RESEARCH ARTICLE

Associations Between Three Polymorphisms in the Interleukin-4 Receptor Gene and Risk of Cancer: a Meta-analysis

Jia-Yi Wang[&], Yu-Qiao Zhou[&], Xiao-Xu Li, Xin Jin, Li-Li Wang, Lei Lei, Yu Zhou, Jiang Lu, Xin Zeng, Hong-Xia Dan*, Ga Liao*, Qian-Ming Chen

Abstract

Interleukin-4 receptor (IL-4R) gene single nucleotide polymorphisms (SNPs) are implicated in cancer development. However, results from the published reports have remained inconclusive. The objective of this study was to conduct a meta-analysis investigating the association between polymorphisms in IL-4R gene and cancer risk. Pubmed, EMBASE and China National Knowledge Infrastructure (CNKI) were searched for case-control studies published up to October 30, 2012 that investigated IL-4R polymorphisms and cancer risk. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strength of any associations. Three IL-4R polymorphisms (Q576R, rs1801275; I75V, rs1805010; S503P, rs1805015) in 21 case-control studies were analyzed. Our meta-analysis indicated that these three polymorphisms are not associated with cancer risk when all studies were pooled together. In the subgroup analysis by tumor site, the results showed that Q576R G allele carriers were associated with a significantly decreased cervical cancer risk (recessive model: OR = 0.77, 95%CI = 0.60-0.98; homozygote comparison: OR = 0.76, 95%CI = 0.58-0.98). I75V G allele carriers were associated with a decreased risk of renal cancer (dominant model = 0.71, 95%CI = 0.57-0.89, heterozygote comparison: OR = 0.69, 95%CI = 0.55-0.87). When stratified by ethnicity, Q576R G allele carriers were associated with a decreased cancer risk in Caucasians (dominant model: OR = 0.90, 95%CI = 0.83-0.98; heterozygote comparison: OR = 0.89, 95%CI = 0.82-0.98). I75V G allele carriers were associated with a decreased cancer risk in Asians (heterozygote comparison: OR = 0.76, 95%CI = 0.62-0.94). S503P C allele carriers were also associated with a decreased cancer risk in Asians (CC VS TT: OR = 0.29, 95%CI = 0.08-0.99). Our results suggest that Q576R, I75V and S503P may be associated with a decreased cancer risk for certain types of cancers and in some specific ethnic groups. Future case-control studies with large sample size are needed to evaluate these associations in detail.

Keywords: Cancer - interleukin-4 receptor - polymorphisms - meta-analysis

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Introduction

Cancer is a multifactorial disease which has a strong genetic predisposition (Hamajima et al., 2001; Engle et al., 2006). Although the etiology of cancer hasn't been totally illuminated (Hanahan et al., 2000), evidence shows that the development of cancer depends on immune conditions (de Visser et al., 2006). It has been estimated that cancer is preceded by chronic inflammation in up to a third of all case (Ames et al., 1995), in which cytokines play a crucial role such as tumor necrosis factor alpha, IL-10 and IL-4 (Sheu et al., 2008; Ali et al., 2012; Sim et al., 2012) .

IL-4R is a heterodimeric complex that can bind to the T helper 2 cytokines IL-4 and IL-13 (Nakamura et al., 2002). There is evidence to suggest that Il-4R may be associated with carcinogenesis progress. For instance, high level of IL-4R expression has been observed on the surface of ovarian and breast carcinoma cells (Obiri et al., 1993, 1994). Moreover, IL-4 level was higher in higher-stage tumor tissues compare with tissues from lower-stage patient (Onishi et al., 1999). IL-4 can inhibit the differentiation of Th1 lymphocytes and down-regulate the immune response of immune cells against malignant cells, thus promote tumor cells escape from immune surveillance (Grivennikov et al., 2010).

