RESEARCH ARTICLE

Positive Association Between *IL-16* rs11556218 T/G Polymorphism and Cancer Risk: a Meta-analysis

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Abstract

Background: Interleukin-16 (*IL-16*) is a multifunctional cytokine which plays a key role in inflammatory and autoimmune diseases as well as in cancer. Genetic polymorphisms of *IL-16* have been implicated in susceptibility to cancer. However, associations remain inconclusive. The present meta-analysis was therefore carried out to establish a more conclusive association of *IL-16* polymorphisms with cancer risk. Materials and Methods: Relevant studies were searched through the PubMed, Embase, Web of Science, Google Scholar and Wan fang electronic databases updated in October 2013. Odds ratios (OR) and 95% confidence intervals (95% CI) were used to assess the association between *IL-16* polymorphisms and cancer risk. Results: Eight eligible studies (rs4778889 T/C: 8, rs11556218 T/G: 7, rs4072111 C/T: 6) that met our selection criteria were included. The meta-analysis indicated that rs11556218 T/G was associated with a significant increased risk of cancer (G vs. T, OR=1.321, 95% CI=1.142-1.528, *P* <0.001; TG vs. TT, OR=1.665, 95% CI=1.448-1.915, *P*<0.001; GG+TG vs. TT, OR=1.622, 95% CI=1.416-1.858, *P*<0.001),as well as nasopharyngeal carcinoma and colorectal cancer. Furthermore, in the subgroup of Chinese, significant associations were found between rs11556218 polymorphism and cancer risk. There was no statistically significant association between the other two variants (rs4778889, rs4072111) and risk of cancer. Conclusions: This meta-analysis suggests that the *IL-16* rs11556218 polymorphism is associated with increased cancer risk. Large well-designed studies involving various cancer types and different populations are now needed.

Keywords: Interleukin-16 - cancer - polymorphism - meta-analysis

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Introduction

Cancer is one of the leading causes of human death especially in the developing countries and it also becomes the second killer for people in the developed countries (Weiderpass et al., 2010; Kimman et al., 2012). Cancer is a multifactorial disease with a complex etiology of interplay among genetic constitution, environmental exposures, and other factors (Bredberg et al., 2011). Many intracellular and extracellular factors were involved in carcinogenesis, cancer growth and metastasis. Increasing evidence has shown that molecular biomarkers can improve the diagnostic and therapeutic efficacy of cancer and genetic markers play an important role in the prevention of some hereditary cancers (Quinn et al., 2012; Almendro et al., 2013). Preclinical and clinical studies has identified that inflammation was a risk factor for cancer and about 25% of cancer cases worldwide relate to cases of inflammation (Hussain et al., 2007). Inflammation-associated molecules including cytokines, chemokines and immune cells are associated with carcinogenesis and exist in many precancerous and cancerous tissues (Mantovani et al., 2005; Sethi et al., 2012). Cytokines can facilitate cancer promotion and progression via involving in immune surveillance and inflammatory reactions, such as tumor necrosis factor (TNF) (Muc-Wierzgon et al., 2006), interleukin (IL)-1, and IL-6 (Kai et al., 2005) have been reported to play roles in human cancer.

Interleukin-16 (*IL-16*) is a pro-inflammatory cytokine that is initially known as a lymphocyte chemoattractant factor (LCF) and has a wide array of biological functions (Center et al., 1982). The *IL-16* gene located on chromosome 15q26.3 in the human genome and was initially translated into a precursor protein consisting of 631 amino acids which was cleared by caspase-3 to active C-terminal domain containing 121 amino acids (Drwinga et al., 1993; Baier et al., 1997; Zhang et al., 1998). *IL-16* can activate $CD4^+$ T cells, monocytes, macrophages, eosinophils and dendritic cells by binding CD4 receptor (Center et al., 1996). In addition, *IL-16* can stimulate the monocyte to secrete tumor-associated inflammatory cytokines TNF-α, IL-1β, IL-6 and IL-15 which have been demonstrate to play critical roles in tumorigenesis (Center et al., 1982; Mathy et al., 2000; Muc-Wierzgon et al., 2006; Shanmugham et al., 2006).

