Int J Clin Exp Med 2015;8(8):14335-14344
www.ijcem.com /ISSN:1940-5901/IJCEM0010596

Original Article

Little association between the interleukin 10-3575T/A polymorphism and cancer risk: pooled analysis of 15608 cancer cases and 17539 controls

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Received May 24, 2015; Accepted July 11, 2015; Epub August 15, 2015; Published August 30, 2015

Abstract: The aim of the present work was to evaluate the association between the interleukin 10 (IL-10) -3575T/A (rs1800890) polymorphism and cancer risk. We performed a met-analysis based on 15 studies, including 15608 cancer cases and 17539 controls. We used odds ratios (ORs) with 95% confidence intervals (CIs) to assess the strength of the association, and performed sensitivity analyses. In the stratified analyses by all included studies, no association between IL-10-3575T/A (rs1800890) polymorphism and cancer risk (OR=0.966, 95% CI=0.889-1.05, P=0.417 for A *vs.* T; OR=1.035, 95% CI=0.975-1.1, P=0.257 for AA *vs.* AT+TT; OR=1.008, 95% CI=0.964-1.054, P=0.723 for AA+AT *vs.* TT) was observed. In the stratified analyses by cancer type of lymphoma and non-lymphoma, no association between them was also detected (Lymphoma: OR=1.021, 95% CI=0.962-1.083, P=0.496 for A *vs.* T; OR=1.029, 95% CI=0.967-1.095, P=0.363 for AA *vs.* AT+TT; OR=1.017, 95% CI=0.952-1.086, P=0.626 for AA+AT *vs.* TT; Non-lymphoma: OR=0.966 95% CI=0.889-1.51, P=0.245 for A *vs.* T; OR=1.035, 95% CI=0.975-1.1, P=0.287 for AA *vs.* AT+TT; OR=1.017, 95% CI=0.948-1.091, P=0.967 for AA+AT *vs.* TT). The results were the same by sensitivity analyses. No publication bias was existed in the analysis. The interleukin 10-3575T/A polymorphism may have no association with cancer risk.

Keywords: Interleukin 10, polymorphism, cancer, meta-analysis

Introduction

The burden of cancer is increasing globally. A total of 12.7 million new cases and 7.6 million deaths from cancer are estimated to have occurred in 2008 [1]. The complex interactions of genetic and environment can lead to multifactorial disease of cancer [2]. Thus, gene, results in tumorigenesis, is one of the most important risk factors. Single nucleotide polymorphisms (SNPs) may influence cancer risk in various ways, like encoding cytokine to influence immune response, inflammatory reactions etc. or affecting binding to nuclear factors and influence the rate of transcription to mediating cell apoptosis [3, 4].

Interleukin-10 (IL-10) is one of multifunctional cytokines, which has anti-angiogenic and immunosupptessive properties. It participates in the development and progression of various malignant tumors [5]. The human IL-10 gene is located on chromosome 1 (1q31-32) [6] and contains three important single nucleotide polymorphisms (SNPs) in the promoter [rs1800896 (-1082A>G), rs1800871 (-819C>T), rs1800872 (-592C>A)]. These polymorphisms have been approved that people possessing one of the SNPs have an increasing risk of cancer susceptibility [7-9]. However, IL-10 contains other SNPs (rs3024509, rs3024496, rs3024491 and rs1800890) [10] and IL-10-3575T/A (rs1800890) associated with Diffuse large B cell lymphoma (DLBCL) [11].

To date, a number of studies were conducted to investigate the association between IL-10-3575T/A (rs1800890) and cancer risk in humans [12-26]. However, the results of these studies remain conflicting rather than conclusive. So, we performed the present meta-analysis to evaluate the association between IL-10-3575T/A polymorphism and cancer risk.