As shown in the HapMap (http://www.hapmap.org/) and dbSNP databases (http://www.ncbi.nlm.nih.gov/projects/SNP/), the IL4R gene is highly polymorphic. Single nucleotide polymorphisms of IL-4R that have been identified included I75V (rs1805010), S503P (rs1805015), Q576R (rs1801275), Ser752Ala (rs1805016), -29429 >T (rs2057768), 49359G >A (rs3024656) and so on

State Key Laboratory of Oral Diseases, West China Hospital of Stomatology, Sichuan University, Chengdu, China [&]Equal contributors
**For correspondence: hxdan@foxmail.com, liaoga@gmail.com*

(Ruan et al., 2011; Sarpatwari et al., 2011; Welsh et al., 2011). The most extensively studied polymorphisms for their implications in cancer risk are three polymorphic sites: I75V (rs1805010), Q576R (rs1801275) and S503P (rs1805015). I75V is located in the extracellular domain of the protein which can result in the substitution of Ile for Val (Mitsuyasu et al., 1998). Q576R is located in the cytoplasmic domain and can cause the substitution of Arg for Gln. S503P is also located in the cytoplasmic domain and can cause the substitution of and Ser for Pro. Many studies suggested that these three polymorphisms were involved in the etiology of various cancers, including renal cell carcinoma, gastric cancer, pancreatic cancer, cervical cancer (Olson et al., 2007; Castro et al., 2009; Mohan et al., 2009; Chu et al., 2012). However, the results of these studies were somehow inconclusive or even contradictory. For example, Chu H and his colleagues found that I75V was associated with a decreased risk of renal cell carcinoma (Chu et al., 2012). While Nakamura E found that I75V is related to an increased risk of renal cell carcinoma (Nakamura et al., 2002). In order to gain a more comprehensive knowledge of the association between the three polymorphisms of IL-4R and cancer risks, we conducted a meta-analysis on eligible case-control studies.

Materials and Methods

Publication search

A comprehensive literature search was conducted on Pubmed, EMBASE and China National Knowledge Infrastructure (CNKI) for studies reported up to October 30, 2012. Two reviewers independently identified articles evaluating the association of cancer risk and IL-4R polymorphisms. The search terms were used as follows: (cancer or carcinoma) and (IL-4R or interleukin-4 receptor) AND (Polymorphism or mutation or variant). Hand-searching references of original articles or review articles on this topic were also performed to identify additional articles. All languages were searched. Studies included in this meta-analysis have to meet the following criteria: (1) investigation of the polymorphisms of IL-4R and cancer risk; (2) use of a case-control design based on unrelated individuals; (3) sufficient genotype distributions for cases and controls so that an odds ratio (OR) with 95% confidence interval (CI) could be assessed. Of the studies published using the same case series, we selected the most recent ones with the largest sample size.

Data extraction

Information was carefully extracted from identified studies by two independent reviewers and a consensus on all items had been reached. The following data were collected from each manuscript: author, year of publication, country, cancer type, ethnicity, diagnosis method, case and control number, genotyping information, as well as source of control groups (population-based or hospital-based).

Statistical Analysis

OR [odds ratio] and 95% CI were used to estimate the strength of association between the IL-4R polymorphisms and cancer risk. The statistical significance of summary OR was determined using Z-test.

The genetic models that we used to evaluated the pooled ORs were dominant model (GA+ GG vs. AA for Q576R and I75V; CC+CT vs.TT for S503P), recessive model (GG vs. AA+AG for Q576R and I75V; CC vs. CT+TT for S503P), homozygote comparison (GG vs. AA for Q576R and I75V; CC vs. TT for S503P) and heterozygote comparison (GA vs. AA for Q576R and I75V; CT vs. TT for S503P).

Heterogeneity was evaluated by a χ^2-based Q statistic, and statistical significance was assumed for P value less than 0.05. When P value was above 0.05, OR was pooled using the fixed-effect model, otherwise the random effect model was used. If the heterogeneity was significant, the Galbraith plot would be used to detect the potential sources of heterogeneity (Wei et al., 2010). The statistical significance of OR was analyzed by Z test, $P < 0.05$ was considered statistically significant.

In addition to the comparison among all subjects, we also performed stratification analyses by cancer type (cancer types were combined into "others" group if each of them contained only one study), ethnicity and source of controls.

The possible publication bias was examined visually by the Begg's funnel plot and the degree of asymmetry was tested by Egger's test. All of the statistical tests were performed by STATA11.0.