Genetic studies have reported that some gene polymorphisms of cytokine pathway were associated with the severity of cancers (Jim et al., 2012). Polymorphisms

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located in the regulatory and coding regions may influence the gene transcription and cause person-to-person deviation in the *IL-16* production. There are three validated polymorphisms of *IL-16* gene including non-synonymous SNP C/T Ser (Serine) to Pro (Proline) substitution (rs4072111), SNP T/C (rs4778889) located at 295 bp upstream from the start site of transcription and T/G Asn (Asparagine) to Lys (Lysine) substitution (rs11556218) in exon 6 of *IL-16* gene sequence (Nakayama et al., 2000). Recently, several studies have investigated the association between *IL-16* polymorphisms and cancer risk, such as nasopharyngeal carcinoma (NPC), colorectal cancer (CRC), cervical cancer, hepatocellular carcinoma (HCC), gastric cancer (GC) and so on. However, these studies yielded different or even controversial results. Considering the limits of the single study with small sample size, we carried out the present meta-analysis of all eligible studies to derive a more powerful estimation of the association between *IL-16* polymorphisms and cancer risk.

Materials and Methods

Search strategy

We conducted a systematic literature search to October, 2013, using the electronic databases of PubMed, Embase, Web of Science, Google Scholar and Wan fang without language ,time period and sample size limitations covering all publications regarding the association between *IL-16* polymorphisms and cancer susceptibility. The following search terms were used: "cancer or carcinoma or tumor or neoplasms", "interleukin16 or *IL-16* or IL16", and "polymorphism or mutation or variant or single nucleotide polymorphism or SNP". The references of articles and reviews were also searched to find other eligible studies. When multiple articles researched the same case series, we selected the one with the largest population. When an article reported results on different subpopulations, we treated each subpopulation as a separate comparison.

Selection criteria

The following inclusion criteria were used in the meta-analysis: 1) population- or hospital-based case-control studies published as original articles; 2) evaluating *IL-16* gene polymorphisms and cancer risk; 3) studies must provided sufficient genotype distribution information, rs4778889, rs11556218 and rs4072111 in the cases and controls; 4) independent studies without repeat reports on the same population. Studies were excluded if one or more of the following criteria existed: 1) case reports, reviews, repeated literature, non-human studies; 2) genotype frequency and genotype distribution were not included; 3) not enough information for data extraction; (4) the distribution of genotypes among controls are not fitted in Hardy-Weinberg equilibrium (HWE).

Data extraction

The information was carefully extracted from each eligible study by two reviewers independently and any disagreements were settled down by group discussion. The data extracted from each publication in this meta-analysis were as follows: the surname of first author, year of publication, ethnicity population, cancer type, genotyping method, source of controls, sample size of cases and controls, genotype distribution in cases and controls, and HWE, respectively.

Statistical analysis

The meta-analysis was performed using Stata version 12.0 software (Stata Corp, College Station, TX). The pooled odds ratio (OR) with 95% confidence intervals (CIs) was used to assess the strength of association between *IL-16* gene polymorphisms and cancer risk based on the genotype frequencies in cases and controls. Subgroup analyses were also performed to test the effects of ethnicity and cancer type. The 95%CI without 1 for OR indicated a significant increased or reduced cancer risk. Chi-square-based Q statistic test and inconsistency indexes (I^2 statistic) were calculated for the heterogeneity of studies in the meta-analysis. P_Q<0.1 or I^2≥50% indicated the existence of heterogeneity among studies and the DerSimonian-Laird random-effects model was conducted to calculate the pooled OR. Otherwise, the Mantel-Haenszel fixed-effects model was used. The funnel plots and Egger's test were used to detect the publication bias. An Egger's test *P* value <0.05 was considered statistically significant publication bias. All *P* values were two-sided, and *P*<0.05 for any test was considered to be statistically significant.

