK3CA* gene. It consists of a catalytic subunit p110 and regulatory subunit p85.

Akt is a cytoplasmic serine-threonine protein kinase which promotes the progression of cell cycle and inhibits cell apoptosis. The PI3K/Akt signaling pathway is implicated in different cellular functions, including survival, growth, proliferation, metabolism and angiogenesis. Currently, the relationships between polymorphisms in genes of PI3K/Akt signaling pathway and PCa risk have been an area of intense investigations but with mixed results[4,5]. For instance, Balistreri *et al.*[6] pointed out that there existed a significant association between polymorphisms in *TRL4* and an increased risk of PCa, a result consistent with both Wang *et al.*'s[7] and Chen *et al.*'s[8] work. However, Shui *et al.*[9] has conducted a case-control study comprising 1,267 controls and 1,286 PCa cases and found that genetic variation across *TLR4* alone is not strongly associated with PCa risk. As for polymorphisms in *IGF1*, Schildkraut *et al.*[10] revealed the significant association between genetic polymorphisms in *IGF1* and PCa risk among Black and White men. On the contrary, Neuhausen *et al.*[11] failed to find any positive connection between *IGF1* polymorphisms and PCa risk. In addition, for *IL-6*-rs1800795, both Kesarwani *et al.*[12] and Mandal *et al.*'s[13] studies supported the role of *IL-6*-rs1800795 polymorphism in PCa, while the result was inconsistent with Bao *et al.*'s[14] work.

Hence, previous studies had presented inconsistent views between polymorphisms encompassed in genes of PI3K/Akt signaling pathway and PCa risk. Considering that, we conducted the current updated meta-analysis in order to precisely evaluate their associations on the foundation of all available eligible studies, providing with convincible evidence for the prevention and/or targeted therapy for PCa patients.

Material and Methods

Acquisition of the PI3K/Akt Pathway Gene Set

The gene set of PI3K/Akt pathway was referenced to the Kyoto Encyclopedia of Genes and Genomes (KEGG) website (http://www.kegg.jp/kegg-bin/show_pathway?hsa04151). The gene set was originally provided via the KEGG signaling database, and encompassed the following 101 genes: *ANGPT2*, *ANGPT4*, *IL2RB*, *CD19*, *COL1A*, *IL3*, *COL2A*, *IL3RA*, *COL4A*, *COL6A*, *IL6*, *COL9A*, *CSF1*, *CSF1R*, *CSF3*, *CSF3R*, *EFNA*, *EGF*, *EGFR*, *EPHA2*, *EPO*, *EPOR*, *FGF*, *FGF1*, *FGF2*, *FGFR1*, *FGFR2*, *FGFR3*, *FGFR4*, *FLT1*, *FLT4*, *GH*, *GHR*, *IL6R*, *GRB2*, *HGF*, *HRAS*, *IFNA*, *IFNAR1*, *IFNAR2*, *IFNB*, *IGF1*, *IGF1R*, *IGH*, *IL2*, *IL2RA*, *IL2RG*, *IL4*, *IL4R*, *IL7*, *IL7R*, *INS*, *INSR*, *IRS1*, *JAK1*, *JAK2*, *JAK3*, *KDR*, *KIT*, *KITLG*, *KRAS*, *LAMA1_2*, *LAMA3_5*, *LAMA4*, *LAMB1*, *LAMB2*, *LAMB3*, *LAMB4*, *LAMC1*, *LAMC2*, *MAP2K1*, *MAP2K2*, *MAPK1*, *MAPK2*, *MAPK3*, *MET*, *NGFA*, *NGFB*, *NGFR*, *NRAS*, *OSM*, *OSMR*, *PDGFA*, *PDGFB*, *PDGFC_D*, *PDGFRA*, *PDGFRB*, *PGF*, *PIK3AP1*, *PRL*, *PRLR*, *RAC1*, *RAF1*, *SOS*, *SYK*, *TEK*, *TLR2*, *TLR4*, *VEGFA*, *VEGFB* and *VEGFC-D*.

Study Description

To evaluate the connections between polymorphisms in genes of PI3K/Akt pathway and PCa risk, we conducted the present study by combining all accessible studies together from diverse databases, including Web of Science, PubMed, and China National Knowledge Infrastructure (CNKI) databases. The integrated keywords were: ('genes' OR 'abbreviations of genes') AND ('cancer' OR 'tumor' OR 'carcinoma' OR 'neoplasms') AND ('polymorphism' OR 'mutation' OR 'variant' OR 'SNP' OR 'genotype'). At the same time, we used the integrated keywords (Gene_ID & prostate cancer) to search on Google, and performed the hand screening from all highly connected results. Besides, extra studies were collected via the reference lists of the identified studies. The final date of retrieval was in October 1, 2017. The whole studies in the analysis were firstly published in the primary literature with no reproduction in other studies.

Inclusion and Exclusion Criteria

The inclusion criteria in this analysis were: (1) the cases were PCa patients and the controls were no history of cancers; 2) cohort studies or case-control studies concerning the relationships between polymorphisms in genes of PI3K/Akt signaling pathway and PCa risk; (3) the raw data of genotype frequency can be extracted. The exclusion criteria were as follows: (1) the raw data were not accessible; (2) case-only studies that didn't have control groups; (3) family-based association studies; and (4) Review papers.

Data Extraction

All of the data extraction work should be completed independently by 2 of the authors according to the prelisted inclusion criteria. And the arguments should be solved by another expert(s). You didn't mention the procedure in your article. In addition, we extracted data from each case-control study, including genotype frequencies, name of first author; year of publication; ethnicity and number of cases and controls. In addition, we used The Newcastle-Ottawa Scale (NOS) to evaluate the quality of enrolled studies.