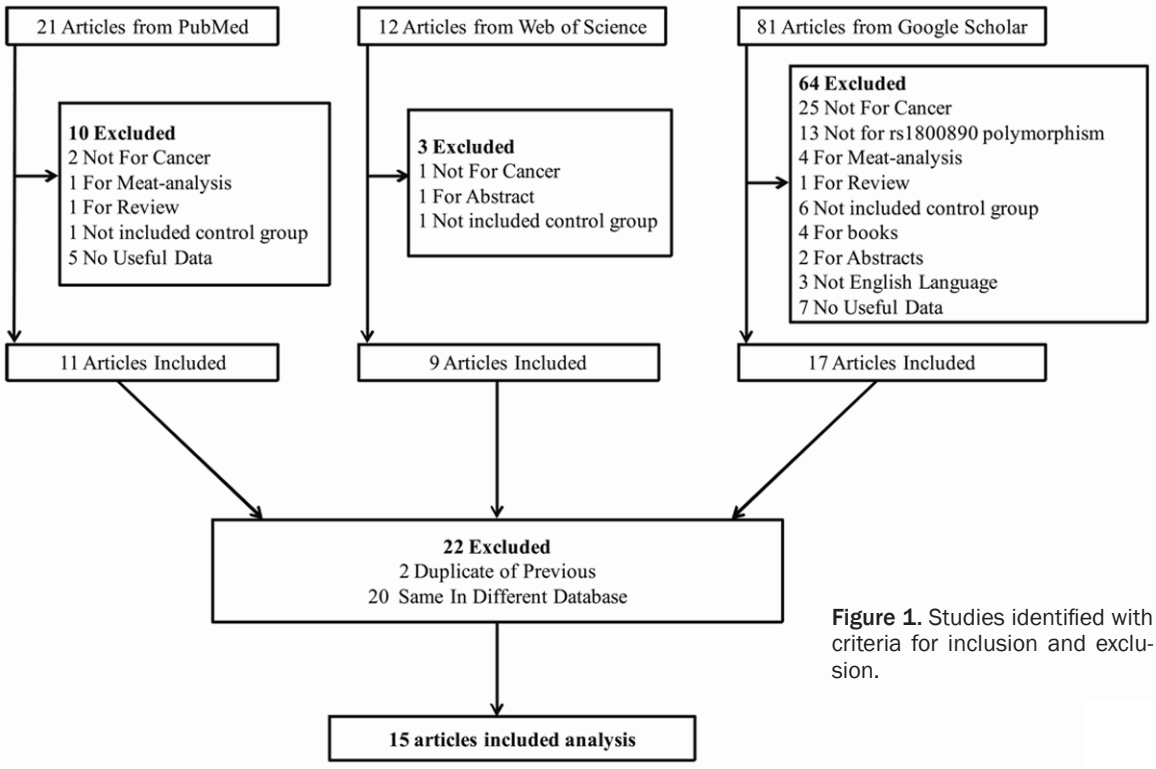


Figure 1. Studies identified with criteria for inclusion and exclusion.