Results

Characteristics of studies

The detailed study selection process was shown in Figure 1. A total of 15 publications regarding *IL-16* gene polymorphisms and cancer risk were identified. Nine publications were excluded after reading the full article in detail, because they were editorial comment, letter, case report, other polymorphism of *IL-16*, without sufficient data, repeated literatures and violated HWE (Thomas et al., 2008; Obara et al., 2010; Azimzadeh et al., 2012; Batai et al., 2012; Lin et al., 2012; Deng et al., 2012; Du, et al., 2012; Hughes et al., 2013; Zhang et al., 2013). The study of Gao et al. (2009b) presented separate OR by colorectal and gastric two cancer types and each of them was considered as a separate study. Finally, eight case-control studies from

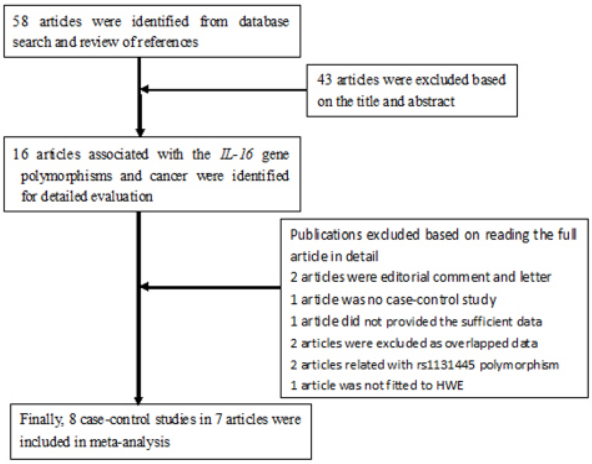

Figure 1. Flow Chart for the Literature Search in this Meta-Aanalysis

seven publications (6 in English, 1 in Chinese) involving 3944 cases were finally included into the meta-analysis (Gao et al., 2009a; 2009b, Zhu et al., 2010; Azimzadeh et al., 2011; Li et al., 2011; Zhao et al., 2012; Qin et al., 2014). The main characteristics of the studies are listed in Table 1. Among these publications, only one study on Iranian population (Azimzadeh et al., 2011) and the remaining six studies on Chinese population (Gao et al., 2009a; 2009b; Zhu et al., 2010; Li et al., 2011; Zhao et al., 2012; Qin et al., 2014). Eight eligible case-control studies associated with rs4778889 T/C polymorphism, seven for rs11556218 T/G polymorphism, and six for rs4072111 C/T polymorphism. The studies focused on the following cancer types: 2 studies investigated colorectal carcinoma (Gao et al., 2009b; Azimzadeh et al., 2011), 2 nasopharyngeal carcinoma (Gao et al., 2009a; Qin et al., 2014), 1 gastric cancer (Gao et al., 2009b), 1 hepatocellular carcinoma (Li et al., 2011), 1 renal cell carcinoma (Zhu et al., 2010) and 1 cervical cancer (Zhao et al., 2012). All of the study designs were hospital based (HB) and used polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) genotyping method.