Statistical analysis

The meta-analysis was conducted to assess the associations between polymorphisms in genes of

PI3K/Akt pathway and PCa risk. Hardy-Weinberg equilibrium (HWE) in the control group was tested[15]. To make a more comprehensive meta-analysis, five genetic models were adopted, including allele contrast (M vs. W), codominant (MM vs. WW and MW vs. WW), dominant (MM + MW vs. WW) and recessive models (MM vs. MW + WW). The impact of relationship was evaluated by odds ratio (OR) with a corresponding 95% confidential intervals (95%CI). What's more, when the heterogeneity (P > 0.1 as the standard) [16] was assessed, the I^2-based Q statistic was used (I^2 = 0–25%: no heterogeneity; I^2 = 25%-50%: moderate heterogeneity; I^2 = 50%-75%: large heterogeneity; I^2 = 75%-100%: extreme heterogeneity) [17], which represented the weighted sum of the squared difference between the overall effect size and the effect size from every study. When I^2 > 50% or P_Q ≤ 0.1, substantial heterogeneity was existed, then, a random-effects model was used; otherwise, the fixed-effects model was be applied. It has been recognized that when results of the component studies differ among themselves, random effects incorporate an estimate of the inter-study variance and provide wider 95%CIs[18]. The analyses were conducted using Stata 12.0 (Stata Corporation, USA), and all P values were two-tailed.

Results

Main Characteristics of the Enrolled Studies

After initial screening, there were 1,166 results related to the search words enrolled. After reading the important information such as the titles and abstracts, 51 potential eligible studies were selected for next step full-text view. When a further screening was conducted, 13 of these studies were excluded for not associated with PCa risk. Finally, 38 articles with 62 case-control studies were left for data extraction (**Table 1**) [12,19-54].

Of them, there were 2,170 cases and 1,587 controls for *TLR4*-rs1927914 polymorphism (from three studies), 3,842 cases and 3,143 controls for *TLR4*-rs10759932 polymorphism (from 4 studies), 3,508 cases and 2,960 controls for *TLR4*-rs2149356 polymorphism (from 4 studies), 1,467 cases and 1,551 controls for *TLR4*-rs4986790 polymorphism (from 4 studies), 3,985 cases and 3,438 controls for *TLR4*-rs11536889 polymorphism (from 5 studies), 2,380 cases and 2,357 controls for *TLR4*-rs7873784 polymorphism (from 3 studies), 632 cases and 685 controls for *VEGF*-rs833061 polymorphism (from three studies), 1,511 cases and 821 controls for *VEGF*-rs1570360 polymorphism (from three studies), 1,243 cases and 1,620 controls for *IRS1*-rs1801278 polymorphism (from four studies), 2,289 cases and 2,114 controls for *FGFR4*-rs351855 polymorphism (from three studies), 1,805 cases and 3,235 controls for *IL-6*-rs1800796 polymorphism (from three studies), 10,625 cases and 12,353 controls for *IL-6*-rs1800795 polymorphism (from eight studies), 2,217 cases and 2,471 controls for *IGF1*-(CA) 19 polymorphism (from seven studies), respectively. In addition, the study selection processes for these polymorphisms were showed in **Figure S3-8**.

Furthermore, of the 62 case-control studies, 41 sets were performed on Caucasian populations, seven sets on Asian populations, six sets on African populations, and the other eight were based on mixed ethnic groups (including at least one race). Controls of 42 studies were population-based (P-B), while the other 20 studies were hospital-based (H-B). The quality of the enrolled studies was assessed by NOS and presented in **Table S1**.

Quantitative synthesis

Results of the association between polymorphisms in genes of PI3K/Akt pathway and PCa risk were showed in **Table 2 and Table S2.** However, the pooled results suggested negative associations between all the 13 polymorphisms in six genes of PI3K/Akt signaling pathway and PCa risk.

However, in the subgroup analysis by ethnicity, we found that *IL-6*-rs1800795 polymorphism was associated with an increased risk of PCa in dominant model for Caucasian population (MM + MW vs. WW: OR=1.245, 95%CI = 1.176-1.318, P < 0.001, **Figure 1A**). Furthermore, in the subgroup analysis by source of control, we also found an increased risk of PCa for P-B groups in dominant model (MM + MW vs. WW; OR = 1.246, 95%CI = 1.177-1.319, P < 0.001, **Figure 1B**). Although subgroup analyses were also conducted for other polymorphisms in genes of PI3K/Akt signaling pathway, negative results were found.

Sensitivity analysis and Publication bias

Sensitivity analysis was conducted by excluding one single study each time, and no evidence was observed suggesting pooled ORs shift (**Table S3**). In addition, we used Begg's funnel plot and Egger's regression test to assess potential publication bias. As for *TLR4*-rs1927914, *TLR4*-rs10759932, *TLR4*-rs2149356, *TLR4*-rs4986790, *TLR4*-rs11536889, *TLR4*-rs7873784, *VEGF*-rs833061, *VEGF*-rs1570360, *IRS1*-rs1801278, *FGFR4*-rs351855, *IL-6*-rs1800796, *IGF1*-(CA)19 polymorphisms, no evidence of publication bias was identified by viewing the shape of Begg's funnel plot, which was further validated by Egger's regression test. However, for *IL-6*-rs1800795 polymorphism, potential publication bias was existed (P = 0.016) **(Table S4)**. In that case, we further

conducted sensitivity analysis by using the trim and fill method[55], and imputed studies provide a symmetrical funnel plot (data not shown), indicating publication bias was not existed.

Table 1. Characteristics of the enrolled studies.