Table 1. Characteristics of studies included in the meta-analysis

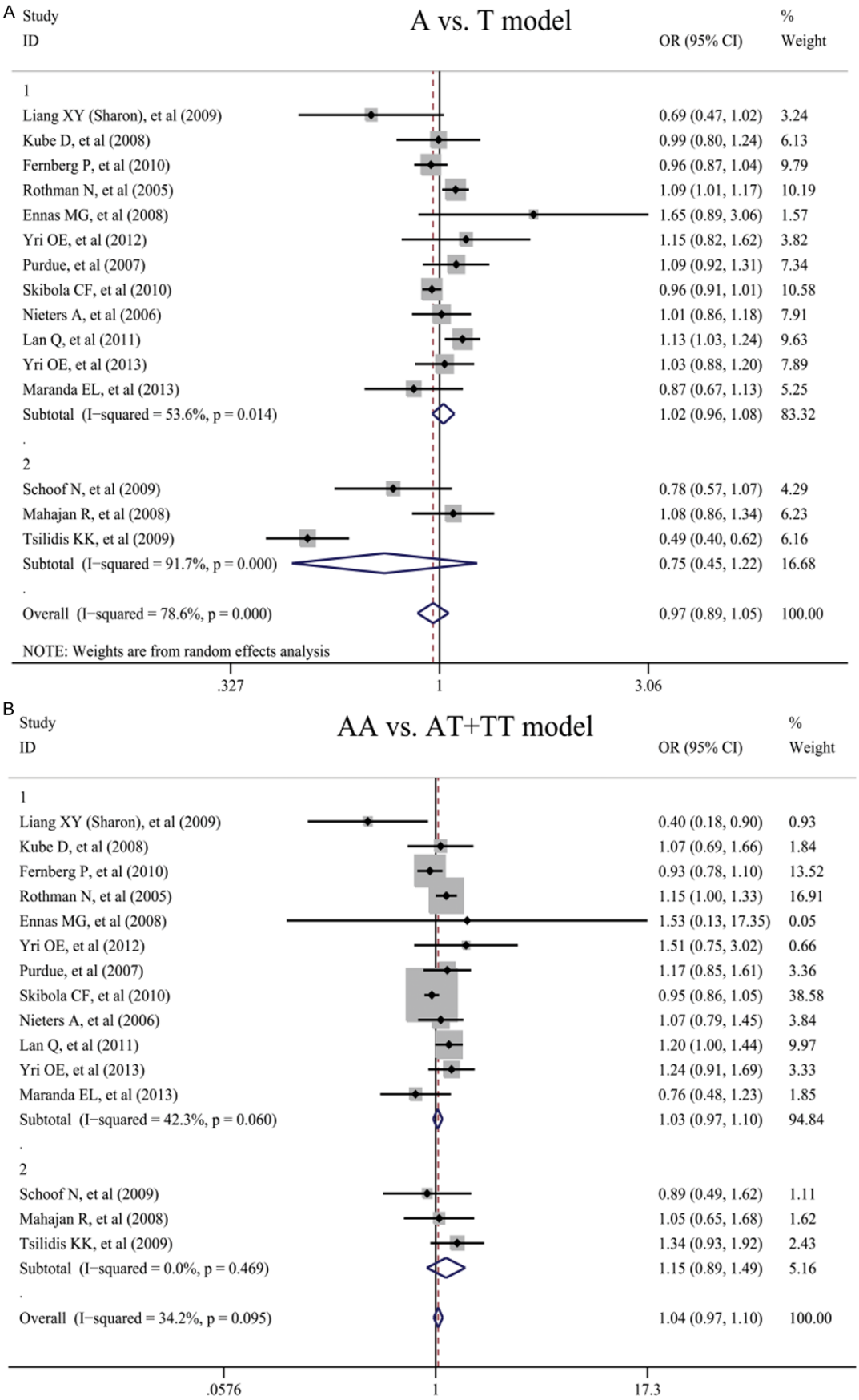
Author	Year	Cancer type	Cases/Controls	HWE	Reference
Tsilidis KK, et al	2009	Colorectal cancer	190/352	Yes	[12]
Liang XY (Sharon), et al	2009	NHL: CLL, WM	106/102	Yes	[13]
Kube D, et al	2008	NHL	500/236	Yes	[15]
Fernberg P, et al	2010	NHL	1838/2312	Yes	[16]
Rothman N, et al	2005	NHL: DLBCL, FL	3030/3462	Yes	[17]
Ennas MG, et al	2008	NHL: CLL	37/112	Yes	[18]
Yri OE, et al	2012	HL	223/100	Yes	[19]
Purdue, et al	2007	NHL: DLBCL, FL	524/475	Yes	[20]
Skibola CF, et al	2010	NHL: DLBCL, FL, CLL/SLL, MCL, MF, MZL, EMZL, OMZL, LPL, MF, PTLC	6391/6170	Yes	[21]
Schoof N, et al	2009	Melanoma	165/162	Yes	[14]
Nieters A, et al	2006	Lymphoma: DLBCL, FL, CLL, MM, HL, T-NHL, MALT	670/661	Yes	[22]
Mahajan R, et al	2008	Gastric cancer	300/414	Yes	[23]
Lan Q, et al	2011	NHL: DLBCL, FL, MZL, CLL/SLL	1868/1751	Yes	[24]
Yri OE, et al	2013	NHL: DLBCL	476/1048	No	[25]
Maranda EL, et al	2013	NHL: CLL	290/182	Yes	[26]

NOTE: NHL: Non-Hodgkin's Lymphoma, DLBCL: Diffuse Large B-cell Lymphoma, FL: Follicular Lymphoma, CLL: Chronic Lymphocytic Leukaemia, SLL: Small Lymphocytic Lymphoma , MCL: Mantle Cell Lymphoma, MF: Mycosis Fungoides, MZL: Marginal Zone Lymphoma, EMZL = Extra-nodal Marginal Zone Lymphoma, OMZL = Other Marginal Zone Lymphoma, LPL: Lymphoplasmacytic Lymphoma, PTCL: Peripheral T-cell Lymphoma, MM: multiple myeloma, HL: Hodgkin's Lymphoma, T-NHL: T-cell non-Hodgkin's lymphoma, MALT: mucosa associated lymphoid tissue. HWE: Hardy-Weinberg Equilibrium.

