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SYSTEMATIC REVIEW AND META-ANALYSIS

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Association of IL-23R Polymorphisms (rs6682925, rs10889677, rs1884444) With Cancer Risk

A PRISMA-Compliant Meta-Analysis

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Abstract: Although interleukin (IL)-23 receptor (*IL-23R*) plays an important role in the pathogenesis of multiple cancers, its association with cancer risk is inconsistent across different studies. We therefore conducted a meta-analysis with the aim of resolving the relationship among the 3 common polymorphisms of *IL-23R* (rs6682925, rs10889677, rs1884444) and cancer risk.

Case-control studies evaluating the association between *IL-23R* polymorphisms (rs6682925, rs10889677, rs1884444) and cancer risk were searched in the PubMed, Web of Science, and CNKI databases.

Data were included in the meta-analysis if they were from original studies adopting a case-control design investigating the association between *IL-23R* polymorphisms and risk of any cancer; all cancer cases must have been confirmed by histology or pathology, and controls selected from noncancer individuals. Case-only studies and review papers were excluded.

Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the relationship of *IL-23R* polymorphisms (rs6682925, rs10889677, rs1884444) with cancer risk. A random-effects model or fixed-effects model was used depending on the heterogeneity of the data.

Ultimately, 15 studies, involving 8784 cancer patients and 10,321 cancer-free controls, were included in our meta-analysis. In the overall analysis, the rs10889677 polymorphism was associated with breast cancer (BC) under the allelic, homozygous, dominant, and heterozygous models. Rs1884444 polymorphism was relevant to hepatocellular carcinoma (HCC) under the homozygous, recessive, and allelic models. However, no evidence of a relationship between *IL-23R* polymorphisms (rs6682925, rs10889677, rs1884444) and cancer risk was found in the overall population.

Our meta-analysis provides no evidence supporting a global association of *IL-23R* polymorphisms (rs6682925, rs10889677, rs1884444) with the risk of cancer. However, rs10889677 may be associated with BC susceptibility and rs1884444 had association with HCC risk. Further large and well-designed studies are warranted to confirm this finding.

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Abbreviations: BC = breast cancer, CI = confidence interval, CNKI = China National Knowledge Infrastructure, CRC = colorectal cancer, HCC = hepatocellular carcinoma, HWE = Hardy-Weinberg equilibrium, IL-23R = Interleukin-23 receptor, OR = odds ratio, Th17 = T helper 17.

INTRODUCTION

Cytokines are critical coordinators of the immune response necessary for resolving bacterial and viral assaults on the immune system. In particular, members of the *IL-12* family of cytokines are key players in the regulation of T-cell responses, comprising the only heterodimeric cytokines, including *IL-12*, *IL-23*, *IL-27*, and *IL-35*. In this family, there is a balanced dichotomy of T-cell regulation, in which *IL-12* and *IL-23* are positive regulators and *IL-27* and *IL-35* are negative regulators.[1,2] *IL-12* and *IL-23* bind to the β1 receptor of T-cells and natural killer cells via their shared p40 subunit. Together, *IL-23R* and *IL-12R* β1 comprise the *IL-23R* complex in *IL-23*-responsive cells.[3] The *IL-23R* gene is located on chromosome 1p31 and encodes a subunit of the *IL-23* receptor. Interleukin (IL)-23 is a pro-inflammatory cytokine comprised of the *IL-12* p40 and IL-23 p19 subunits. It is mainly secreted by macrophages and dendritic cells, and can promote autoimmunity through T-cell-mediated inflammation by affecting the T helper 17 (Th17) cell response.[4] Th17 cells are a recently discovered proinflammatory $CD4^+$-effector T-cell population that contribute to pathogen clearance and tissue inflammation by expressing high levels of the proinflammatory cytokine *IL-17*.[5] *IL-17*, which is an inflammatory cytokine, plays an important role in the regulation of leukocyte migration in the inflammatory reaction.[6]

The novel inflammation pathway *IL-23/IL-17* axis has proven to serve as a useful biomarker for renal disease activity and for predicting the response to immunosuppressive treatment.[7] *IL-23R* affects the *IL23/IL17* axis by increasing the expression and production of *IL-17A* and *IL-17F* in Th17 cells.[8] In a murine melanoma model, Tang et al[9] demonstrated that high-mobility group box 1 stimulated the production of *IL-23* in a RAGE-dependent manner. Some studies found that genetic variants of *IL-23R* may contribute to the pathological development from hepatitis to HCC,[10,11] and that hepatitis B virus could induce hepatitis by increasing *IL-23* expression in a mannose

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receptor/endocytosis-dependent or -independent manner, and result in liver damage through the *IL-23/IL-17* axis.[12] Besides Th17 cells, some innate immunity-like T-cells such as TCR γδ 17 and iNKT17 cells have been found to play a key role in the *IL-23/IL-17* pathway and to potentially have a vital function in the development of spondyloarthritis-related pathology.[13] *IL-23* signals work through the *IL-23* receptor (*IL-23R*), which is also comprised of 2 subunits, *IL12R1* and *IL-23R*, and is unique to *IL-23*.[14] Moreover, previous studies have indicated that *IL-23R* exerts an immunosurveillance function via $CD8^+$ T-cells and accelerates tumor growth.[15] These findings suggest that *IL-23R* may play an important role in cancer development and progression.

Recently, some case-control studies have investigated the association of *IL-23R* polymorphisms with the risk of cancer, including esophageal squamous cell carcinoma, bladder cancer, acute myeloid leukemia, gastric cancer, ovarian cancer, breast cancer, lung cancer, colorectal cancer, and nasopharyngeal cancer.[16–25] However, the results from different studies remain controversial. Wrobel et al[26] found a correlation between the *IL-17F* rs763780 polymorphism and AML, but no relationship between IL-23R and AML was observed. However, Qian et al[27] reported that genetic variants of *IL-23*R may contribute to AML risk. Based on these findings, the effects of *IL-23R* polymorphisms (rs6682925, rs10889677, rs1884444) have been widely discussed, but no conclusive relationships have been determined. Therefore, we conducted a meta-analysis to achieve a more comprehensive evaluation of the association among 3 *IL-23R* polymorphisms (rs6682925, rs10889677, rs1884444) with cancer risk.