Gene	SNP	First Author	Year	Genotyping Method	Ethnicity	Source of Control	Case			Control			
							WW	WM	MM	WW	WM	MM	Y(HWE)
TLR4	rs1927914	Chen *et al.*	2005	MassARRAY	Caucasian	P-B	297	301	60	290	288	91	Y
	rs1927914	Zheng *et al.*	2004	MassARRAY	Caucasian	P-B	625	596	154	341	354	81	Y
	rs1927914	Song *et al.*	2009	PCR-RFLP	Asian	H-B	69	54	14	48	87	7	N
	rs10759932	Chen *et al.*	2005	MassARRAY	Caucasian	P-B	511	155	11	472	197	12	Y
	rs10759932	Zheng *et al.*	2004	MassARRAY	Caucasian	P-B	991	350	34	571	194	13	Y
	rs10759932	Shui *et al.*	2012	MALDI-TOF	Caucasian	P-B	897	260	27	908	244	27	N
	rs10759932	Cheng *et al.*	2007	Sequencing	Caucasian	H-B	370	117	119	358	143	4	N
	rs2149356	Chen *et al.*	2005	MassARRAY	Caucasian	P-B	320	286	61	305	275	91	N
	rs2149356	Zheng *et al.*	2004	MassARRAY	Caucasian	P-B	603	423	136	331	224	74	N
	rs2149356	Shui *et al.*	2012	MALDI-TOF	Caucasian	P-B	579	489	106	576	460	119	Y
	rs2149356	Cheng *et al.*	2007	Sequencing	Caucasian	H-B	197	223	85	210	213	82	N
	rs4986790	Chen *et al.*	2005	MassARRAY	Caucasian	P-B	588	66	3	605	59	5	N
	rs4986790	Cheng *et al.*	2007	TaqMan	Caucasian	H-B	439	66	1	456	48	2	Y
	rs4986790	Wang *et al.*	2009	TaqMan	Caucasian	P-B	230	24	0	216	35	0	Y
	rs4986790	Balistreri *et al.*	2010	PCR-RFLP	Caucasian	H-B	49	1	0	111	13	1	Y
	rs11536889	Chen *et al.*	2005	MassARRAY	Caucasian	P-B	515	167	10	513	159	15	Y
	rs11536889	Zheng *et al.*	2004	MassARRAY	Caucasian	P-B	1047	318	15	625	141	12	Y
	rs11536889	Shui *et al.*	2012	MALDI-TOF	Caucasian	P-B	909	202	32	897	291	27	Y
	rs11536889	Cheng *et al.*	2007	Sequencing	Caucasian	H-B	385	105	16	401	93	12	N
	rs11536889	Wang *et al.*	2009	TaqMan	Caucasian	P-B	178	79	7	175	71	6	Y
	rs7873784	Chen *et al.*	2005	MassARRAY	Caucasian	P-B	475	178	16	459	180	30	N
	rs7873784	Shui *et al.*	2012	MALDI-TOF	Caucasian	P-B	887	295	24	861	302	19	Y
	rs7873784	Cheng *et al.*	2007	Sequencing	Caucasian	H-B	362	130	13	346	146	14	Y
IL-6	rs1800796	Wang *et al.*	2009	TaqMan	Caucasian	P-B	233	19	1	225	25	0	Y
	rs1800796	Pierce *et al.*	2009	TaqMan	Caucasian	P-B	156	19	0	1740	192	2	Y
	rs1800796	Pierce *et al.*	2009	TaqMan	Mixed	P-B	37	2	1	251	41	6	N
	rs1800796	Sun *et al.*	2004	Microarray	Caucasian	P-B	1226	109	2	675	74	4	Y
	rs1800795	Mandal *et al.*	2014	PCR	Mixed	H-B	108	44	12	74	44	22	N
	rs1800795	Zhang *et al.*	2010	Sequenom	Mixed	P-B	80	86	27	100	75	22	Y
	rs1800795	Zabaleta *et al.*	2009	TaqMan	Caucasian	H-B	19	34	21	126	163	112	N
	rs1800795	Zabaleta *et al.*	2009	TaqMan	Mixed	H-B	10	2	3	41	10	6	N
	rs1800795	Dossus *et al.*	2010	GoldenGate	Caucasian	P-B	3594	3218	1125	3832	3402	274	N
	rs1800795	Wang *et al.*	2009	TaqMan	Caucasian	P-B	91	116	43	84	128	40	Y
	rs1800795	Moore *et al.*	2009	TaqMan	Caucasian	P-B	191	485	281	196	401	250	Y
	rs1800795	Pierce *et al.*	2009	TaqMan	Caucasian	P-B	48	96	31	648	805	305	N
	rs1800795	Pierce *et al.*	2009	TaqMan	Mixed	P-B	34	5	1	216	43	1	Y
	rs1800795	Kesarwani *et al.*	2008	PCR	Asia	H-B	102	84	14	103	87	10	Y
	rs1800795	Bao *et al.*	2008	TaqMan	Asia	P-B	136	0	0	120	0	0	N
	rs1800795	Michaud *et al.*	2006	TaqMan	Caucasian	P-B	170	223	91	230	293	90	Y
IGF1	(CA)19	Chu *et al.*	2006	Sequenom	Caucasian	P-B	75	28	21	73	76	25	Y
	(CA)19	Chu *et al.*	2006	Sequenom	Mixed	P-B	4	17	17	2	20	16	Y
	(CA)19	Neuhausen *et al.*	2005	PCR	Caucasian	H-B	78	86	29	107	124	32	Y
	(CA)19	Schildkraut *et al.*	2005	PCR	Mixed	P-B	20	39	35	28	33	20	Y
	(CA)19	Norihiko *et al.*	2005	PCR	Asian	H-B	155	130	18	289	172	20	Y
	(CA)19	Friedrichsen *et al.*	2005	PCR-RFLP	Mixed	P-B	73	289	219	64	237	219	Y
	(CA)19	Nam *et al.*	2003	PCR-RFLP	Mixed	P-B	64	230	189	103	253	192	Y
	(CA)19	Wenndy *et al.*	2007	PCR	Mixed	H-B	324	28	49	289	26	51	N
VEGF	rs833061	Fukuda *et al.*	2007	PCR-RFLP	Asian	H-B	143	103	24	132	97	23	Y
	rs833061	Onen *et al.*	2008	PCR-RFLP	Mixed	P-B	33	89	11	50	94	13	N
	rs833061	Lin *et al.*	2003	PCR-RFLP	Asian	H-B	60	32	4	43	72	4	N
	rs833061	Onen *et al.*	2008	PCR-RFLP	Caucasian	P-B	33	89	11	50	94	13	N
	rs1570360	Sfar *et al.*	2006	RFLP-PCR	Caucasian	H-B	58	37	6	36	50	14	Y
	rs1570360	Jacobs *et al.*	2008	TaqMan	Caucasian	P-B	557	489	126	210	194	54	Y
	rs1570360	McCarron *et al.*	2013	TaqMan	Caucasian	P-B	114	109	15	120	109	34	Y
IRS1	rs1801278	Andrea *et al.*	2011	PCR	Caucasian	H-B	56	5	0	106	12	1	Y
	rs1801278	Fall *et al.*	2008	PCR	Mixed	H-B	489	73	2	662	90	6	Y
	rs1801278	Li *et al.*	2013	PCR	Mixed	P-B	386	50	2	422	65	1	Y
	rs1801278	Neuhausen *et al.*	2005	PCR	Caucasian	P-B	118	50	12	160	81	14	Y
FGFR4	rs351855	FitzGerald *et al.*	2009	SNPlex™	Caucasian	P-B	587	544	123	631	496	124	Y
	rs351855	FitzGerald *et al.*	2009	SNPlex™	Mixed	P-B	104	39	3	60	18	2	Y
	rs351855	Lee *et al.*	2010	TaqMan	Caucasian	P-B	183	182	32	235	167	37	Y
	rs351855	Zhiyong *et al.*	2010	PCR	Asian	H-B	133	196	163	67	152	125	Y