Materials and methods

Identification and eligibility of relevant studies

We searched the electronic literature from NCBI PubMed, Google Scholar and Web of Science for all relevant reports (the last search update was Oct 15, 2013), using the key words: (cancer OR carcinoma OR tumor) and (IL10-3575T/A or rs180089). The search was limited to English language papers. In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. Studies were selected if there was available


A
Study ID
A vs. T model
OR (95% CI)
% Weight
1
Liang XY (Sharon), et al (2009) 0.69 (0.47, 1.02) 3.24
Kube D, et al (2008) 0.99 (0.80, 1.24) 6.13
Fernberg P, et al (2010) 0.96 (0.87, 1.04) 9.79
Rothman N, et al (2005) 1.09 (1.01, 1.17) 10.19
Ennas MG, et al (2008) 1.65 (0.89, 3.06) 1.57
Yri OE, et al (2012) 1.15 (0.82, 1.62) 3.82
Purdue, et al (2007) 1.09 (0.92, 1.31) 7.34
Skibola CF, et al (2010) 0.96 (0.91, 1.01) 10.58
Nieters A, et al (2006) 1.01 (0.86, 1.18) 7.91
Lan Q, et al (2011) 1.13 (1.03, 1.24) 9.63
Yri OE, et al (2013) 1.03 (0.88, 1.20) 7.89
Maranda EL, et al (2013) 0.87 (0.67, 1.13) 5.25
Subtotal (I−squared = 53.6%, p = 0.014) 1.02 (0.96, 1.08) 83.32
2
Schoof N, et al (2009) 0.78 (0.57, 1.07) 4.29
Mahajan R, et al (2008) 1.08 (0.86, 1.34) 6.23
Tsilidis KK, et al (2009) 0.49 (0.40, 0.62) 6.16
Subtotal (I−squared = 91.7%, p = 0.000) 0.75 (0.45, 1.22) 16.68
Overall (I−squared = 78.6%, p = 0.000) 0.97 (0.89, 1.05) 100.00
NOTE: Weights are from random effects analysis
.327
1
3.06
B
Study ID
AA vs. AT+TT model
OR (95% CI)
% Weight
1
Liang XY (Sharon), et al (2009) 0.40 (0.18, 0.90) 0.93
Kube D, et al (2008) 1.07 (0.69, 1.66) 1.84
Fernberg P, et al (2010) 0.93 (0.78, 1.10) 13.52
Rothman N, et al (2005) 1.15 (1.00, 1.33) 16.91
Ennas MG, et al (2008) 1.53 (0.13, 17.35) 0.05
Yri OE, et al (2012) 1.51 (0.75, 3.02) 0.66
Purdue, et al (2007) 1.17 (0.85, 1.61) 3.36
Skibola CF, et al (2010) 0.95 (0.86, 1.05) 38.58
Nieters A, et al (2006) 1.07 (0.79, 1.45) 3.84
Lan Q, et al (2011) 1.20 (1.00, 1.44) 9.97
Yri OE, et al (2013) 1.24 (0.91, 1.69) 3.33
Maranda EL, et al (2013) 0.76 (0.48, 1.23) 1.85
Subtotal (I−squared = 42.3%, p = 0.060) 1.03 (0.97, 1.10) 94.84
2
Schoof N, et al (2009) 0.89 (0.49, 1.62) 1.11
Mahajan R, et al (2008) 1.05 (0.65, 1.68) 1.62
Tsilidis KK, et al (2009) 1.34 (0.93, 1.92) 2.43
Subtotal (I−squared = 0.0%, p = 0.469) 1.15 (0.89, 1.49) 5.16
Overall (I−squared = 34.2%, p = 0.095) 1.04 (0.97, 1.10) 100.00
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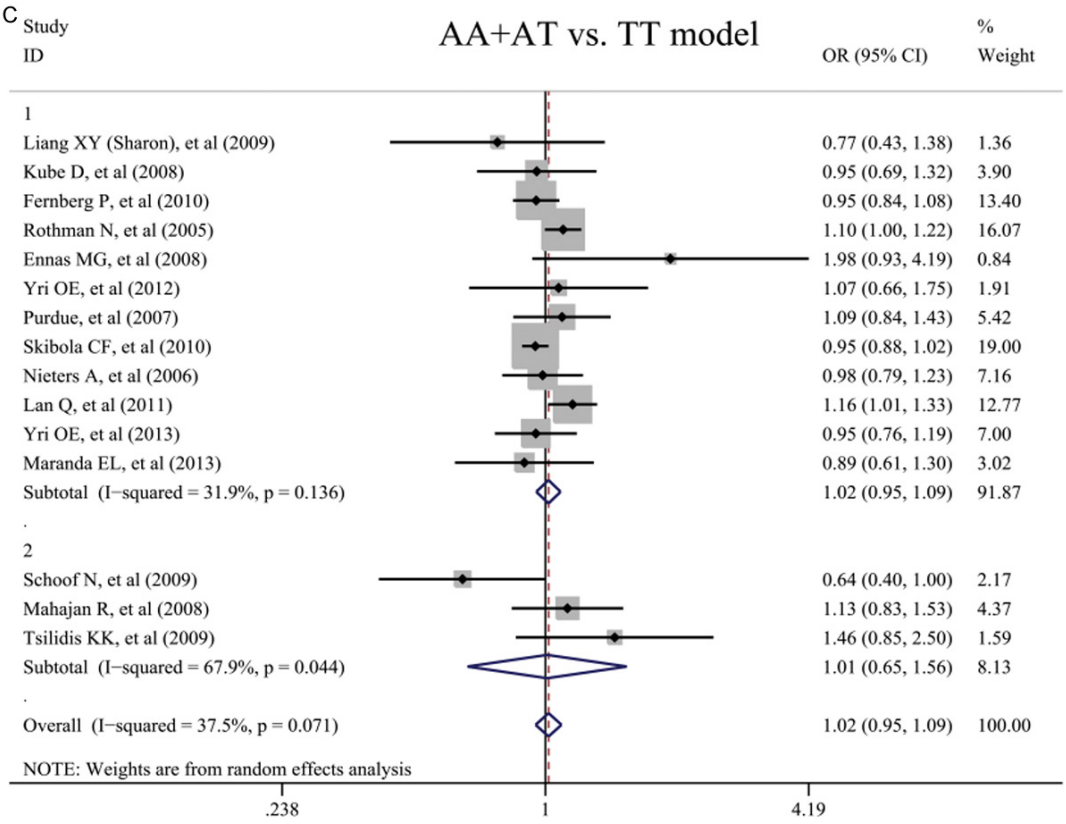