Results

Meta-analyses database

178 relevant publications were identified after initial screening based on our search criteria (up to September 13, 2012). Among these, 27 articles were subjected to further examination after reading the titles and abstract. 5 articles were excluded for not relevant to the 3 studied SNPs (Brown et al., 2007; Seno et al., 2007; Wilkening et al., 2008; Johnson et al., 2011; Xia et al., 2011). Two articles were excluded for not providing detailed genotype data (Brenner et al., 2007; Schwartzbaum et al., 2007). Finally, our meta-analysis database consisted of 21 publications (Figure1), and each article provided an individual case-control study. Overall, there were 18 articles for the IL-4R Q576R polymorphism, 10 articles for the IL-4R I75V polymorphism and 8 articles for the IL-4R S503P polymorphism. Of these, 5 studies were conducted in Asians, 13 studies were conducted in Caucasians and one study was conducted in Indians. Two studies were subjected to the mixed group for

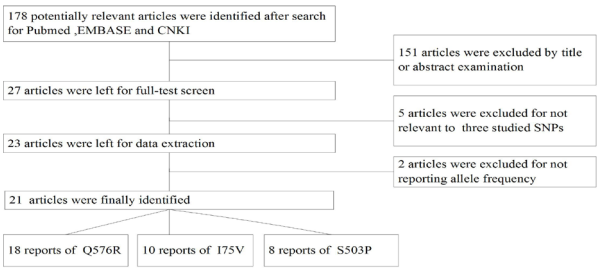

Figure 1. Flow Chart for the Process of Selecting Related Publications

Table 1. Associations Between the IL-4R Q576 R Polymorphism and Cancer Risk

Varibles	n[a]	GG VS AA+AG		GG+AG VS AA		GG VS AA		AG VS AA	
		OR(95%CI)	P[b]	OR(95%CI)	P[b]	OR(95%CI)	P[b]	OR(95%CI)	P[b]
Total	19	1.02 (0.88-1.18)	0.13	0.99(0.89-1.02)	0.36	0.98(0.84-1.14)	0.21	0.95(0.89-1.02)	0.25
Tumor site									
Bladder	2	1.27(0.86-1.87)	0.83	0.93(0.73-1.18)	0.11	1.22(0.83-1.81)	0.98	0.90(0.68-1.18)	0.08
Brain	3	1.00 (0.46-2.17)[c]	0.02	0.98(0.83-1.15)	0.75	0.98(0.47-2.04)[c]	0.04	0.99(0.84-1.17)	0.68
Other	4	1.21(0.87-1.68)	0.95	0.93(0.81-1.06)	0.38	1.17(0.84-1.62)	0.91	0.90(0.78-1.03)	0.39
Cervical	3	0.77 (0.60-0.98)	0.40	0.93(0.82-1.06)	0.78	0.76(0.58-0.98)	0.39	0.97(0.84-1.11)	0.88
Hematological	2	1.31 (0.77-2.23)	0.53	0.88(0.33-2.35)	0.13	1.27(0.49-3.26)	0.31	0.77(0.35-1.69)	0.22
Pancreatic	2	2.05 (0.73-5.75)	0.25	0.81(0.54-1.22)	0.82	1.80(0.72-4.49)	0.31	0.71(0.46-1.10)	0.48
Renal	3	1.22 (0.52-2.88)	0.21	1.12(0.71-1.76)	0.07	1.22(0.51-2.94)	0.20	1.08(0.67-1.74)	0.07
Ethnicity									
Caucasian	12	1.01 (0.85-1.20)	0.08	0.90(0.83-0.98)	0.78	0.96(0.80-1.16)	0.17	0.89(0.82-0.98)	0.57
Asian	5	0.94 (0.68-1.30)	0.18	1.04(0.92-1.17)	0.12	0.95(0.68-1.31)	0.17	1.05(0.93-1.19)	0.15
Mixed	2	1.21 (0.72-2.06)	0.92	1.02(0.82-1.27)	0.40	1.21(0.71-2.07)	0.98	0.99(0.79-1.25)	0.35
Control resource									
HB	7	1.02 (0.80-1.29)	0.50	0.92(0.84-1.01)	0.22	0.98(0.77-1.25)	0.60	0.92(0.83-1.01)	0.11
PB	12	1.01 (0.84-1.21)	0.05	0.98(0.90-1.08)	0.51	0.98(0.80-1.19)	0.08	0.98(0.89-1.09)	0.50

[a]Number of comparisons; [b]P value of Q-test for heterogeneity test; [c]Random-effects model was used when P value for heterogeneity test< 0.05; otherwise, fixed-effects model was used