METHODS

Publication Search

A comprehensive literature search was conducted using the following search terms: ''Interleukin-23 receptor'' or ''*IL-23R*,'' ''polymorphism'' or ''SNP,'' ''cancer,'' and ''tumor.'' The PubMed, Web of Science, and Chinese National Knowledge Infrastructure (CNKI) databases were searched up to April 1, 2015. Only articles published in English were eligible for inclusion. Furthermore, the reference lists of all eligible articles, including review articles, were also checked to find additional relevant publications. This study was approved by the ethics committee of Xi'an Jiaotong University.

Selection Criteria

The following criteria were used to select eligible studies for further meta-analysis: (1) original studies; (2) case-control design investigating the association between *IL-23R* polymorphisms and risk of any cancer; and (3) all cancer cases were confirmed by histology or pathology, and the controls were selected from noncancer individuals. Case-only studies and review papers were excluded. If 2 or more studies contained overlapping cases or controls, the study with the largest sample size was included in the meta-analysis.

Data Extraction

Articles were reviewed independently by 2 authors, and any discrepant data were discussed by all authors to reach a consensus. For each included study, the raw data and demographic information, including first author, publication year, country of origin, ethnicity, source of controls, total number of cases and controls, cancer type, and genotypes, were independently extracted. Different ethnic groups were categorized as Caucasian, Asian, and ''mixed.''

Data Synthesis

Using the genotype and allele frequencies in cases and controls, we applied crude odds ratios (ORs) with corresponding 95% confidence intervals (CIs) to evaluate the associations between *IL-23R* (rs6682925, rs10889677, rs1884444) polymorphisms and cancer risk. The Z test was used to test the significance of all pooled ORs and a P value $<5\%$ was considered significant.

Five different genetic models were used in the meta-analysis to assess the association: allelic comparison of B versus A, homozygous comparison of BB versus AA, dominant comparison of AB+BB versus AA, recessive comparison of BB versus AA+AB, and heterozygous comparison of AB versus AA (A: the major allele, B: the minor allele). Statistical heterogeneity among studies was assessed with the Q and I^2 statistic.[28] The meta-regression and stratified analyses were also used to analyze the heterogeneity. Publication bias was evaluated with a funnel plot and further assessed by Egger's linear regression test, and $P < 0.05$ was considered statistically significant. All statistical analyses were carried out with the software STATA (Version 11.0; Stata Corp, College Station, TX).

RESULTS

Characteristics of the Included Studies

The literature search for this meta-analysis started in January 2010 and ended in April 2015 through primary literature retrieval in the PubMed, Web of Science, and CNKI databases. As shown in Figure 1, a total of 134 studies were identified that evaluated *IL-23R* polymorphisms (rs6682925, rs10889677, rs1884444), and 41 of these studies were excluded as duplicate publications. According to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA), after manually screening the titles and abstracts, 51 studies were ultimately excluded. After reading the full texts of the remaining 42 articles, 27 were excluded due to lack of complete necessary data (20 articles) or because of reporting unrelated *IL-23* polymorphisms (7 articles). Finally, a total of 15 studies with 8784 cases and 10,321 cancer-free controls were found to meet the inclusion criteria for assessing the influence of the rs6682925, rs10889677, and rs1884444 polymorphisms on cancer risk. All of the included eligible studies were published in English.

Among the eligible 15 studies, 2 were carried out in Caucasians from Iran and Tunis. Thirteen studies were based on subjects with an Asian background and all were performed in China. All studies were case–control studies, including 2 hepatocellular carcinoma (HCC) studies, 2 colorectal cancer studies, 2 breast cancer (BC) studies, 2 gastric cancer studies, 1 bladder cancer study, 1 esophageal squamous cell carcinoma study, 1 acute myeloid leukemia study, 1 oral cancer study, 1 ovarian cancer, 1 esophageal cancer study, and 1 nonsmall-cell lung cancer. There were 5 hospital-based studies and 10 population-based studies. The main characteristics of the included studies are listed in Tables 1 and 2.

Meta-Analysis of the rs6682925 Polymorphism and Cancer Risk

There were 7 studies with 6272 cases and 7848 controls for rs6682925. Evaluation of the association between the