Figure 2. Forest plots of the meta-analysis for the association between IL-10-3575T/A (rs1800890) polymorphism and cancer risk. (A) A *vs.* T, (B) AA *vs.* AT+AT, (C) AA+AT *vs.* TT.

data for the IL-10-3575T/A polymorphism with cancer risk. As studies with the same population by different investigators or overlapping data by the same authors were found, the most recent or complete articles with the largest number of subjects were included. Studies included in our meta-analysis have to meet the following criteria: i) evaluation of the IL-10-3574T/A polymorphism and cancer risk, ii) using control study design and iii) containing available the number of patients with each individual gene and genotype frequency. Major reasons for exclusion of studies were: i) only case population and ii) duplicate of previous publication.

Data extraction

Two of the authors (Zhu BY and Zhu BQ) extracted all data independently complying with the selection criteria with disagreements resolved in consultation with a third investigator (Xiao CL) and reached a consensus on all items. For each eligible research, the following information was extracted: the first author's name, year of publication, population, frequencies of genotyped in cases and controls and cancer type, Hardy-Weinberg equilibrium (HWE). If it was not calculated in a study, the HWE was calculated by the frequencies of A/T allele.

Statistical analysis

The strength of the association between the IL-10-3575T/A polymorphism and cancer risk was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The estimate of effect was determined using the Peto for fixed effects model [27] or DerSimonian and Laird method for random effects model [28]. Study heterogeneity was assessed by the I^2 test, with I^2>50% suggesting substantial heterogeneity [29]. Sensitivity analyses were performed to assess the stability of the results. Briefly, a single study which the data cannot agreement with HWE in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication

Table 2. Pooled analyses of the IL-10-3575T/A (rs1800890) polymorphism on cancer risk