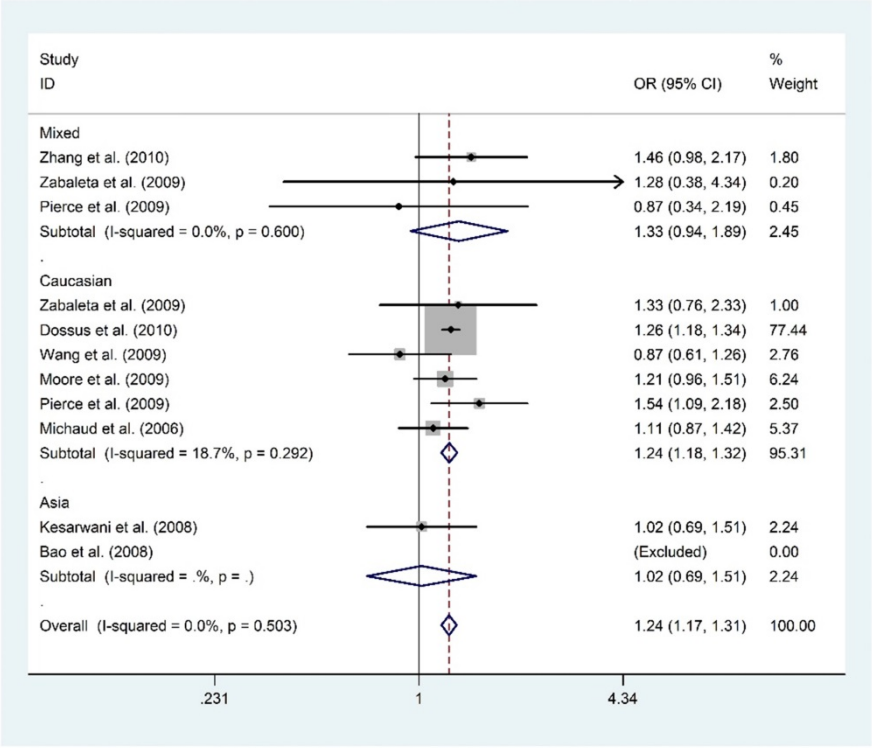
Note: Hardy-Weinberg equilibrium (HWE); population-based (P-B); hospital-based (H-B); Mixed: more than two descendants; W: wild allele; M: mutated allele; PCR: Polymerase chain reaction; RFLP-PCR: restriction fragment length polymorphism-Polymerase chain reaction

Table 2. Details of the association between *IL-6*-rs1800795 polymorphism and prostate cancer risk.

Comparison	Subgroup	N	P_H	P_Z	Random	Fixed
M vs. W	Overall	11	0.000	0.207	1.108 (0.945-1.300)	1.347 (1.292-1.403)
M vs. W	Asia	1	1.000	0.692	1.065 (0.780-1.453)	1.065 (0.780-1.453)
M vs. W	Caucasian	6	0.000	0.071	1.171 (0.986-1.391)	1.370 (1.313-1.429)
M vs. W	H-B	4	0.020	0.772	0.946 (0.648-1.380)	0.926 (0.765-1.122)
M vs. W	P-B	7	0.000	0.038	1.188 (1.010-1.397)	1.371 (1.315-1.431)
M vs. W	N	5	0.000	0.528	1.106 (0.809-1.514)	1.430 (1.365-1.499)
M vs. W	Y	6	0.710	0.053	1.090 (0.999-1.190)	1.090 (0.999-1.190)
WM vs. WW	Overall	11	0.103	0.269	1.080 (0.951-1.227)	1.033 (0.975-1.096)
WM vs. WW	Asia	1	1.000	0.903	0.975 (0.650-1.463)	0.975 (0.650-1.463)
WM vs. WW	Caucasian	6	0.061	0.177	1.112 (0.953-1.296)	1.036 (0.975-1.100)
WM vs. WW	H-B	4	0.380	0.678	0.941 (0.709-1.250)	0.943 (0.716-1.243)
WM vs. WW	P-B	7	0.054	0.156	1.116 (0.959-1.299)	1.038 (0.978-1.102)
WM vs. WW	N	5	0.048	0.512	1.101 (0.826-1.466)	1.022 (0.958-1.089)
WM vs. WW	Y	6	0.353	0.217	1.088 (0.935-1.266)	1.092 (0.950-1.256)
MM vs. WW	Overall	11	0.000	0.211	1.411 (0.823-2.421)	2.609 (2.359-2.885)
MM vs. WW	Asia	1	1.000	0.428	1.414 (0.600-3.329)	1.414 (0.600-3.329)
MM vs. WW	Caucasian	6	0.000	0.214	1.529 (0.783-2.986)	2.778 (2.502-3.085)
MM vs. WW	H-B	4	0.043	0.960	0.982 (0.473-2.036)	0.912 (0.606-1.372)
MM vs. WW	P-B	7	0.000	0.119	1.671 (0.877-3.184)	2.790 (2.513-3.097)
MM vs. WW	N	5	0.000	0.464	1.431 (0.548-3.734)	3.601 (3.177-4.082)
MM vs. WW	Y	6	0.682	0.025	1.233 (1.028-1.479)	1.231 (1.027-1.477)
WM + MM vs. WW	Overall	11	0.047	0.040	1.147 (1.006-1.308)	1.228 (1.162-1.298)
WM + MM vs. WW	Asia	1	1.000	0.920	1.020 (0.689-1.510)	1.020 (0.689-1.510)
WM + MM vs. WW	Caucasian	6	0.292	**<0.001**	1.224 (1.113-1.346)	1.245 (1.176-1.318)
WM + MM vs. WW	H-B	4	0.114	0.505	0.936 (0.631-1.390)	0.917 (0.710-1.184)
WM + MM vs. WW	P-B	7	0.296	**<0.001**	1.227 (1.117-1.349)	1.246 (1.177-1.319)
WM + MM vs. WW	N	5	0.017	0.359	1.150 (0.853-1.552)	1.252 (1.178-1.331)
WM + MM vs. WW	Y	6	0.500	0.082	1.124 (0.985-1.283)	1.124 (0.985-1.282)
MM vs. WM + WW	Overall	11	0.000	0.315	1.331 (0.762-2.323)	2.292 (2.093-2.509)
MM vs. WM + WW	Asia	1	1.000	0.402	1.430 (0.620-3.300)	1.430 (0.620-3.300)
MM vs. WM + WW	Caucasian	6	0.000	0.366	1.388 (0.682-2.826)	2.404 (2.189-2.640)
MM vs. WM + WW	H-B	4	0.087	0.866	0.949 (0.516-1.746)	0.899 (0.618-1.308)
MM vs. WM + WW	P-B	7	0.000	0.218	1.543 (0.774-3.074)	2.429 (2.211-2.669)
MM vs. WM + WW	N	5	0.000	0.585	1.323 (0.485-3.606)	3.390 (3.015-3.812)
MM vs. WM + WW	Y	6	0.449	0.171	1.114 (0.956-1.298)	1.112 (0.955-1.296)