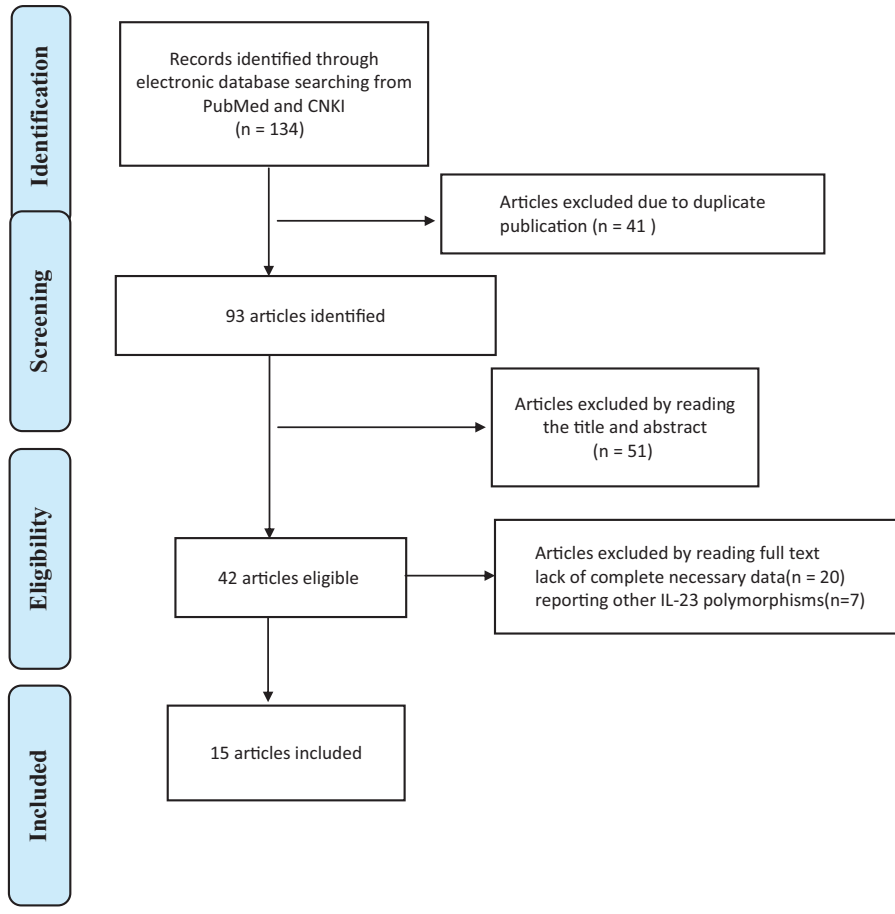

FIGURE 1. Flow diagram of included studies for the meta-analysis. CNKI = China National Knowledge Infrastructure.

TABLE 1. Characteristics of the Studies Included in the Meta-Analysis

Study	Year	Country	Ethnicity	Genotyping Method	Source of Control	Cancer Type	Case/Control	SNP No.
Nemati K[25]	2015	Iran	Caucasian	PCR-RFLP	Hospital	CRC	202/203	2
Omrane I[23]	2014	Tunisia	Caucasian	TaqMan	Population	CRC	100/137	2
Tang T[24]	2014	China	Asian	PCR-RFLP	Hospital	BLC	226/270	2
Ni B[22]	2014	China	Asian	MassArray	Population	ESCC	684/1064	1,2,3
Peng Q[10]	2013	China	Asian	PCR-RFLP	Hospital	HCC	87/94	2,3
Qian X[27]	2013	China	Asian	TaqMan	Population	AML	545/1146	1,3
Xu Y[11]	2013	China	Asian	TaqMan	Population	HCC	837/1642	1,3
Zheng J[21]	2012	China	Asian	PCR-RFLP	Population	BC	1010/1014	1,2,3
Wang L[20]	2012	China	Asian	SNaPshot	Population	BC	491/502	2,3
Chien MH[30]	2012	China	Asian	PCR-RFLP	Hospital	Oral cancer	240/240	2
Chu H[19]	2012	China	Asian	TaqMan	Population	EC	1645/1694	1,3
Chen B[18]	2011	China	Asian	PCR-RFLP	Population	GC	1010/800	2
Chen J[16]	2010	China	Asian	PIRA-PCR	Population	GC	1043/1089	1,3
Zhang Z[17]	2010	China	Asian	PCR-RFLP	Hospital	Ovarian cancer	96/115	2
Dai J[29]	2012	China	Asian	TaqMan	Population	NSCLC	568/311	1

AML = acute myeloid leukaemia, BC = breast cancer, BLC = bladder cancer, CRC = colorectal cancer, EC = esophageal cancer, ESCC = esophageal squamous cell carcinoma, GC = gastric cancer, HCC = hepatocellular carcinoma, NSCLC = nonsmall-cell lung cancer, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism, SNP = single-nucleotide polymorphism. SNP No.1: rs6682925; 2: rs10889677; 3: rs1884444.

TABLE 2. IL-23R Polymorphisms Genotype Distribution and Allele Frequency in Cases and Controls

	Genotype (N)								Allele Frequency (N)				
	Case	Control							Case		Control		
Study	Total	AA	AB	BB	Total	AA	AB	BB	A	B	A	B	HWE
rs6682925													
Ni B 2014	684	251	335	98	1064	391	490	183	837	531	1272	856	0.17
Qian X 2013	525	184	247	94	1117	452	522	143	615	435	1426	808	0.68
Xu Y 2013	829	282	399	148	1607	613	769	225	963	695	1995	1219	0.51
Zheng J 2012	1010	385	479	146	1014	361	487	166	1249	771	1209	819	0.94
Chu H 2012	1635	578	797	260	1685	670	767	248	1953	1317	2107	1263	0.24
Chen J 2010	1021	264	533	224	1050	275	554	221	1061	981	1104	996	0.06
Dai J 2012	568	191	285	92	311	93	158	60	667	469	344	278	0.63
rs10889677													
Nemati K 2015	188	32	105	51	195	33	105	57	169	207	171	219	0.19
Omrane I 2014	100	40	48	12	137	56	63	18	128	78	175	99	0.97
Tang T 2014	226	111	99	16	270	185	71	14	321	131	441	99	0.05
Ni B 2014	684	360	279	45	1064	498	462	104	999	369	1458	670	0.83
Peng Q 2013	84	55	26	3	94	55	34	5	136	32	144	44	0.93
Zheng J 2012	1010	522	422	66	1014	463	432	119	1466	554	1358	670	0.24
Wang L 2012	491	267	182	42	502	231	221	50	716	266	683	321	0.79
Chien MH 2012	240	134	85	21	240	159	64	17	353	127	382	98	<0.01
Chen B 2011	941	40	325	576	775	62	295	418	405	1477	419	1131	0.33
Zhang Z 2010	96	48	42	6	115	79	30	6	138	54	188	42	0.18
rs1884444													
Ni B 2014	684	350	274	60	1064	519	431	114	974	394	1469	659	0.09
Peng Q 2013	84	38	36	10	94	60	24	10	112	56	144	44	<0.01
Qian X 2013	537	223	254	60	1137	519	496	122	700	374	1534	740	0.83
Xu Y 2013	814	334	367	113	1560	688	705	167	1035	593	2081	1039	0.49
Zheng J 2012	1010	528	379	103	1014	510	406	98	1435	585	1426	602	0.19
Wang L 2012	491	219	216	56	502	204	234	64	654	328	642	362	0.81
Chu H 2012	1635	676	760	199	1683	753	740	190	2112	1158	2246	1120	0.69
Chen J 2010	974	400	457	117	1055	360	519	176	1257	691	1239	871	0.63