Association of rs11556218 T/G polymorphism with cancer risk

As shown in Table 2, we observed a significant

Table 1. Characteristics of Case Control Studies Included in Meta-Analysis

First author	Ethnicity	Cancer types	Genotyping method	Control sources	Sample Size (case/control)	Genotype Distribution (Case/Control)			HWE
						rs4778889 T/C			
						TT	TC	CC	
Gao (2009)	Chinese	nasopharyngeal carcinoma	PCR-RFLP	HB	206/373	131/228	65/128	10/17	Y
Li (2011)	Chinese	hepatocellular carcinoma	PCR-RFLP	HB	206/264	158/182	42/76	6/6	Y
Azimzadeh (2011)	Iranian	colorectal cancer	PCR-RFLP	HB	260/405	178/274	73/112	9/19	Y
Qin (2013)	Chinese	nasopharyngeal carcinoma	PCR-RFLP	HB	75/75	39/49	36/26	0/0	Y
Zhao (2012)	Chinese	cervical cancer	PCR-RFLP	HB	136/193	84/115	48/73	4/65	Y
Gao (2009)	Chinese	colorectal cancer	PCR-RFLP	HB	376/480	246/294	119/164	11/22	Y
Gao (2009)	Chinese	gastric cancer	PCR-RFLP	HB	220/480	117/294	90/164	13/22	Y
Zhu (2010)	Chinese	renal cell carcinoma	PCR-RFLP	HB	335/340	199/171	122/135	14/34	Y
						rs11556218 T/G			
						TT	TG	GG	
Gao (2009)	Chinese	nasopharyngeal carcinoma	PCR-RFLP	HB	206/373	91/210	109/151	6/12	Y
Li (2011)	Chinese	hepatocellular carcinoma	PCR-RFLP	HB	206/264	122/160	62/78	22/26	Y
Azimzadeh (2011)	Iranian	colorectal cancer	PCR-RFLP	HB	260/405	62/124	178/226	20/55	Y
Qin (2013)	Chinese	nasopharyngeal carcinoma	PCR-RFLP	HB	75/75	32/46	37/26	6/3	Y
Zhao (2012)	Chinese	cervical cancer	PCR-RFLP	HB	136/193	52/102	78/84	6/7	Y
Gao (2009)	Chinese	colorectal cancer	PCR-RFLP	HB	376/480	143/265	219/197	14/18	Y
Gao (2009)	Chinese	gastric cancer	PCR-RFLP	HB	220/480	94/265	112/197	14/18	Y
						rs4072111 C/T			
						CC	CT	TT	
Gao (2009)	Chinese	nasopharyngeal carcinoma	PCR-RFLP	HB	206/373	111/221	87/139	8/13	Y
Li (2011)	Chinese	hepatocellular carcinoma	PCR-RFLP	HB	206/264	110/136	80/104	16/24	Y
Azimzadeh (2011)	Iranian	colorectal cancer	PCR-RFLP	HB	260/405	196/324	56/77	8/4	Y
Qin (2013)	Chinese	nasopharyngeal carcinoma	PCR-RFLP	HB	75/75	41/44	34/31	0/0	Y
Gao (2009)	Chinese	colorectal cancer	PCR-RFLP	HB	376/480	235/283	123/179	18/18	Y
Gao (2009)	Chinese	gastric cancer	PCR-RFLP	HB	220/480	144/283	72/179	4/18	Y

HB, Hospital–based; HWE, Hardy–Weinberg equilibrium in control population; PCR–RFLP, Polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Meta-Analysis of Eligible Studies Included in the Study

SNP	Comparison	No. of	Test of association			Mode	Test of heterogeneity			Publication
		studies	OR	95%CI	*p* Value		X^2	P_Q Value	I^2	bias P_{bias}
rs4778889 T/C	C *vs* T	8	0.925	0.780-1.098	0.374	R	17.19	0.016	59.3	0.373
	CC *vs* TT	8	0.742	0.546-1.008	0.056	F	10.31	0.112	41.8	0.336
	TC *vs* TT	8	0.945	0.784-1.139	0.551	R	13.47	0.061	48	0.524
	TC+CCvs. TT	8	0.929	0.764-1.130	0.462	R	16.01	0.025	56.3	0.401
	CCvs. TT+TC	8	0.761	0.562-1.030	0.076	F	8.48	0.205	29.3	0.247
rs11556218 T/G	G *vs* T	7	1.321	1.142-1.528	<0.001	R	11.32	0.079	47	0.561
	GG *vs* TT	7	1.235	0.922-1.656	0.157	F	7.24	0.299	17.2	0.153
	TG *vs* TT	7	1.665	1.448-1.915	<0.001	F	7.92	0.244	24.3	0.692
	GG+TGvs. TT	7	1.622	1.416-1.858	<0.001	F	8.89	0.18	32.5	0.921
	GGvs.TG+TT	7	0.946	0.716-1.250	0.697	F	8.9	0.18	32.5	0.193
rs4072111 C/T	T vs.C	6	0.993	0.879-1.120	0.905	F	8.7	0.12	42.5	0.47
	TT *vs* CC	6	1.036	0.719-1.492	0.851	F	6.63	0.157	39.7	0.723
	CT *vs* CC	6	0.971	0.836-1.127	0.696	F	6.05	0.301	17.4	0.312
	TT+CT *vs* CC	6	0.981	0.849-1.134	0.796	F	7.66	0.176	34.7	0.402
	TT *vs* CT+CC	6	1.055	0.736-1.512	0.771	F	6.04	0.196	33.8	0.75

*SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence intervals; R, random-effect model; F, fixed-effects model

increased risk of cancer susceptibility in allele model (G *vs* T: OR= 1.321, 95%CI: 1.142-1.528, *p*<0.001, Figure 2), heterozygous model (TG *vs* TT: OR=1.665, 95%CI: 1.448-1.915, *p*<0.001) and dominant model (GG+TG *vs* TT: OR= 1.622, 95%CI: 1.416-1.858; *p*<0.001) of overall the populations. However, no significant association were found from the homozygous model (GG *vs* TT: OR=1.235, 95%CI: 0.922-1.656, *p*=0.157) and recessive model (GG *vs* TG+TT: OR=0.946, 95%CI: 0.716-1.250, *p*=0.687). Subgroup analysis by ethnicity suggested that there was a significant association between rs11556218 T/G polymorphism with cancer risk under four genetic models (G *vs* T: OR= 1.403, 95%CI: 1.251-1.574, *p*<0.001; GG *vs* TT: OR=1.486, 95%CI:1.058-2.087, *p*=0.022; TG *vs* TT: OR=1.682, 95%CI: 1.445-1.957, *p*<0.001; GG+TG *vs* TT: OR= 1.662, 95%CI: 1.435-1.926, *p*<0.001)in Chinese population. Subgroup analyses in Iranian were not analyzed because of only one included study from this population. In the stratified analyses by cancer types, increased cancer risk was found in nasopharyngeal carcinoma and colorectal cancer (Table 4).

Association of rs4778889 T/C and rs4072111 C/T polymorphisms with cancer risk

As shown in Table 2 and Table 3, we found no significant association of the rs4778889 T/C and rs4072111 C/T polymorphisms in *IL-16* with cancer risk neither in overall populations nor in Chinese population for any genetic models. While, the results of the overall meta-analysis suggested a decreased trend between rs4778889 T/C polymorphism and cancer susceptibility in the homozygous model (CC *vs* TT: OR=0.742, 95%CI: 0.546-1.008, *p*=0.056) and recessive model (CC *vs* TT+TC: OR=0.761, 95%CI: 0.562-1.030, *p*=0.076), but non-significant.