Note: Hardy-Weinberg equilibrium (HWE); P-B: population-based; H-B: hospital-based; Y: Studies conformed to HWE; N: studies did not conform to HWE; Mixed: more than two descendant; *P value less than [0.05/ (5*13)] means statistically significant.

A



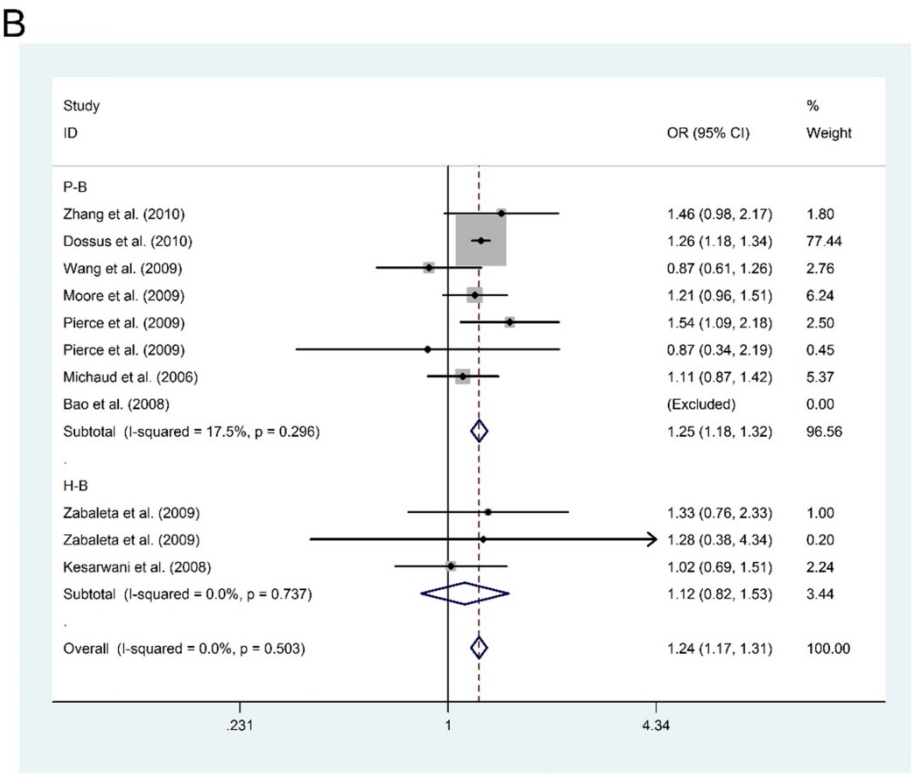


Figure 1. Forest plots of the association between *IL-6*-rs1800795 polymorphism and prostate cancer risk. Subgroup analysis by ethnicity (A) and source of control (B).

Discussion

Recently, enormous studies suggested that polymorphisms in genes of PI3K/Akt pathway may play an important role in the prevention, diagnosis and treatment of PCa. For example, *TLR4* is the main component of *TLRs* and has been positively investigated in inflammation and cancer. Previous studies had confirmed that two polymorphisms in *TLR4* (rs4986790 and rs4986791) owned susceptibility to various type of cancers, including PCa[56]. *VEGF* is the most significant regulator of angiogenesis in human, and it plays a significant role in the occurrence and development of PCa[49,50]. It had been identified that there were many genetic variants in the *VEFG* gene[57], but the conclusions were remained inconsistent[23,52-57]. The *IRS1* gene Gly972Arg (rs1801278) polymorphisms had been found a significant association with increased cancer risk[58]. *In vitro* studies have proved that the *IRS1* gene rs1801278 polymorphism impaired insulin-stimulated signaling pathway, especially through the PI3-kinase pathway[59]. What's more, as a docking protein for the insulin-like growth factor receptor 1 (IGF1R) [60,61], IRS1 controls IGF-1 mediated cell growth and survival[60]. Thus the polymorphisms of *IGF-1* gene also related to the cancer risks including PCa[61]. Fibroblast growth factor receptor 4 (FGFR4) is one member of the family of fibroblast growth factor receptors (FGFR1-4), which displays complicated biological activities such as angiogenic and mitogenic activity. Previous study had presented that its gene polymorphism was related to PCa risks[62]. The human *IL-6* gene encodes IL-6, a cytokine which adjusts the level of inflammation. Two polymorphisms on the promoter region of IL-6, rs1800795 (-174G/C) and rs1800796 (-572C/G) have been identified to be associated with IL-6 production[63]. And these association with risks of cancer have been published in a previous meta-analysis[64,65]. Furthermore, although these studies and meta-analysis provided some clues for separate polymorphisms in one or more genes of PI3K/Akt pathway and PCa risk, these results were not fully consistent, or even contradictory at sometimes. Therefore, we performed current meta-analysis in order to provide a comprehensive accurate assessment of the associations of these polymorphisms in genes of PI3K/Akt pathway with PCa risk. To the best of our knowledge, this is the first pooled study that analyzed the associations between 13 polymorphisms in six pivotal genes of PI3K/Akt pathway and PCa risk. Meanwhile, further analyses were conducted in different subgroups to explore the potential associations or heterogeneity sources.