A = the major allele, B = the minor allele, HWE = Hardy–Weinberg equilibrium.

rs6682925 polymorphism and cancer risk is summarized in Table 3 and Figure 2. No significant association was observed under the 5 allele/genotype comparisons (T vs C: OR = 1.04, 95% CI = 0.95–1.15, P = 0.39, TT vs CC: OR = 1.08, 95% CI = 0.88–1.32, $P = 0.47$; TT vs CC+TC: OR = 1.05, 95% CI = 0.89–1.23, $P = 0.58$; TC+TT vs CC: OR = 1.07, 95% CI = 0.96–1.19, $P = 0.25$; TC vs CC: OR = 1.07, 95% CI = 0.997–1.16, $P = 0.06$).

TABLE 3. Meta-Analysis Results

	B vs A		BB vs AA		BB vs AA+AB		AB+BB vs AA		AB vs AA	
SNPs	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
rs6682925										
Overall	1.04 (0.95–1.15)	0.39	1.08 (0.88–1.32)	0.47	1.05 (0.89–1.23)	0.58	1.07 (0.96–1.19)	0.25	1.07 (0.997–1.16)	0.06
PB	0.04 (0.95–1.15)	0.39	1.08 (0.88–1.32)	0.47	1.05 (0.89–1.23)	0.58	1.07 (0.96–1.99)	0.25	1.07 (0.997–1.16)	0.06
rs10889677										
Overall	1.07 (0.87–1.32)	0.50	0.99 (0.67–1.46)	0.95	0.91 (0.68–1.21)	0.51	1.16 (0.88–1.53)	0.30	1.18 (0.91–1.53)	0.23
HWE	1.04 (0.84–1.29)	0.71	0.95 (0.62–1.44)	0.80	0.88 (0.64–1.20)	0.42	1.12 (0.84–1.49)	0.45	1.14 (0.86–1.49)	0.36
HB	1.29 (0.95–1.75)	0.11	1.27 (0.89–1.81)	0.19	1.05 (0.77–1.44)	0.74	1.46 (0.99–2.16)	0.06	1.51 (1.02–2.24)	0.04
PB	0.93 (0.73–1.18)	0.52	0.83 (0.48–1.45)	0.52	0.81 (0.52–1.26)	0.35	0.93 (0.71–1.21)	0.59	0.93 (0.74–1.16)	0.52
Caucasian	1.00 (0.80–1.25)	0.99	0.93 (0.56–1.52)	0.76	0.90 (0.61–1.33)	0.60	1.02 (0.70–1.48)	0.94	1.05 (0.71–1.55)	0.81
Asian	1.09 (0.86–1.39)	0.48	1.01 (0.63–1.62)	0.97	0.91 (0.64–1.31)	0.61	1.19 (0.87–1.65)	0.28	1.21 (0.89–1.64)	0.22
CRC	1.00 (0.80–1.25)	0.99	0.93 (0.56–1.52)	0.76	0.90 (0.61–1.33)	0.60	1.02 (0.70–1.48)	0.94	1.05 (0.71–1.55)	0.81
BC	0.77 (0.69–0.86)	0.000	0.56 (0.43–0.73)	0.000	0.65 (0.41–1.04)	0.07	0.76 (0.66–0.88)	0.000	0.81 (0.70–0.95)	0.007
rs1884444										
Overall	1.00 (0.89–1.12)	0.98	0.98 (0.78–1.23)	0.87	0.98 (0.82–1.16)	0.80	0.96 (0.84–1.10)	0.59	1.01 (0.89–1.15)	0.87
HWE	0.98 (0.88–1.09)	0.72	0.96 (0.76–1.21)	0.73	0.97 (0.81–1.17)	0.76	0.93 (0.83–1.05)	0.25	0.98 (0.88–1.10)	0.78
PB	0.98 (0.88–1.09)	0.72	0.96 (0.76–1.21)	0.73	0.97 (0.81–1.17)	0.76	0.98 (0.86–1.12)	0.73	0.98 (0.88–1.10)	0.78
HCC	1.18 (1.04–1.33)	0.009	1.41 (1.08–1.83)	0.01	1.33 (1.04–1.70)	0.02	1.45 (0.79–2.67)	0.23	1.49 (0.69–3.21)	0.31
BC	0.94 (0.84–1.05)	0.25	0.94 (0.74–1.20)	0.61	0.99 (0.79–1.25)	0.94	0.90 (0.78–1.04)	0.15	0.89 (0.76–1.03)	0.13

A = the major allele, B = the minor allele, BC = breast cancer, CI = confidence interval, CRC = colorectal cancer, HCC = hepatocellular carcinoma, HB = hospital-based, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, PB = population-based.