Publication bias

We used Begg's funnel plot and Egger's test to assess

Table 3. Meta-Analysis of Eligible Studies in Chinese

SNP	Comparison	Test of association			Mode	Test of heterogeneity		
		OR	95%CI	*p* value		X^2	P_Q value	I^2
rs4778889 T/C	C *vs* T	0.927	0.759-1.132	0.458	R	17.15	0.009	65
	CC *vs* TT	0.744	0.535-1.035	0.079	F	10.3	0.067	51.5
	TC *vs* TT	0.938	0.755-1.166	0.566	R	13.3	0.038	54.9
	TC+CC *vs* TT	0.927	0.737-1.166	0.518	R	15.89	0.014	62.3
	CC *vs* TT+TC	0.766	0.553-1.062	0.11	F	8.46	0.133	40.9
rs11556218 T/G	G *vs* T	1.403	1.251-1.574	<0.001	F	5.05	0.41	1
	GG *vs* TT	1.486	1.058-2.087	0.022	F	3.02	0.697	0
	TG *vs* TT	1.682	1.445-1.957	<0.001	F	7.81	0.167	36
	GG+TG *vs* TT	1.662	1.435-1.926	<0.001	F	8.17	0.147	38.8
	GGvs.TG+TT	1.209	0.868-1.685	0.261	F	2.3	0.806	0
rs4072111 C/T	T vs.C	0.946	0.831-1.078	0.406	F	4.67	0.323	14.3
	TT *vs* CC	0.91	0.617-1.344	0.637	F	2.86	0.414	0
	CTvs. CC	0.935	0.796-1.100	0.419	F	4.69	0.321	14.7
	TT+CT *vs* CC	0.933	0.798-1.092	0.388	F	5.02	0.285	20.3
	TT *vs* CT+CC	0.936	0.638-1.373	0.737	F	2.61	0.456	0

*SNP, single nucleotide polymorphisms; OR, odds ratio; CI, confidence intervals; R, random-effect model; F, fixed-effects model

Table 4. Meta-Analysis of IL-16 rs11556218 T/G Polymorphism for Studies According to Cancer Type

SNP	Comparison	No. of studies	Test of association			Mode	Test of heterogeneity		
rs11556218 T/G			OR	95%CI	*P* Value		X^2	P_Q Value	I^2
	NPC								
	G *vs* T	2	1.442	1.134-1.833	0.003	F	0.86	0.354	0
	GG *vs* TT	2	1.573	0.704-3.518	0.27	F	1.02	0.313	1.9
	TG *vs* TT	2	1.74	1.2775-2.370	<0.001	F	0.28	0.596	0
	GG+TG *vs* TT	2	1.726	1.275-2.337	<0.001	F	0.51	0.474	0
	GGvs.TG+TT	2	1.198	0.543-2.645	0.654	F	0.89	0.344	0
	CRC								
	G *vs* T	2	1.249	0.840-1.856	0.272	R	6.63	0.01	84.9
	GG *vs* TT	2	0.948	0.600-1.499	0.82	F	2.03	0.154	50.9
	TG *vs* TT	2	1.861	1.491-2.323	<0.001	F	1.32	0.251	24.1
	GG+TG *vs* TT	2	1.756	1.412-2.182	<0.001	F	2.39	0.122	58.2
	GGvs.TG+TT	2	0.658	0.431-1.007	0.054	F	1.9	0.168	47.4
	Other								
	G *vs* T	3	1.315	1.114-1.553	0.001	F	2.99	0.224	33.2
	GG *vs* TT	3	1.478	0.955-2.287	0.08	F	1.98	0.371	0
	TG *vs* TT	3	1.453	1.163-1.815	0.001	F	3.83	0.147	47.8
	GG+TG *vs* TT	3	1.457	1.177-1.802	0.001	F	4.32	0.115	53.7
	GG *vs* TG+TT	3	1.303	0.851-1.995	0.223	F	0.97	0.615	0

*SNP, single nucleotide polymorphisms; OR, Crude odds ratio; CI, confidence intervals; R, random-effect model; F, fixed-effects model

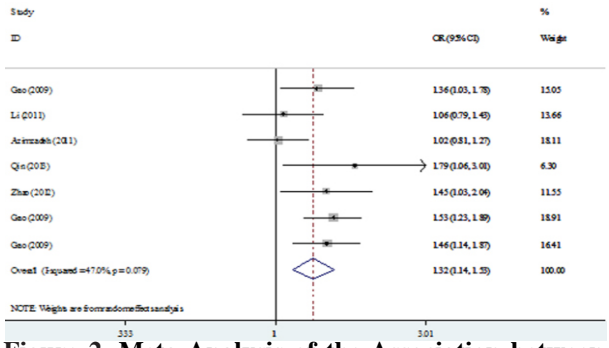

Figure 2. Meta-Analysis of the Association between IL-16 rs11556218 Polymorphism and Cancer Risk Under the Allele Model