Nevertheless, overall results revealed that none of these polymorphisms was associated with PCa risk. Then, we performed subgroup analysis based on ethnicity, source of control (population-based or

hospital-based) and HWE status (conform or not conform). For *IL-6*-rs1800795 polymorphism, when the stratification analysis was conducted by ethnicity, we found that a statistically significant increased risk of PCa was identified in the dominant model for Caucasians. However, in the meta-analysis conducted by *Liu et al*.[66], they did not reveal a significant connection between *IL-6*-rs1800795 polymorphism and PCa risk in Caucasian. For other polymorphisms, null association was uncovered when the stratified analyses were conducted based on ethnicity, source of control or HWE status.

Although we were surprised by these negative results, the high quality of these included studies and the substantial amount of data strengthened the possibility that the lack of association was not caused by chance. For those comparisons that did not exhibit a statistically significant association, may be as a result of the characteristics of low-penetrance genes. Moreover, although these polymorphisms assessed were appropriate candidates, they only account for some of the factors, and ignored other factors such as obesity, diet and environment. We summarized the advantages of current work. Firstly, although many meta-analyses provided some clues for separate polymorphisms in one or more genes of PI3K/Akt pathway and PCa risk, the current one provide a more comprehensive accurate assessment of the associations of all available polymorphisms in genes of PI3K/Akt pathway with PCa risk. To the best of our knowledge, this is the first pooled study that analyzed the associations between 13 polymorphisms in six pivotal genes of PI3K/Akt pathway and PCa risk. Secondly, we applied classic formula to adjust the *P*-values, which removed most of the marginal or false-positive *P*-values, making the final pool results more convincing. Thirdly, we found *IL-6*-rs1800795 polymorphism could be served as a risk prediction marker for Caucasian PCa patients. Our results provided some clues for the future clinical research that polymorphisms in genes of this pathway may not suitable for high-risk prostate cancer patients' screening. There are also several deficiencies that should be addressed. Firstly, other factors such as the density of prostate-specific antigen (PSA), living conditions and histological types, the stage and grades of PCa should be included to get more precise results. Secondly, for many polymorphisms of these inclusive genes, relatively small samples were included for the assessment, such as rs1927914 polymorphism. Finally, we ignored that there were many individual characters such as age, obesity, alcohol, consumption and other lifestyle risk factors which could influence our conclusions.

Overall, our meta-analysis provided no statistically significant association between the 13 polymorphisms in six genes of PI3K/Akt signaling pathway and PCa risk. However, a significantly increased risk of PCa in Caucasian individuals was identified for *IL-6*-rs1800795 polymorphism in the dominant model. Due to the limitations of these included studies, as well as the risk factors we ignored, further well-designed studies with larger samples are warranted to verify our findings.

Supplementary Material

Supplementary figures and tables.
http://www.jcancer.org/v10p1023s1.pdf

Acknowledgments

This study was supported by the Natural Science Foundation of Guangdong Province, China (2017A030313800).

Authors' contributions

W.X., M.Z., J.M. and Z.N. designed the studies and drafted the manuscript. M.Z. and Z.N. performed the statistical analysis. L.Z., S.W. and C.L. managed the experimental design, reviewed the manuscript. All authors read and approved the final manuscript.

Competing Interests

The authors have declared that no competing interest exists.

References

1. Zhao GY, Cai CK, Yang TT, Qiu XC, Liao B, Li W, et al. MicroRNA-221 Induces Cell Survival and Cisplatin Resistance through PI3K/Akt Pathway in Human Osteosarcoma. PloS one. 2013; 8: e53906.
2. Jung HY, Joo HJ, Park JK, Kim YH. The Blocking of c-Met Signaling Induces Apoptosis through the Increase of p53 Protein in Lung Cancer. Cancer Res Treat. 2012; 44: 251-61.
3. Shih MC, Chen JY, Wu YC, Jan YH, Yang BM, Lu PJ, et al. TOPK/PBK promotes cell migration via modulation of the PI3K/PTEN/AKT pathway and is associated with poor prognosis in lung cancer. Oncogene. 2012; 31: 2389-400.
4. Al-Azayzih A, Gao F, Goc A, Somanath PR. TGFbeta1 induces apoptosis in invasive prostate cancer and bladder cancer cells via Akt-independent, p38 MAPK and JNK/SAPK-mediated activation of caspases. Biochemical and biophysical research communications. 2012; 427: 165-70.
5. Park YH, Seo SY, Lee E, Ku JH, Kim HH, Kwak C. Simvastatin Induces Apoptosis in Castrate Resistant Prostate Cancer Cells by Deregulating Nuclear Factor-kappa B Pathway. J Urology. 2013; 189: 1547-52.
6. Balistreri CR, Caruso C, Carruba G, Miceli V, Campisi I, Listi F, et al. A pilot study on prostate cancer risk and pro-inflammatory genotypes: pathophysiology and therapeutic implications. Current pharmaceutical design. 2010; 16: 718-24.
7. Wang MH, Helzlsouer KJ, Smith MW, Hoffman-Bolton JA, Clipp SL, Grinberg V, et al. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. The Prostate. 2009; 69: 874-85.
8. Chen YC, Giovannucci E, Lazarus R, Kraft P, Ketkar S, Hunter DJ. Sequence variants of Toll-like receptor 4 and susceptibility to prostate cancer. Cancer Res. 2005; 65: 11771-8.
9. Shui IM, Stark JR, Penney KL, Schumacher FR, Epstein MM, Pitt MJ, et al. Genetic variation in the toll-like receptor 4 and prostate cancer incidence and mortality. The Prostate. 2012; 72: 209-16.
10. Schildkraut JM, Demark-Wahnefried W, Wenham RM, Grubber J, Jeffreys AS, Grambow SC, et al. IGF1 (CA)19 repeat and IGFBP3 -202 A/C genotypes and the risk of prostate cancer in Black and White men. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for