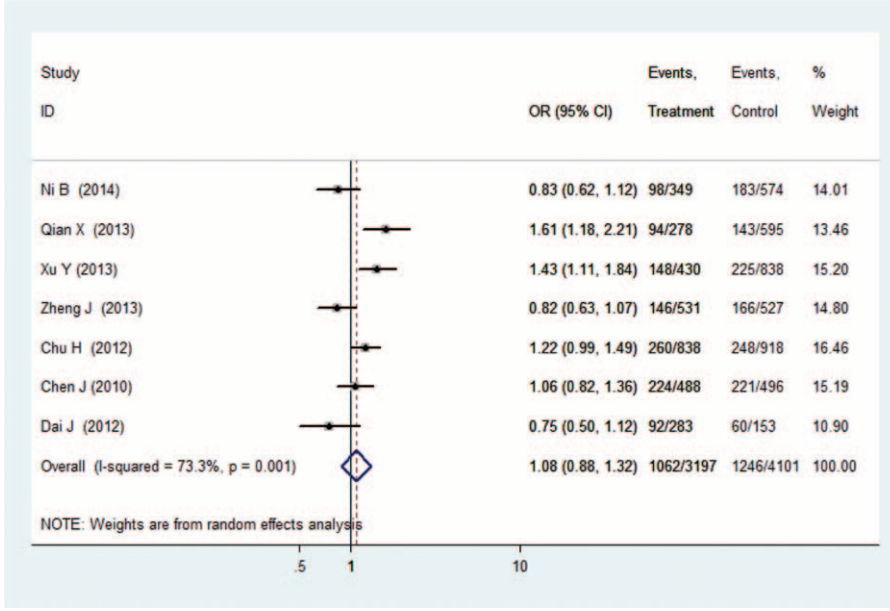

FIGURE 2. Forest plot of cancer risk related to rs6682925 polymorphism under TT versus CC genetic model. C = the major allele in rs6682925 polymorphism, CI = confidence interval, OR = odds ratio, T = the minor allele in rs6682925 polymorphism.

Meta-Analysis of the rs10889677 Polymorphism and Cancer Risk

There were 10 studies with 4060 cases and 4406 controls evaluating the effect of rs10889677 on cancer risk. As shown in Table 3 and Figure 3, there was no association observed in the overall population under the 5 allele/genotype comparisons. Moreover, after omitting the study which was not according with the Hardy–Weinberg equilibrium (HWE), the results were in accordance with the overall population. And in the subgroup analyses based on ethnicity, we failed to find any significant association in Caucasians or Asians (Table 3). However, in the subgroup analyses by cancer type, a significant association was found between rs10889677 polymorphism and BC risk under the allelic, homozygous, dominant, and heterozygous models (C

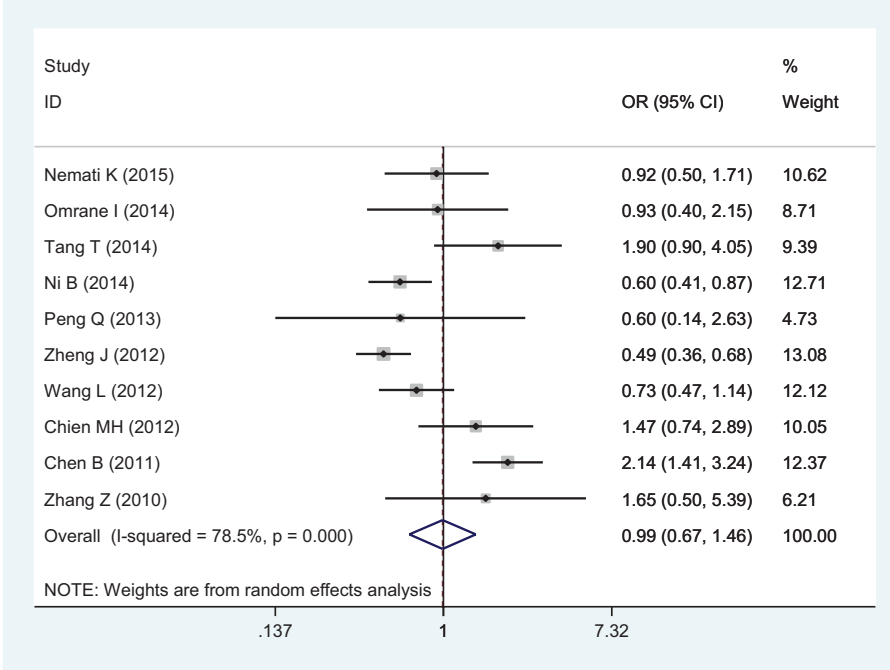

FIGURE 3. Forest plot of cancer risk related to rs10889677 polymorphism under CC versus AA genetic model. A = the major allele in rs10889677 polymorphism, C = the minor allele in rs10889677 polymorphism, CI = confidence interval, OR = odds ratio.

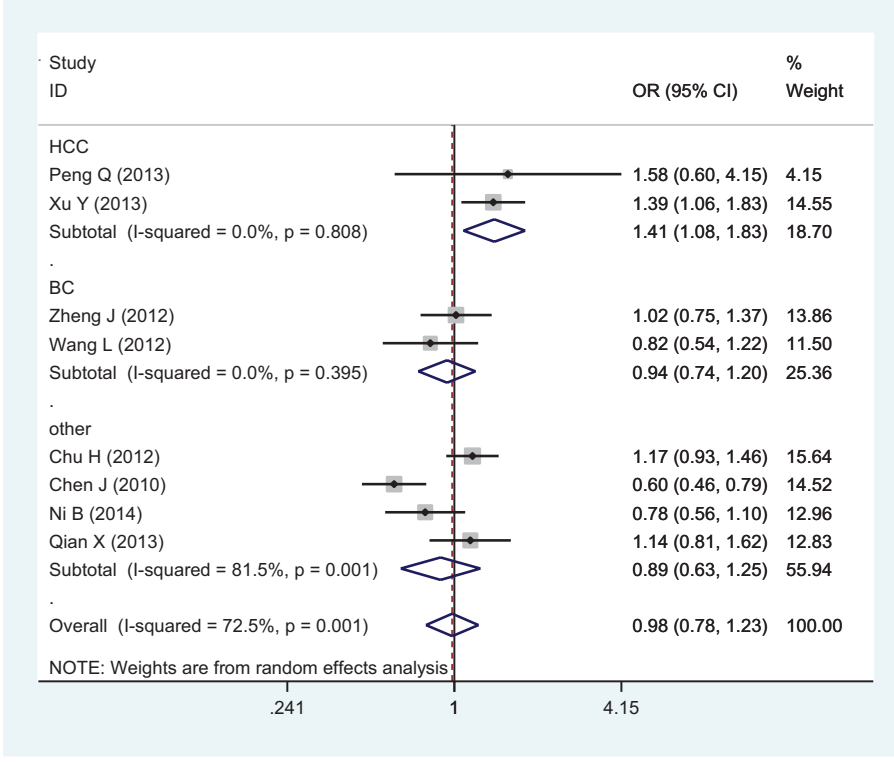

FIGURE 4. Forest plot of cancer risk related to rs1884444 polymorphism under TT versus GG genetic model. CI = confidence interval, G = the major allele in rrs1884444 polymorphism, OR = odds ratio, T = the minor allele in rs1884444 polymorphism.