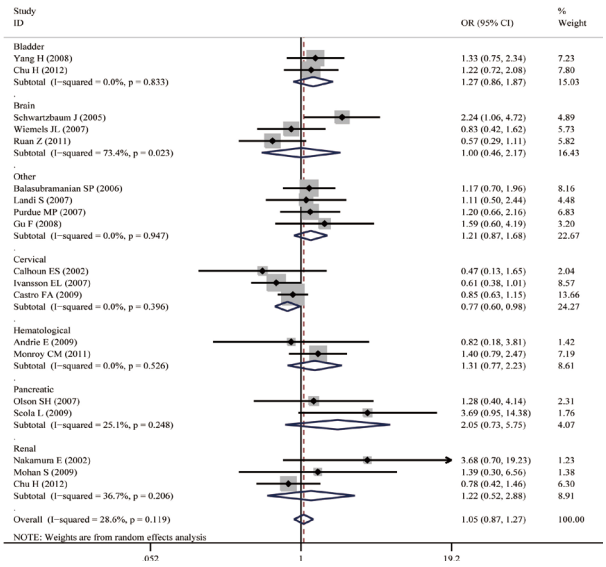

Figure 2. Forest Plot of Cancer Risk Associated with the IL-4R Q576R Polymorphism (GG vs. AA +AG). The squares and horizontal lines correspond to the OR and 95%CI. The area of the squares indicates the study-specific weight

not providing the ethnicity information. Different genotyping methods were used, including TaqMan, polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP), polymerase chain reaction-preferential homoduplex formation assay (PCR-PHFA), polymerase chain reaction-ligation detection reaction (PCR-LDR), Dynamic allele-specific hybridization (DASH), sequencing, multiplex PCR with hybridization, OpenArray™ SNP genotyping system, SNPlex assay. However, only 14 studies described genotyping quality control, such as random repetition of a part of samples, using a different genotyping method to confirm the data or blindness to be case-control status. Cancers were confirmed histologically or pathologically in all the studies. The genotype distributions among the controls were in agreement with Hardy-Weinberg equilibrium, except for two studies for Q576R (Schwartzbaum et al., 2005; Balasubramanian et al., 2006).

IL-4R Q576Rquantitative synthesis

Totally, 7921 cases and 8694 control subjects from 19 case-control studies were included for the analysis of the relationship between Q576R and cancer risk. There was a wide variation in the IL-4R Q576R G allele frequency across different ethnicities. The average frequency of Q576R G allele was 0.17 in Asian controls and 0.27 in Caucasian controls.

Overall, the results did not show any statistical evidence of an association between Q576R polymorphism and overall cancer risk (Table 1). In the stratified analyses by tumor site (Table1 and Figure 2), however, there was evidence that GG genotype was associated with a significantly decreased cervical cancer risk (recessive model: OR = 0.77, 95%CI = 0.60-0.98; homozygote comparison: OR = 0.76, 95%CI = 0.58-0.98). When stratified by ethnicity (Table 1), the G allele was associated with significant decreased cancer risk in Caucasians (dominant model: OR = 0.90, 95%CI = 0.83-0.98; heterozygote comparison: OR = 0.89, 95%CI = 0.82-0.98). When stratified by control resource, no association was found in the two subgroups.

There is no substantial heterogeneity across the 19 studies related to the Q576R polymorphism and cancer risk. Although the genotype distribution in the control group of two studies (Schwartzbaum et al., 2005; Balasubramanian et al., 2006) did not follow HWE, the pooled ORs were not altered after excluding these two studies (data not shown). No publication bias was found by either the funnel plot (Figure 3) or the Egger's test (P = 0.108).

IL-4R I75V quantitative synthesis

The identified publications included 5169 cases and 4704 controls from 10 case-control studies. All of the genotype distributions in the control group were consistent with HWE. The G allele frequency was significantly different among different ethnicities. The average frequency of I75V G allele was 0.58 in Asian controls and 0.44 in Caucasian controls.