Cancer Research, cosponsored by the American Society of Preventive Oncology. 2005; 14: 403-8.
11. Neuhausen SL, Slattery ML, Garner CP, Ding YC, Hoffman M, Brothman AR. Prostate cancer risk and IRS1, IRS2, IGF1, and INS polymorphisms: strong association of IRS1 G972R variant and cancer risk. The Prostate. 2005; 64: 168-74.
12. Kesarwani P, Ahirwar DK, Mandhani A, Mittal RD. Association between -174 G/C promoter polymorphism of the interleukin-6 gene and progression of prostate cancer in North Indian population. Dna & Cell Biology. 2008; 27: 505-10.
13. Mandal S, Abebe F, Chaudhary J. -174G/C polymorphism in the interleukin-6 promoter is differently associated with prostate cancer incidence depending on race. Genetics & Molecular Research. 2014; 13: 139-51.
14. Bao S, Yang W, Zhou S, Ye Z. Relationship between Single Nucleotide Polymorphisms in -174G/C and -634C/G Promoter Region of Interleukin-6 and Prostate Cancer. J Huazhong Univ Sci Technolog Med Sci. 2008; 28: 693-6.
15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997; 315: 629-34.
16. Lau J, Ioannidis JP, Schmid CH. Quantitative synthesis in systematic reviews. Annals of internal medicine. 1997; 127: 820-6.
17. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. British medical journal. 2003; 327: 557-60.
18. Yong G, Pan X, Su T, Mo Z, Cao Y, Feng G. Glutathione S-transferase P1 Ile105Val polymorphism and colorectal cancer risk: a meta-analysis and HuGE review. European Journal of Cancer. 2009; 45: 3303-14.
19. Balistreri CR, Ccarruba C. A pilot study on prostate cancer risk and pro-inflammatory genotypes: pathophysiology and therapeutic implications. Current Pharmaceutical Design. 2010; 16: 718-24.
20. Chen C, Freeman R, Voigt LF, Fitzpatrick A, Plymate S, Weiss N. Prostate cancer risk in relation to selected genetic polymorphisms in insulin-like growth factor-I, insulin-like growth factor binding protein-3, and insulin-like growth factor-I receptor. Cancer Epidemiology Biomarkers & Prevention. 2006; 15: 2461-6.
21. Cheng I, Plummer SJ, Casey G, Witte JS. Toll-like receptor 4 genetic variation and advanced prostate cancer risk. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2007; 16: 352-5.
22. Dossus L, Kaaks R, Canzian F, Albanes D, Berndt SI, Boeing H, et al. PTGS2 and IL6 genetic variation and risk of breast and prostate cancer: results from the Breast and Prostate Cancer Cohort Consortium (BPC3). Carcinogenesis. 2010; 31: 455-61.
23. Fall K, Stark JR, Mucci LA, Chan J, Stampfer MJ, Kurth T, et al. No association between a polymorphic variant of the IRS-1 gene and prostate cancer risk. Prostate. 2008; 68: 1416–20.
24. Fitzgerald LM, Karlins E, Karyadi DM, Kwon EM, Koopmeiners JS, Stanford JL, et al. Association of FGFR4 genetic polymorphisms with prostate cancer risk and prognosis. Prostate Cancer & Prostatic Diseases. 2008; 12: 192-7.
25. Friedrichsen DM, Hawley S, Shu J, Humphrey M, Sabacan L, Iwasaki L, et al. IGF-I and IGFBP-3 polymorphisms and risk of prostate cancer. Prostate. 2005; 65: 44–51.
26. Fukuda H, Tsuchiya N, Narita S, Kumazawa T, Horikawa Y, Inoue T, et al. Clinical implication of vascular endothelial growth factor T-460C polymorphism in the risk and progression of prostate cancer. Oncology Reports. 2007; 18: 1155-63.
27. Hernandez W, Grenade C, Santos ER, Bonilla C, Ahaghotu C, Kittles RA. IGF-1 and IGFBP-3 gene variants influence on serum levels and prostate cancer risk in African-Americans. Carcinogenesis. 2007; 28: 2154-9.
28. Giachini FR, Sullivan JC, Lima VV, Carneiro FS, Fortes ZB, Pollock DM, et al. Extracellular signal-regulated kinase 1/2 activation, via downregulation of mitogen-activated protein kinase phosphatase 1, mediates sex differences in desoxycorticosterone acetate-salt hypertension vascular reactivity. Hypertension. 2010; 55: 172-9.
29. Jacobs EJ, Hsing AW, Bain EB, Stevens VL, Wang Y, Chen J, et al. Polymorphisms in angogenesis-related genes and prostate cancer. Cancer Epidemiology Biomarkers & Prevention. 2008; 17: 972-7.
30. Li L, Cicek MS, Casey G, Witte JS. No association between genetic polymorphisms in insulin and insulin receptor substrate-1 and prostate cancer. Cancer Epidemiology Biomarkers & Prevention. 2005; 14: 2462-3.
31. Lin CC, Wu HC, Tsai FJ, Chen HY, Chen WC. Vascular endothelial growth factor gene−460 C/T polymorphism is a biomarker for prostate cancer. Urology. 2003; 62: 374-7.
32. Ma Z, Tsuchiya N, Yuasa T, Narita S, Horikawa Y, Kumazawa T, et al. Polymorphisms of fibroblast growth factor receptor 4 have association with the development of prostate cancer and benign prostatic hyperplasia and the progression of prostate cancer in a Japanese population. International Journal of Cancer. 2008; 123: 2574–9.
33. Mandal S, Abebe F, Chaudhary J. -174G/C polymorphism in the interleukin-6 promoter is differently associated with prostate cancer incidence depending on race. Genetics & Molecular Research Gmr. 2014; 13: 139-51.
34. Michaud DS, Daugherty SE, Berndt SI, Platz EA, Yeager M, Crawford ED, et al. Genetic polymorphisms of interleukin-1B (IL-1B), IL-6, IL-8, and IL-10 and risk of prostate cancer. Cancer Research. 2006; 66: 4525-30.
35. Moore S, Leitzmann MF, Albanes D, Weinstein SJ, Snyder K, Virtamo J, Ahn J, et al. Adipokine genes and prostate cancer risk. International Journal of Cancer. 2009; 124: 869-76.