vs A: OR = 0.77, 95% CI = 0.69–0.86, $P = 0.000$; CC vs AA: OR = 0.56, 95% CI = 0.43–0.73, $P = 0.000$; AC+CC vs AA: OR = 0.76, 95% CI = 0.66–0.88, $P = 0.000$; AC vs AA: OR = 0.81, 95% CI = 0.70–0.95, $P = 0.007$).

Meta-Analysis of the rs1884444 Polymorphism and Cancer Risk

Eight studies with 6229 cases and 8109 controls were used to evaluate the relationship between the rs1884444 polymorphism with cancer risk, which is summarized in Table 3 and Figure 4. In the overall analysis, no association was detected under all the genetic models. Further analysis of the studies which were in agreement with HWE also showed no association between rs1884444 polymorphism and cancer risk generally. However, we found that rs1884444 was significantly associated with HCC risk based on the allelic model, homozygous genetic model, and recessive genetic model (T vs G: OR = 1.18, 95% CI = 1.04–1.33, $P = 0.009$; TT vs GG: OR = 1.41, 95% CI = 1.08–1.83, $P = 0.01$; TT vs GG+TG: OR = 1.33, 95% CI = 1.04–1.70, $P = 0.02$). Furthermore, in the stratified analysis according to the source of controls, no association was observed in the hospital-based or population-based group (Table 3).

Sensitivity Analysis

Sensitivity analyses were performed by sequential removal of each eligible study to assess the influence of each individual study on the pooled OR for the respective comparisons of the rs6682925, rs10889677, and rs1884444 polymorphisms. The omission of any study did not have a significant effect on the results, indicating that the results of this meta-analysis are statistically reliable (Fig. 5).

Heterogeneity Analysis and Publication Bias

The Q test and I^2 value were used to test the variation in the data caused by heterogeneity. The results of the heterogeneity test are shown in Table 4. A random-effects model was applied when the P value of heterogeneity tests was ≤ 0.1, and the fixed-effects model was used for $P \geq 0.1$. There was heterogeneity among studies in both the overall comparisons and the subgroup analyses for all 3 polymorphisms evaluated (rs6682925, rs10889677, and rs1884444). To explore the potential sources of heterogeneity across studies, we analyze the latent factors by the meta-regression analysis. The results shown no evidence of heterogeneity coming from the source of control (rs6682925: $P = 0.30$; rs10889677: $P = 0.10$; rs1884444: $P = 0.06$), ethnicity ($P = 0.30$, 0.68, and 0.68, respectively), and year of publication ($P = 0.89$, 0.36, and 0.14, respectively). Then, we assessed the pooled ORs under all comparisons via subgroup and sensitivity analyses. In the subgroup by race, the heterogeneity of rs10889677 polymorphism was significant in the Asian studies. When stratified by source of control, the heterogeneity of rs1884444 polymorphism in population-based studies was significant in all genetic models.

We constructed a funnel plot and performed Egger's test to assess the extent of publication bias in our dataset. As shown in Figure 6, the funnel plots failed to reveal any obvious asymmetry for the 3 polymorphisms in the overall population, and the results of Egger's test revealed no publication bias (Table 5). Therefore, publication bias was not a significant factor affecting the results of this meta-analysis.