Table 2. Associations Between the IL-4R I75V Polymorphism and Cancer Risk

Varibles	n[a]	GG VS AA+AG		GG+AG VS AA		GG VS AA		AG VS AA	
		OR(95%CI)	P[b]	OR(95%CI)	P[b]	OR(95%CI)	P[b]	OR(95%CI)	P[b]
Total	10	0.98(0.81-1.20)[c]	0.00	0.98(0.85-1.14)[c]	0.02	0.99(0.79-1.26)[c]	0.00	0.98(0.84-1.14)	0.05
Tumor site									
Other	3	0.94(0.75-1.19)	0.83	0.97(0.80-1.19)	0.5	0.93(0.72-1.22)	0.58	0.99(0.80-1.22)	0.58
Cervical	2	1.28(0.77-2.12)[c]	0.01	1.12(0.80-1.56)[c]	0.04	1.33(0.70-2.57) [c]	0.01	1.02(0.87-1.20)	0.18
Gastric	2	0.84(0.56-1.25)	0.09	1.12(0.90-1.39)	0.41	0.97(0.57-1.65)	0.10	1.23(0.98-1.55)	0.65
Renal	3	1.10(0.55-2.20)[c]	0.00	0.71(0.57-0.89)	0.36	0.93(0.44-2.00)[c]	0.01	0.69(0.55-0.87)	0.71
Ethnicity									
Caucasian	6	0.99(0.79-1.24)[c]	0.01	1.04(0.92-1.18)	0.29	1.02(0.79-1.31)[c]	0.02	1.05(0.94-1.17)	0.49
Asian	4	1.02(0.66-1.59)[c]	0.01	0.89(0.61-1.31)	0.07	1.01(0.56-1.82)[c]	0.01	0.76(0.62-0.94)	0.12
Control resource									
PB	7	1.00(0.75-1.34)[c]	0.00	1.03(0.90-1.17)	0.25	1.01(0.75-1.38)[c]	0.00	1.03(0.92-1.16)	0.44
HB	3	0.96(0.79-1.17)	0.78	0.95(0.62-1.44)[c]	0.02	0.95(0.64-1.40)	0.10	0.94(0.61-1.46)[c]	0.02

[a]Number of comparisons; [b]P value of Q-test for heterogeneity test; [c]Random-effects model was used when P value for heterogeneity test< 0.05; otherwise, fixed-effects model was used

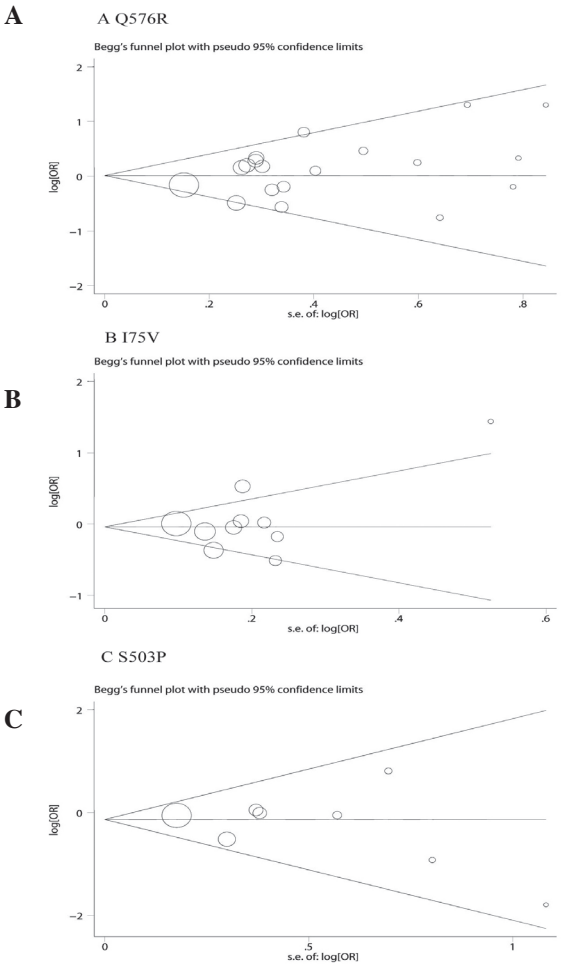

Figure 3. Funnel Plot for Publication Bias of the Identified IL-4R Polymorphisms. (A) Q576R, (B) I75V, (C) S503P. Each point represents a separate study for the indicated association. Log(OR), natural logarithm of OR. Horizontal line, mean effect size