36. Nam RK, Zhang WW, Trachtenberg J, Jewett MA, Emami M, Vesprini D, et al. Comprehensive assessment of candidate genes and serological markers for the detection of prostate cancer. Cancer Epidemiology Biomarkers & Prevention. 2003; 12: 1429-37.
37. Neuhausen SL, Slattery MLGarner CP, Ding YC, Hoffman M, Brothman AR. Prostate cancer risk and IRS1, IRS2, IGF1, and INS polymorphisms: strong association of IRS1 G972R variant and cancer risk. Prostate. 2005; 64: 168-74.
38. Onen IH, Konac E, Eroglu M, Guneri C, Biri H, Ekmekci A. No association between polymorphism in the vascular endothelial growth factor gene at position−460 and sporadic prostate cancer in the Turkish population. Molecular Biology Reports. 2008; 35: 17-22.
39. Pierce BL, Biggs ML, Decambre M, Reiner AP, Li C, Fitzpatrick A, et al. C-reactive protein, interleukin-6, and prostate cancer risk in men aged 65 years and older. Cancer Causes & Control. 2009; 20: 1193-203.
40. Ratliff TL. Sequence Variants of Toll-Like Receptor 4 are Associated With Prostate Cancer Risk: Results From the CAncer Prostate in Sweden Study. Cancer Research. 2004; 172: 2918-22.
41. Saracevic A, Nikolac N, Reljic A, Simundic AM. Insulin receptor H1085H C>T and insulin receptor substrate 1 G972R polymorphisms and prostate cancer risk: a pilot study. Genetic Testing & Molecular Biomarkers. 2011; 15: 127-31.
42. Schildkraut JM, Demarkwahnefried W, Wenham RM, Grubber J, Jeffreys AS, Grambow SC, et al. IGF1 (CA)19 Repeat and IGFBP3 -202 A/C Genotypes and the Risk of Prostate Cancer in Black and White Men. Cancer Epidemiology Biomarkers & Prevention. 2005; 14: 403-8.
43. Sfar S, Hassen E, Saad H, Mosbah F, Chouchane L. Association of VEGF genetic polymorphisms with prostate carcinoma risk and clinical outcome. Cytokine. 2006; 35: 21-8.
44. Shui IM, et al. Genetic variation in the toll-like receptor 4 and prostate cancer incidence and mortality. Prostate. 2012; 72: 209-16.
45. Song J, et al. The association between Toll-like receptor 4 (TLR4) polymorphisms and the risk of prostate cancer in Korean men. Cancer Genet Cytogenet. 2009; 190: 88-92.
46. McCarron SL, et al. Influence of cytokine gene polymorphisms on the development of prostate cancer. Cancer Res. 2002; 62: 3369-72.
47. Sun J, et al. Interleukin-6 sequence variants are not associated with prostate cancer risk. Cancer Epidemiol Biomarkers Prev. 2004; 13: 1677-9.
48. Tsuchiya N, et al. CA repeat polymorphism in the insulin-like growth factor-I gene is associated with increased risk of prostate cancer and benign prostatic hyperplasia. Int J Oncol. 2005; 26: 225-31.
49. Wang MH, et al. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. Prostate. 2009; 69: 874-85.
50. Wang MH, et al. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. Prostate. 2009; 69: 874-85.
51. Zabaleta J, et al. Cytokine genetic polymorphisms and prostate cancer aggressiveness. Carcinogenesis. 2009; 30: 1358-62.
52. Zhang J, et al. Polymorphisms in inflammatory genes, plasma antioxidants, and prostate cancer risk. Cancer Causes Control. 2010; 21: 1437-44.
53. Bao S, et al. Relationship between single nucleotide polymorphisms in -174G/C and -634C/G promoter region of interleukin-6 and prostate cancer. J Huazhong Univ Sci Technolog Med Sci. 2008; 28: 693-6.
54. Zheng SL, et al. Sequence variants of toll-like receptor 4 are associated with prostate cancer risk: results from the CAncer Prostate in Sweden Study. Cancer Res. 2004; 64: 2918-22.
55. Duval S, Tweedie R. Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. Biometrics. 2000; 56: 455-63.
56. Zhu LB, Yuan H, Jiang T, Wang RX, Ma HX, Zhang SY. Association of TLR2 and TLR4 Polymorphisms with Risk of Cancer: A Meta-Analysis. PloS one. 2013; 8: e82858.
57. Giacca M, Zacchigna S. VEGF gene therapy: therapeutic angiogenesis in the clinic and beyond. Gene Ther. 2012; 19: 622-9.
58. Zhang HT, Wang AD, Ma H, Xu Y. Association between insulin receptor substrate 1 Gly972Arg polymorphism and cancer risk. Tumor Biol. 2013; 34: 2929-36.
59. Porzio O, Federici M, Hribal ML, Lauro D, Accili D, Lauro R, et al. The Gly972-->Arg amino acid polymorphism in IRS-1 impairs insulin secretion in pancreatic beta cells. The Journal of clinical investigation. 1999; 104: 357-64.
60. Baserga R. The contradictions of the insulin-like growth factor 1 receptor. Oncogene. 2000; 19: 5574-81.
61. Quan HY, Tang H, Fang L, Bi JJ, Liu YS, Li HL. IGF1(CA)19 and IGFBP-3-202A/C Gene Polymorphism and Cancer Risk: A Meta-analysis. Cell Biochem Biophys. 2014; 69: 169-78.
62. Xu B, Tong N, Chen SQ, Hua LX, Wang ZJ, Zhang ZD, et al. FGFR4 Gly388Arg polymorphism contributes to prostate cancer development and progression: a meta-analysis of 2618 cases and 2305 controls. BMC cancer. 2011; 11: 84.
63. Fishman D, Faulds G, Jeffery R, Mohamed-Ali V, Yudkin JS, Humphries S, et al. The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. The Journal of clinical investigation. 1998; 102: 1369-76.
64. Liu RY, Song XX, Chen P, Lei Z, Miao JC, Yi NJ, et al. Association between IL6-174G/C and cancer: A meta-analysis of 105,482 individuals. Experimental and therapeutic medicine. 2012; 3: 655-64.

65. Du Y, Gao L, Zhang K, Wang J. Association of the IL6 polymorphism rs1800796 with cancer risk: a meta-analysis. Genetics and Molecular Research. 2015; 14: 13236-46.
66. Liu RY, Song X, Chen P, Lei Z, Miao J, Yi N, et al. Association between IL6 -174G/C and cancer: A meta-analysis of 105,482 individuals. Experimental and therapeutic medicine. 2012; 3: 655-64.