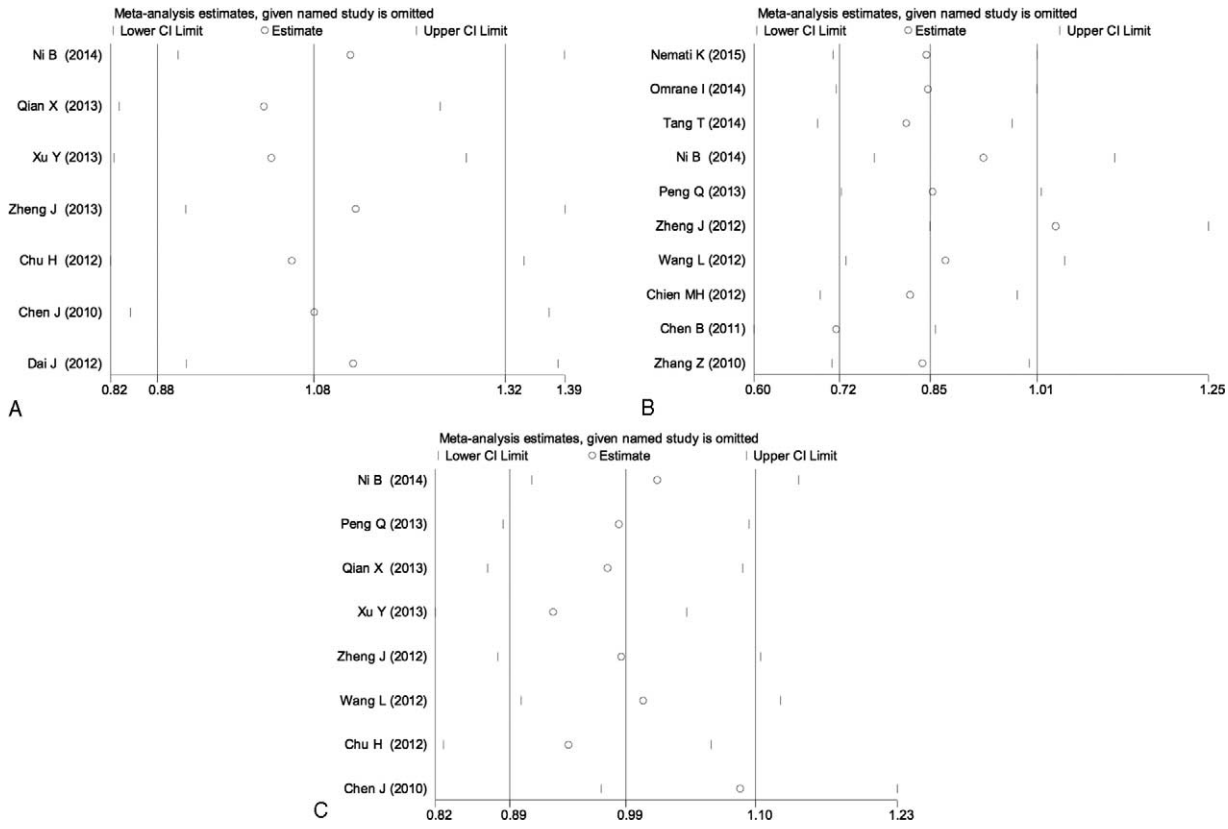

FIGURE 5. Sensitivity analysis of the heterozygous model in IL-23R polymorphisms: rs6682925 (A), rs10889677 (B), rs1884444 (C) under the homozygous model.

TABLE 4. Heterogeneity-Analysis Results

	B vs A			BB vs AA			BB vs AA+AB			AB+BB vs AA			AB vs AA		
Comparisons	I^2	*P*	EM	I^2	*P*	EM	I^2	*P*	EM	I^2	*P*	EM	I^2	*P*	EM
rs6682925															
Overall	72%	0.002	R	73%	0.001	R	68%	0.005	R	55%	0.04	R	19%	0.28	R
PB	72%	0.002	R	73%	0.001	R	68%	0.005	R	55%	0.04	R	19%	0.28	F
rs10889677															
Overall	87%	0.000	R	79%	0.000	R	73%	0.000	R	86%	0.000	R	82%	0.000	R
HWE	87%	0.000	R	80%	0.000	R	75%	0.000	R	86%	0.000	R	82%	0.000	R
HB	74%	0.004	R	0%	0.48	F	0%	0.78	F	71%	0.008	R	69%	0.01	R
PB	89%	0.000	R	88%	0.000	R	87%	0.000	R	80%	0.001	R	68%	0.01	R
Caucasian	0%	0.62	F	0%	0.98	F	0%	1.00	F	0%	0.91	F	0%	0.93	F
Asian	90%	0.000	R	83%	0.000	R	79%	0.000	R	89%	0.000	R	86%	0.000	R
CRC	0%	0.62	F	0%	0.98	F	0%	1.00	F	0%	0.91	F	0%	0.93	F
BC	0%	0.79	F	48%	0.17	F	67%	0.08	R	0%	0.55	F	30%	0.23	F
rs1884444															
Overall	78%	0.000	R	73%	0.001	R	59%	0.02	R	72%	0.001	R	67%	0.003	R
HWE	78%	0.000	R	76%	0.000	R	65%	0.009	R	66%	0.007	R	60%	0.02	R
PB	78%	0.000	R	76%	0.000	R	65%	0.009	R	73%	0.001	R	60%	0.02	R
HCC	52%	0.15	F	0%	0.81	F	0%	0.73	F	75%	0.05	R	81%	0.02	R
BC	0%	0.48	F	0%	0.40	F	0%	0.45	F	0%	0.60	F	0%	0.77	F

A = the major allele, B = the minor allele, BC = breast cancer, CRC = colorectal cancer, EM = Effects model, F = fixed effects model, HCC = hepatocellular carcinoma, HWE = Hardy–Weinberg equilibrium, R = random effects model.