The results did not show any statistical evidence of an association between the I75V polymorphism and overall cancer risk (Table2). After stratified by tumor site, the G allele carrier has a decreased Renal cancer risk (Dominant model: OR = 0.71, 95%CI = 0.57-0.89: heterozygote comparison: OR = 0.69, 95%CI = 0.55-0.87). In the subgroup analysis by ethnicity, the GA genotype was associated a decreased cancer risk compared with the AA

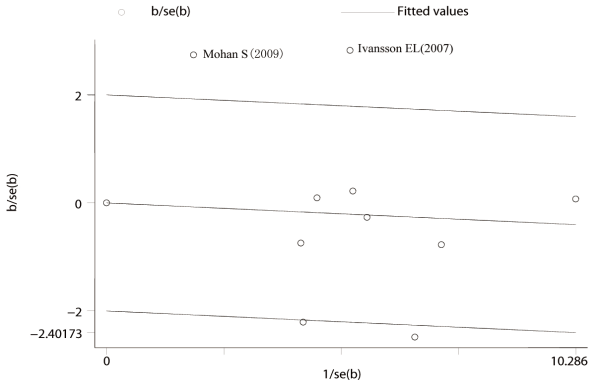

Figure 4. Galbraith Plot Analysis for the Source of Heterogeneity for the IL-4R I75V Polymorphism

genotype in Caucasians (heterozygote comparison: OR = 0.76, 95%CI = 0.62-0.94). However, when stratified by source of controls, no significant association was identified in all genetic models.

Current meta-analysis indicated significant heterogeneity between studies in overall comparisons (P = 0.001). We performed Galbraith plot analysis to explore the source of heterogeneity. The result indicated that two studies (Ivansson et al., 2007; Mohan et al., 2009) were the main source of heterogeneity (Figure 4). Exclusion of these two studied effectively abrogated the heterogeneity (P = 0.27). Moreover, the results were not substantially changed after excluding these two studies (OR = 0.89, 95%CI = 0.79-1.01), suggesting the results of this meta-analysis were stable. No publication bias was identified by either the funnel plot or (Figure 3) or the Egger's test (P = 0.42).

IL-4R S503P quantitative synthesis

The selected publications included 5509 cases and 4958 controls from 8 case-control studies. All of the genotype distributions in the control group were consistent with HWE. The C allele frequency was significantly different in different ethnicities. The average S503P C allele frequency was 0.08 in Asians and 0.19 in Caucasians.

As shown in Table 3, no significant association was found between S503P polymorphism and overall cancer risk. After stratified by ethnicity, the CC carriers seemed to have a reduced cancer risk in Asians compared with TT

Table 3. Associations Between the IL-4R S503P Polymorphism and Cancer Risk

Varibles	n[a]	CC VS TT+TC		CC+TC VS TT		CC VS TT		TC VS TT	
		OR(95%CI)	P[b]	OR(95%CI)	P[b]	OR(95%CI)	P[b]	OR(95%CI)	P[b]
Total	8	0.87(0.68-1.11)	0.39	1.02(0.93-1.12)	0.15	0.87(0.68-1.11)	0.34	1.040.94-1.14)	0.16
Tumor site									
Other	4	0.81(0.33-1.96)	0.15	1.06(0.92-1.22)	0.60	0.82(0.35-1.95)	0.16	1.07(0.93-1.24)	0.42
Cervical	2	0.80(0.52-1.23)	0.18	0.90(0.71-1.13)	0.13	0.77(0.46-1.27)	0.13	0.93(0.77-1.12)	0.23
Brain	2	0.98(0.53-1.82)	0.95	1.28(0.87-1.88)	0.14	1.05(0.56-1.95)	0.88	1.31(0.86-2.00)	0.12
Ethnicity									
Caucasian	5	0.91(0.70-1.18)	0.44	0.99(0.82-1.20)	0.06	0.90(0.69-1.18)	0.37	1.00(0.82-1.22)	0.07
Asian	2	0.28(0.08-0.98)	0.52	1.07(0.89-1.29)	1.00	0.29(0.08-0.99)	0.52	1.11(0.92-1.34)	0.88
Mixed	1	1.05(0.51-2.17)		1.16(0.90-1.49)		1.10(0.53-2.28)		1.16(0.89-1.51)	
Control resource									
HB	3	0.68(0.30-1.52)	0.08	1.02(0.86-1.20)	0.54	0.61(0.14-2.63)	0.10	1.03(0.86-1.24)	0.32
PB	5	0.89(0.69-1.15)	0.70	1.05(0.87-1.26)	0.05	0.89(0.69-1.14)	0.54	1.06(0.89-1.27)	0.08

[a]Number of comparisons; [b]P value of Q-test for heterogeneity test

carriers (homozygote comparison: OR = 0.29, 95% CI = 0.08-0.99). However, when stratified by tumor site or control resource, no significant association was found in the subgroups.