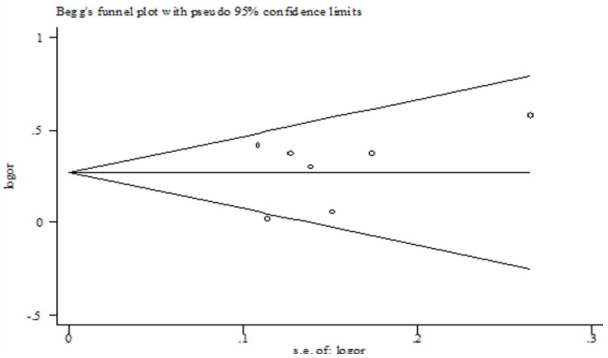

Figure 3. Funnel Plot Analysis to Detect Publication bias for Contrast G *vs* T of IL-16 rs11556218 Polymorphism in Overall Analysis

the publication bias of literatures. The funnel plots showed no obvious publication bias in any meta-analysis. The shape of the Begg's funnel plots for contrast G *vs* T of *IL-16* rs11556218 polymorphism in overall population shown in Figure 3. Egger's test was then performed for statistical test, no publication bias were detected for three polymorphisms (p= 0.373 for C *vs* T of rs4778889; p= 0.561 for G *vs* T of rs11556218; p= 0.470 for T *vs* C of rs4072111; Table 2).

Discussion

It has been proved that inflammatory cytokines and inflammatory cells play important roles in tumor development and chronic inflammation is the pathological basis for most of the human malignant tumors. In 1863, Virchow first indicated that inflammation was related to the tumor formation when he noticed the presence of leukocytes in neoplastic tissues (Balkwill et al., 2001). IL16, as a proinflammatory cytokines involved in tumor growth and progression, but the definite mechanism is still under evaluation. *IL-16* can induce the expression of the TNF-α which plays an important role in apoptosis and cell survival and these phenomena do propose a pathophysiological task for *IL-16* as a mediator of cancer (van Horssen et al., 2006). Previous studies have shown that higher levels of *IL-16* presented in tumor patients, associated with advanced stages of cancer and a worse patient outcome depending on the type of tumor (Kovacs et al., 2001, Alexandrakis et al., 2004). It is biologically reasonable to hypothesize a potential relationship between the *IL-16* gene polymorphisms and cancer risk.

Single nucleotide polymorphisms have emerged as important determinants of disease susceptibility and severity. Recently, studies have revealed that the genetic variants of the *IL-16* were associated with cancer, but the association remained inconclusive. In this study, we conducted a meta-analysis of the current literature to clarify this relationship. To our knowledge, this is the first meta-analysis to explore the association between rs4778889, rs11556218, rs4072111 polymorphisms in *IL-16* gene and cancer risk. In the present meta-analysis, these three SNPs were located in the exon or promoter region, and that their single-nucleotide changes result in an amino acid substitution. Eight eligible studies including 1814 cases and 2130 controls for rs4778889 polymorphism, 1479 cases and 1791 controls for rs11556218, and 1343 cases and 1597 controls for rs4072111 polymorphism were identified and analyzed.