Cancer type	Studies	Cases/ Controls	A vs. T			Bias test		AA vs. AT+TT			Bias test		AA+AT vs. TT			Bias test	
			OR (95% CI)	I^2	P	Begg's	Egger's	OR (95% CI)	I^2	P	Begg's	Egger's	OR (95% CI)	I^2	P	Begg's	Egger's
Included cancers	15	15608/ 17539	0.966 (0.889-1.05)	78.6%	0.417	0.621	0.549	1.035 (0.975-1.1)	34.2%	0.257	0.322	0.738	1.008 (0.964-1.054)	37.5%	0.723	0.767	0.678
Lymphoma	12	14953/ 16431	1.021 (0.962-1.083)	53.5%	0.496	-		1.029 (0.967-1.095)	42.3%	0.363	-		1.017 (0.952-1.086)	31.9%	0.626	-	
Colorectal cancer/ Melanoma/Gastric cancer	3	655/928	0.966 (0.889-1.51)	91.7%	0.245	-		1.035 (0.975-1.1)	0%	0.287	-		1.017 (0.948-1.091)	67.9%	0.967	-	

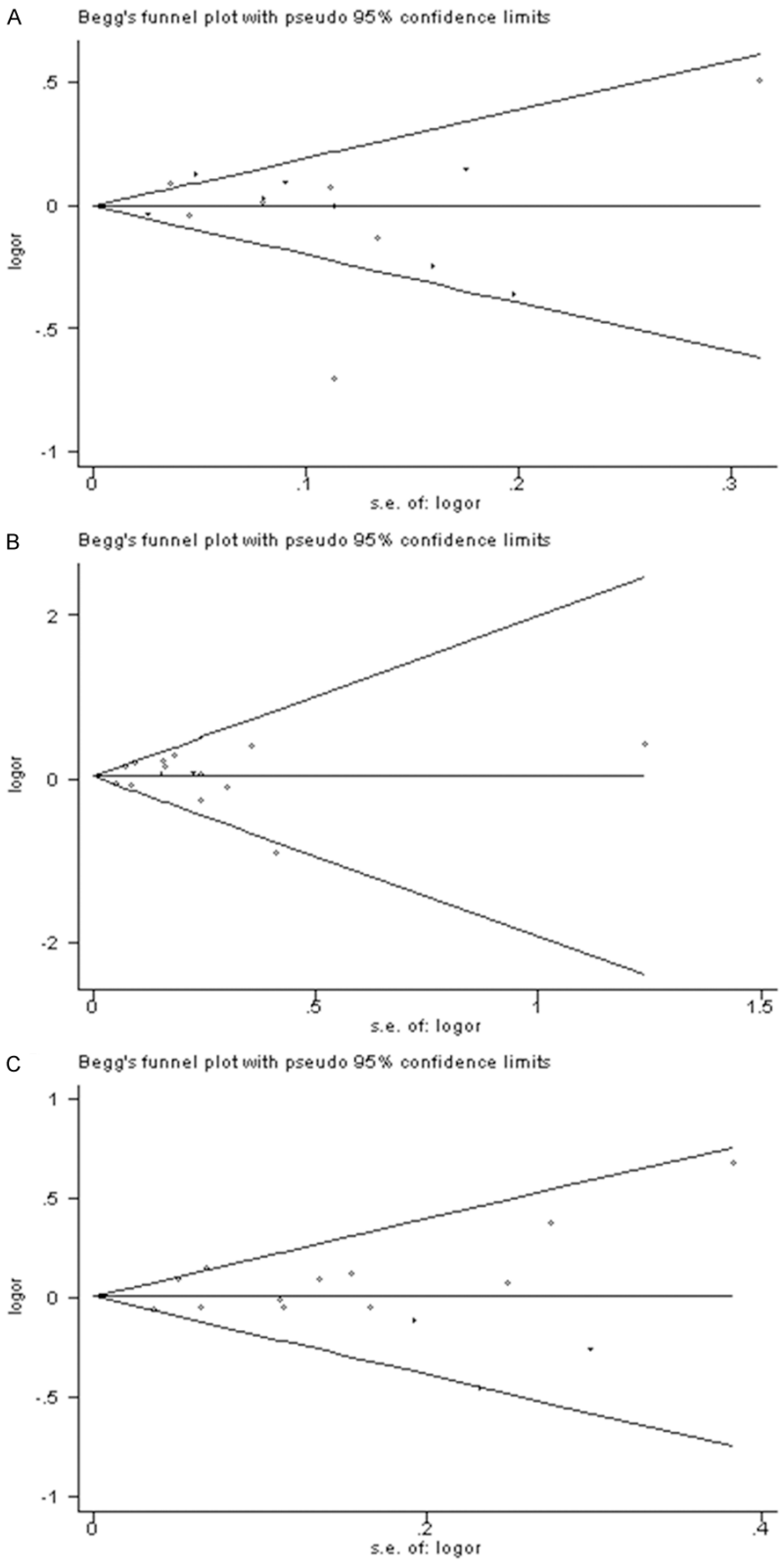

Figure 3. Begg's funnel plot for publication bias in selection of studies on IL-10-3575T/A (rs1800890) polymorphism. (A) A vs. T, (B) AA vs. AT+AT, (C) AA+AT vs. TT.