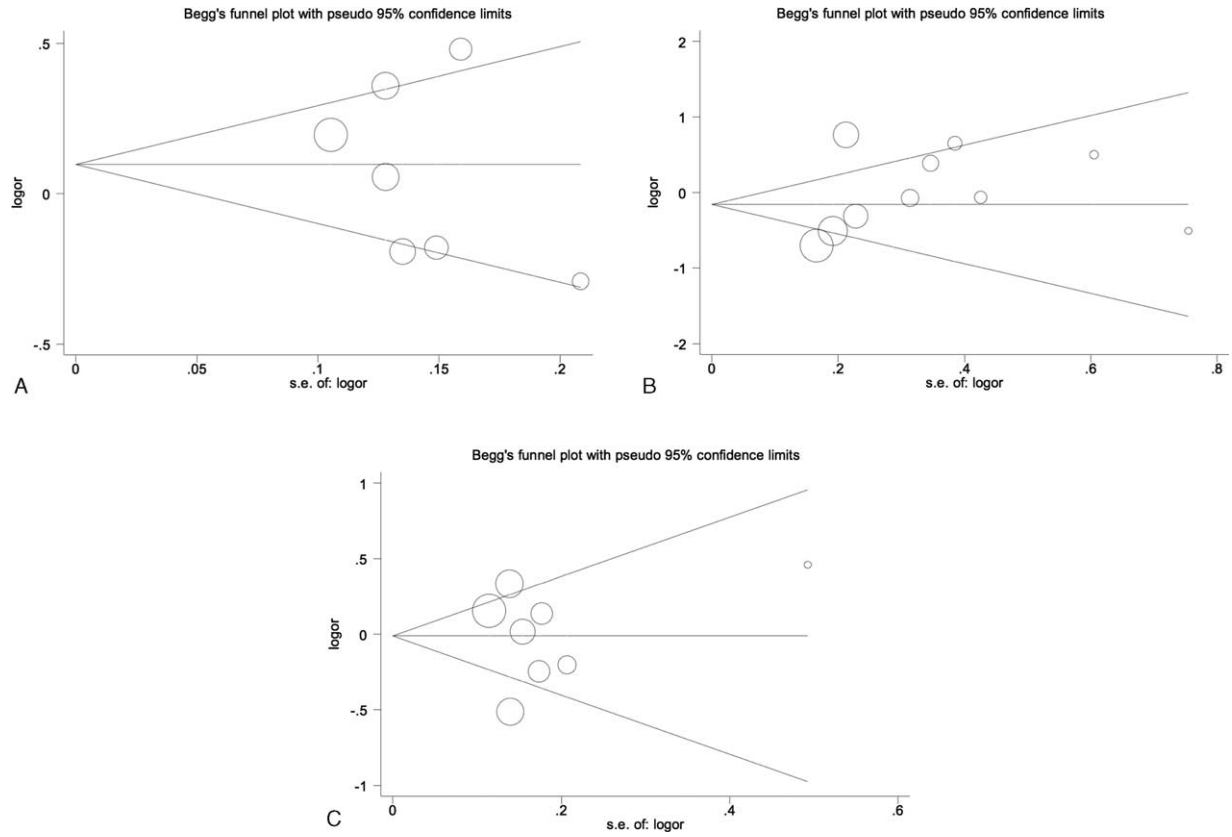

FIGURE 6. Begg funnel plot for publication bias test of IL-23R polymorphisms: rs6682925 (A), rs10889677 (B), rs1884444 (C) under the homozygous model.

DISCUSSION

In the present stratified meta-analysis based on cancer type, there was no significant association between rs6682925, rs10889677, or rs1884444 and cancer risk in the overall population. Our meta-analysis involved 15 independent case-control studies involving 8784 cancer patients and 10,321 cancer-free controls, and the results showed that the rs6682925 polymorphism was not associated with the susceptibility to any cancer and rs10889677 polymorphism may only increase BC susceptibility. Contradictory results have been obtained among individual studies on these associations. Qian et al[27] found that rs6682925 TC/CC variant genotypes were associated with an increased risk of acute myeloid leukemia, and this polymorphism was also proposed to have predictive value for nonsmall-cell lung cancer clinical outcomes.[29] Individuals with at least 1 variant C allele of the rs10889677 polymorphism showed a higher risk of developing oral cancer and tumor lymph node metastasis compared with patients carrying the wild-type A/A and C/C homozygous genotypes, and *IL23R* was suggested to play an important role in the susceptibility and prognosis of ovarian cancer in the Chinese population.[30] A recent meta-analysis indicated individuals with AC and CC genotype of rs10889677 polymorphism may decrease risk of multiple solid tumors ($P < 0.001$).[31] Zheng et al[21] demonstrated rs10889677A > C genotype could affect T-cell proliferation rate, the proportion of Tregs and IL-23R expression, which

TABLE 5. Egger's Test for Publication Bias Test of IL-23R Polymorphisms Under the Homozygous Model

Egger's Test	Std Eff	Coef.	Std. Err.	*t*	$P > \|t\|$	[95% Conf. Interval]
rs6682925						
	Slope	0.5580945	0.5517428	1.01	0.358	−0.8602055 1.976395
	Bias	−3.434047	4.035347	−0.85	0.434	−13.80724 6.939143
rs10889677						
	Slope	−0.6649081	0.4459395	−1.46	0.184	−1.677419 0.3792573
	Bias	1.999505	1.668805	1.20	0.265	−0.1.848767 5.84776
rs1884444						
	Slope	−0.0035931	0.3904393	−0.01	0.993	−0.9589637 0.951775
	Bias	−0.490381	2.446154	−0.02	0.985	− 6.034562 5.936485

further influenced cancer susceptibility. Furthermore, IL-23 promoted the expression of *IL-17*, which is mainly generated by γδ T-cells, thereby accelerating tumor growth through *IL-6* induction to activate *STAT3* in cancers. The present meta-analysis revealed an increased risk of HCC in carriers of the rs1884444 polymorphism; indeed, significant associations were observed between rs1884444 and HCC risk in 3 genotype models, but not the dominant and heterozygous models, in the overall population.

Though there was heterogeneity among the studies for the 3 polymorphisms, the meta-regression and subgroup analyses indicated that the ''source of control,'' ''ethnicity,'' and ''cancer type'' could explain the heterogeneity. All of the studies included in this meta-analysis met our inclusion criteria and no evidence of publication bias was found. Nevertheless, several limitations of this meta-analysis should be acknowledged. First, the meta-analysis was performed at the study level only, and owing to lack of detailed information from the included studies, we were unable to analyze potential correlative factors such as sex, age, life-style habits, and environmental factors, which are generally considered to contribute to increasing cancer risks. Second, some studies evaluated a specific subtype of cancer, such as the study of Dai et al,[29] which was based only on nonsmall-cell lung cancer. Third, we aimed to explore the distinction between Caucasians and Asians, but the subgroup of the 3 polymorphisms involved relatively fewer data in the Caucasian group. Our results did not find any difference between different ethnics, and this conclusion may have some bias. Fourth, meta-analysis is the statistical analysis of large collection of analysis from individual studies for the purpose of integrating the findings, but there were few studies evaluated the association between rs10889677 and bladder cancer, HCC, oral cancer and other cancer, rs1884444 and esophageal squamous cell carcinoma, acute myeloid leukemia, esophageal cancer, and other cancer. So we fail to get the relationship about them. Therefore, further large-scale multicenter studies combined with biochemical and statistical approach are warranted to validate the association between *IL-23R* and cancer risk.

In conclusion, the current evidence does not support a significant association between the rs6682925, rs10889677, and rs1884444 polymorphisms of *IL-23R* with cancer susceptibility in the overall population, although rs10889677 appears to influence the susceptibility to BC and rs1884444 may increase the risk of HCC. However, available prospective data are still sparse. In addition, further studies investigating the effect of gene–gene and gene–environment interactions are clearly needed to better understand the association between these 3 polymorphisms and cancer risk.

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