Among 7 eligible studies based on rs11556218, most of the studies found that the G allele and TG genotype were associated with increased risk of cancers, including NPC (Gao et al., 2009a; Qin et al., 2014), CRC (Gao et al., 2009b; Azimzadeh et al., 2011,), GC (Gao et al., 2009b), cervical cancer (Zhao et al., 2012). Li (Li et al., 2011) indicated that the rs11556218T/G TG and GG genotypes were not associated with risk of HBV-related HCC compared the healthy controls, while there were significant association versus chronic hepatitis B patients. This is the only negative result among all eligible studies. In this study, we found that the G allele (G *vs* T: p<0.001), TG genotype (TG *vs* TT: p<0.001) and TG + GG dominant model genotype (GG+TG *vs* TT: p<0.001) were associated with significantly increased risk of cancer consistent with the results from most of the previous studies. Due to the control populations of Azimzadeh (Azimzadeh et al., 2011) deviated from HWE and it was the only study not on the Chinese population, significant association of increased cancer risk was also found in Chinese population after excepting for this case-control study. There was no heterogeneity existing in the Chinese subgroup in the allele comparison model. So the study of Azimzadeh (Azimzadeh et al., 2011) may be the main cause of the heterogeneity. In the subgroup analyses of cancer type, we found that the G allele, TG genotype and TG + GG dominant model genotype were associated with increased cancer risk except the G allele in the CRC. From these results, we speculated that heterogeneity and cancer types affected the association between *IL-16* rs11556218 polymorphism and cancer risk.

In the case of rs4778889 and rs4072111, all of the studies were in the confirmation of HWE in the controls defining as high-quality studies. For the rs4778889 T/C polymorphism, Zhu (Zhu et al., 2009) indicated that the CC genotype had a significantly decreased RCC risk and Azimzadeh (Azimzadeh et al., 2011) found that the CC genotype decreased the CRC risk in male subjects. The other studies did not found any significantly different between rs4778889 T/C polymorphism and cancer risk. This meta-analysis did not suggest the association between the rs4778889 T/C polymorphism and the risk of cancer both in overall population and Chinese population. But there was a trend of reducing cancer risk in the

homozygous model (CC *vs* TT: p=0.056) and recessive model (CC *vs* TT+TC: p=0.076). The small sample size and significant heterogeneity might result in the negative findings in the meta-analysis.

For the rs4072111 C/T polymorphism, six of the studies did not reported any significant association with cancer risk in the entire genotype model. Only GAO (Gao et al., 2009b) suggested that rs4072111 C/T had a significantly decreased risk for both CRC and GC in women carrying the T allele. We found non-significant association between this polymorphism and cancer risk. Because of all the studies were agreed with HWE in the controls and no heterogeneity existed in different genetic models, the result of this meta-analysis was credible.

To the best of our knowledge, the current report is a timely, updated analysis that combines the findings of all previous publications evaluating the *IL-16* polymorphisms and cancer risk. There were some advantages to our meta-analysis. First, a systematic review of the association of *IL-16* polymorphisms with cancer risk is statistically more powerful than any single study. Second, most of eligible studies including in current meta-analysis were defined as high-quality studies for in the confirmation of HWE in the controls except the distribution of rs11556218 in Azimzadeh studies. Third, no significant differences in age, gender distribution, BMI , smoking and alcohol consumption status were identified between cancer patients and control subjects in eligible studies, it suggested that subject matching based on these variables were adequate. However, like other meta-analysis, there are some limitations to our meta-analysis. First, we mainly focused on the three polymorphisms in *IL-16* gene and ignored the possible existence of linkage disequilibrium with another variation of this gene or gene-environment interactions. Second, all the eligible studies used the hospital patients without organic cancer as the reference group, which may have caused some bias. Last, the sample size was relatively small which may provide low statistical power to detect the association for the variants. In addition, the number of studies for each site-specific cancer was too small to give enough power to reveal a reliable association. Most of the studies were related to Chinese population and only one study related to the Iranian. It is necessary to extend the research with more sample sizes, more cancer types and other populations in the future.

In summary, this present meta-analysis demonstrate that *IL-16* gene rs11556218 T/G was significantly associated with overall cancer risk, especially in nasopharyngeal carcinoma and colorectal cancer. There was no statistically significant association between rs4778889, rs4072111 polymorphisms and risk of cancer. Large well-designed studies involving various cancer types and different populations are needed.

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