bias [30]. All statistics were computed using STATA 11.0 (StataCorp LP, College Station, TX, USA), and all tests were with two sides.

Results

Characteristics of including studies

Finally, a total of 15 studies that included 15608 cancer cases and 17539 controls met the inclusion criteria (**Figure 1**). Study characteristics are summarized in **Table 1**. Cancers were confirmed by histologically or pathologically in the studies. In this meta-analysis, most cancer types were Non-Hodgkin's Lymphoma (NHL). The distribution of genotype in the controls of the studies was in agreement with Hardy-Weinberg equilibrium for all except one research [25], which was further tested in the sensitivity analyses. The HWE was calculated by us in the three study [19, 21, 24].

IL-10-3575T/A polymorphism (rs1800890) for included cancers

Pooled ORs and heterogeneity test resulting for the association of IL-10-3575T/A polymorphism and cancers risk are shown in **Figure 2** (A: A allele vs. T allele; B: AA vs. TA+TT; C: AA+AT vs. TT) and summarized in **Table 2**. Significant heterogeneity was detected between these 15 studies in A vs. T model (I^2= 78.6%), a random effects model was used. IL-10-3575T/A variant was found

to be no significant associated with an increased risk of cancers (A vs. T: OR=0.966, 95% CI=0.889-1.05, P=0.417). No publication bias was determined in these studies (**Figure 3A**, Begg's test: P=0.621, Egger's test: P=0.549).

Since no significant heterogeneity was detected in AA vs. AT+TT model (I^2=34.2%), a fixed effects model was used. IL-10-3575T/A variant was found to be no significantly associated with an increased risk of cancers (AA vs. AT+TT: OR=1.035, 95% CI=0.975-1.100, P=0.257). No publication bias was determined in these studies (**Figure 3B**, Begg's test: P=0.322, Egger's test: P=0.738).

No significant heterogeneity was also detected in the AA+AT vs. TT model (I^2=37.5%), a fixed effects model was used. The variant was also found to be no significantly associated with an increased risk of cancers (AA+AT vs. TT: OR=1.008, 95% CI=0.964-1.054, P=0.723). No publication bias was determined in these studies (**Figure 3C**, Begg's test: P=0.767, Egger's test: P=0.678).

IL-10-3575T/A polymorphism (rs1800890) for different type cancer

Considering of different type cancer, we grouped the 15 studies for two groups. One group is for lymphoma including non-Hodgkin's lymphoma (NHL), diffuse large B-cell lymphoma (DLBCL), Follicular Lymphoma (FL), Chronic Lymphocytic Leukaemia (CLL), marginal zone lymphoma (MZL) and Hodgkin's lymphoma (HL) etc. The other for non-lymphoma group contains colorectal cancer, melanoma and gastric cancer.

For lymphoma, a total of 12 studies that including 14953cancer cases and 16431 controls in this meta-analysis. For non-lymphoma, a total of 3 studies that including 655 cancer cases and 928 controls in this meta-analysis. Significantly heterogeneity exists in the two subgroups with A vs. T model (I^2=53.6% and 91.7% respectively), a random effect was used. IL-10-3575T/A variant was found to be no significantly associated with an increased risk of different type cancers (For lymphoma, OR=1.021, 95% CI=0.962-1.083, P=0.496 and for non-lymphoma, OR=0.966, 95% CI=0.889-1.051, P=0.245). As no significant heterogeneity exists in these two subgroups with the AA vs. AT+TT model (I^2=42.3% and 0% respectively), a fixed effects model was used. IL-10-3575T/A variant was found to be no significantly associated with an increased risk of different type cancers with AA vs. AT+TT models (For lymphoma, OR=1.029, 95% CI=0.967-1.095, P=0.363 and for non-lymphoma, OR=1.035, 95% CI=0.975-1.100, P=0.287). As significant heterogeneity exists with AA+AT vs. TT model (I^2=31.9% and 67.9% respectively), a random effect was used. IL-10-3575T/A variant was also found to be no significantly associated with an increased risk of different type cancers (For lymphoma, OR=1.017, 95% CI=0.952-1.086, P=0.626 and for non-lymphoma, OR=1.017, 95% CI=0.948-1.091, P=0.967).