No significantly heterogeneity was identified in the main meta-analysis. Leave-one-out sensitivity procedure showed that the combined ORs were not substantially changed. This indicated that the results were stable. No publication bias was found by either the funnel plot or (Figure 3) or the Egger's test (P = 0.53).

Discussion

IL-4R, an important cytokine receptor, has been demonstrated to play a vital important role in different cancers. A lot of studies have been performed to investigate the association between the IL-4R polymorphisms and cancer risks; however, the results are inconclusive. To derive a more precise conclusion, we performed a comprehensive meta-analysis including 21 case-control studies to explore the association between 3 most extensively studied polymorphisms of IL-4R (Q576R, I75V and S503P) and cancer risk.

The overall meta-analysis showed that the three polymorphism sites were not associated with cancer risk. When stratified by tumor site, the G carriers of Q576R were associated with a decreased cervical cancer risk and the G carriers of I75V were shown to have a lower renal cancer risk. As different type of cancer exposed to different environmental factors, gene-environment interaction may be different in each kind of cancer. Furthermore, different tissue have different expression profiles of IL-4R, thus the same polymorphism may play different role in different tissues. However, all the results should be treated with reservation. Because in some cancer types, there were only two case-control studies were recruited, which may limit the statistic power to gain a reliable conclusion.

In the subgroup analysis by ethnicity, the results indicated that Q576R G allele carriers in Caucasians had a decreased cancer risk. I75V G allele carriers had a decreased cancer in Asian subgroup. S503P C allele carriers were also associated with a decreased cancer risk in Asians. While the specific mechanisms by which the IL4R polymorphisms examined here may be associated with decreased cancer risk in certain ethnic groups were unknown, certain IL4R SNPs, such as I75V, have already been shown up-regulate the receptor's response to IL-4, which in turn results in activation of the Stat6 pathway (Mitsuyasu et al., 1998) and mediate growth inhibition and induction of apoptosis in cancer cells (Gooch et al., 2002). In addition, as people from different ethnicities are exposed to different environment factors and have different life styles, these factors can interact with gene polymorphisms and strengthen or weaken the effect of the studied polymorphisms. As there were only two case-control studies in some ethnic subgroup, the statistic power was limited by the small sample size. Furthermore, there was no study based on African participants. Additional large sample case-control studies should be carried out especially in Africans.

Hardy–Weinberg equilibrium (HWE) is an important issue to consider when performing meta-analysis. Deviation from HWE in controls may reflect defects in the process of conducting genetic association research, such as genotyping error, population stratification or selection bias. All the studies were in consist with HWE except two studies (Schwartzbaum et al., 2005; Balasubramanian et al., 2006) for Q576R, so we performed sensitivity analysis by excluding these two studies. The results were stable which indicated that our conclusion was reliable. Heterogeneity is another important issue in meta-analysis. Significant heterogeneity was detected the overall analysis of I75V. After Galbraith plot analysis, we identified two studies were the main source of heterogeneity. Excluding of these two studies hadn't changed the results which indicated that our results were stable. Publication bias is also important in meta-analyses. In the current study, we didn't detect any significant publication bias in the three polymorphisms.

There were some limitations of this meta-analysis. First of all, only published papers were recruited in current meta-analysis, and it is possible that there were some unpublished data was missed. Secondly, there were only two studies in some subgroups; this may limit the statistical power. Thirdly, lacking of detailed genotype data of the reviewed studies limited our further analysis of gene-gene or gene-environment interaction analysis.

In summary, our mete-analysis suggested that Q576R, I75V and S503P may be associated with decreased cancer risk for certain types of cancers and in some specific ethnic groups. Future case-control studies with large sample size and muti-ethnic groups are needed to further these associations in detail. Moreover, detailed gene-gene and gene-environment interaction data is needed to get a

comprehensive understanding of the association between the IL-4R polymorphisms and cancer risk.

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