Sensitivity analyses

One independent study showed that the SNP of controls was not agreement with Hardy-Weinberg Equilibrium (HWE) [25]. So, the sensitivity analyses were performed by omitting this study. The heterogeneity was effectively decreased or removed by exclusion of this study (AA+AT vs. TT: I^2=41.2%), but the all pooled ORs were not changed by the sensitivity analyses. Thus, the results of this meta-analysis were stable.

Discussion

The present meta-analysis investigated the association between the IL-10-3575T/A polymorphisms and cancer risk, based on 15 published studies. The results provided evidence that the IL-10-3575T/A polymorphism was no association with the susceptibility of overall cancer, especially in the lymphoma.

IL-10 plays an important role in regulation of immune responses in health and immune-mediated disease. It has dual biological function in potentially cancer-promoting (as an anti-inflammatory cytokine) and inhibiting (as an anti-angiogenic cytokine) [31]. Both IL-10 deficiency and overproduction may be responsible for some lesions. Due to the possible influence on gene transcription and protein production, promoter region polymorphisms are studied most closely [32, 33]. Three major biallelic SNPs of IL-10 located at -1082G/A (rs1800896), -819C/T (rs1800871) and -592C/A (rs1800872) positions from the transcription start site. More evidences proved that these three SNPs

increased risk of cancer susceptibility (IL10-592C>A, -1082A>G and -819C>T) [7-9], such as lung cancer, gastric cancer and NHL and so on.

IL-10-3575T/A polymorphism has been identified the relationship with IL-10 variants, such as IL-10-3575A could decrease levels of IL-10 [34]. So, this SNP may be associated with cancer susceptibility. However, in our meta-analysis, the results showed that this SNP (IL-10-3575T/A) was definitely no association with the cancers in any of the three models (A vs. T; AA vs. AT+TT and AA+AT vs. TT). Our results were opposite with the research that IL-10-3575T>A was a high risk factor for diffuse large B-cell lymphoma (DLBCL) [11]. However, due to the small ORs for DLBCL (A vs. T: OR=1.16, AA+TA vs. TT: OR=1.20; AA vs. TA+TT: OR=1.25), this IL-10-3575T/A polymorphism may have no impact on the susceptibility of cancers when considered other more relevant SNPs and other factors such as IL10-592C>A, -1082A>G and -819C>T.

In this meta-analysis, we included three non-lymphoma which are colorectal cancer, melanoma and gastric cancer [12, 14, 23]. The pooled OR of IL-10-3575T/A polymorphism was no significantly differences for these cancers. A number of risk factors have been identified to these three cancers, such as age, gender, family history of cancer, personal habit of alcohol consumption and smoking and ethnicity etc. [35-37], and cancer origin and evolution have been proposed to be the consequence of the merged effects of a number of the alleles, which may control intrinsic and/or extrinsic functions [38]. Thus, this SNP may be not the risk factor, and there is only one study for each cancer. So this result of no association between non-lymphoma and IL-10-3575T/A need more researches to definite.

Several limitations and strengths are in this meta-analysis. This study is potentially limited in several ways. First, as a result of lack raw data, some relevant studies were excluded. Second, the sample sizes in this study analyses were small. In addition, this meta-analysis was based on adjusted data, so a more precise analysis could be performed if individual data were available. Finally, the number of included studies of non-lymphoma was small. Nonetheless, advantages in this analysis should also be approved. First, the quality of included studies was satisfactory according to our selection criteria. Second, because of a substantial number of cases and controls pooled from different studies, the statistical power was greatly increased. Third, the sensitivity analysis had not changed the results of no association between IL-10-3575T/A and cancer risk, and no publication bias were detected interpreting that the whole pooled ORs should be unbiased.

This meta-analysis suggests that the IL-10-3575T/A polymorphism was not associated with overall cancer risk. However, large studies using standardized unbiased genotyping methods, enrolling precisely defined cancer patients and well-matched controls with more detailed personal and environmental data are needed to define the results of this analysis.

Disclosure of conflict of interest

None.

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