

Review Article

The role of CD14 159C/T polymorphism in susceptibility of cancers

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Abstract: CD14 (cluster of differentiation 14), a kind of lipopolysaccharide (LPS) receptor, plays an important role in the innate immune system. Up to now, accumulating studies have reported the association between CD14-159C/T polymorphism and susceptibility of cancers, with divergent results. We thus conducted this meta-analysis to demonstrate the possible association between CD14-159C/T polymorphism and cancer risk. All eligible case-control studies were identified by searching PubMed, Embase and CNKI database up to November 2017. Pooled odds ratio (OR) was used to assess the strength of association. Subgroup analysis was also conducted based on cancer type, ethnicity and language. Statistical analyses were performed by using STATA 12.0 software. A total of 21 case-control studies involving 11241 participants (4136 cases and 7105 controls) were included in the current meta-analysis. The result indicated that the T allele of CD14-159C/T polymorphism did not confer risk for overall cancers (TT + CT vs. CC: OR = 0.98, 95% CI = 0.83-1.16, P = 0.81; TT vs. CT + CC: OR = 1.13, 95% CI = 0.87-1.46, P = 0.37). However, a subgroup analysis by cancer type indicated the CD14-159C/T polymorphism was significantly correlated with acute lymphoblastic leukemia (TT vs. CT + CC: OR = 1.80, 95% CI = 1.37-2.38, P < 0.001; C vs. T: OR = 0.81, 95% CI = 0.67-0.98, P = 0.03) and prostate cancer (TT vs. CC: OR = 0.62, 95% CI = 0.39-0.99, P = 0.04). Nevertheless, we failed to detect any relationship in the subgroup analysis by ethnicity and language. This meta-analysis suggested that CD14-159C/T polymorphism may be associated with acute lymphoblastic leukemia and prostate cancer, but no significant relationship was found between CD14-159C/T polymorphism and overall cancer. Further well-designed studies with larger sample size on different cancer types and ethnicities are needed.

Keywords: CD14, polymorphism, cancer, meta-analysis

Introduction

Cancer is a leading cause of death all over the world, and about 14.1 million new cancer cases and 8.2 million mortalities occurred in 2012 worldwide based on GLOBOCAN estimates [1]. Cancer was a multi-factor disease, and the precise etiology of which still remained unclear. So far, a combination of genetic polymorphism and environmental factor was widely accepted regarding to carcinogenesis [2]. Recently, numerous genetic studies have found the association between several immunity genes and cancer, especially the CD14 (cluster of differentiation 14) gene [3].

The CD14 gene is located on chromosome 5q31.3 and consists of 3,900 bp [4]. Wei and

colleagues once conducted a meta-analysis, by analyzing 12 case-control studies, to study the association between CD14 gene and cancers [5]. The gene encodes 2 glycoproteins, one of which, known as membrane CD14 (mCD14), is expressed on the surface of monocytes, macrophages, and neutrophils. Besides, there is also a soluble form (sCD14) existing in serum [6]. CD14 acts as a receptor protein binding to endotoxins, and also as lipopolysaccharides (LPS) interacting with toll-like receptor 4 (TLR4). As a result, innate immune system can be activated, and large amount of cytokines would be released, which are closely related to the apoptosis of cells [7, 8]. Furthermore, some researchers reported that an association between CD14 gene expression and the process of carcino-

genesis. There were several single nucleotide polymorphisms (SNPs) identified in the CD14 gene, of which the CD14 159C/T (rs2569190), also reported as CD14 260C/T, was most extensively investigated for the susceptibility of cancer, such as gastric cancer, lymphoblastic leukemia, prostate cancer and so on. However, the results of previous studies were divergent and inconsistent. For example, Hold [9] suggested that CD14 159C/T polymorphisms were not associated with gastric cancer risk in Caucasian populations, while Tahara [10] claimed that CD14 159C/T polymorphism was associated with reduced risk of intestinal-type gastric cancer in a Japanese population. In addition, the results of some subgroup analysis, such as ethnicity, were still not clear. Although Wei and colleagues studied the 159C/T polymorphism in the CD14 gene, here we intended to perform another meta-analysis, by enrolling more recent studies, to comprehensively investigate the associations between CD14 159C/T polymorphisms and susceptibility of cancer.

Materials and methods

Identification and eligibility of relevant studies

Two independent authors performed systematic searches in PubMed, Embase and CNKI for relevant studies with the following terms: "CD14" or "cluster of differentiation 14" or "159C/T" or "260C/T" or "rs2569190", "polymorphism" or "variant" or "mutation", and "cancer" or "carcinoma" or "malignancy" (updated until Nov 10, 2017). The reference language and published date were not limited in our search. Some potential references were acquired by manually searching from review articles. A study was included based on these criteria: (1) case-control studies or cohort studies; (2) evaluating the associations between the CD14 159C/T polymorphism and cancer risk; (3) genotype distributions in the cases and controls were available in order to calculate the odds ratios (ORs). The exclusion criteria were: (1) reviews, conference abstracts, case reports, animal studies or editorials; (2) without detailed genotype frequency of the CD14 159C/T; (3) when studies include the same or overlapped population, only the study with largest number and sufficient information of participants was included; (4) duplicated publication.

Data extraction

Eligible studies were checked again by the two reviewers and a consensus was reached prior to further process. The following information were recorded: author, publication year, country, ethnicity, number of cases and controls, gender, age, source of controls, sample, quality control, quality health, cancer type, genotype distributions of cases and controls, genotyping method, and HWE of the control groups, language, study design and so on.

Quality assessment

The quality of all included studies is assessed by two researchers following Newcastle-Ottawa Scale (NOS) from three aspects: selection, comparability and outcome, respectively. Studies with scores above 5 were regarded as high quality. Disagreements were resolved by discussion with another author.

Statistical analysis

ORs with 95% CIs were used in this meta-analysis to determine the strength of the association between CD14 159C/T gene polymorphism and the risk of cancer. We used following genetic models to evaluate the susceptibility: dominant model (TT + CT vs. CC), recessive model (TT vs. CT + CC), homozygote model (TT vs. CC), heterozygote model (CT vs. CC), and allelic contrast model (T vs. C). Besides, subgroup analyses were conducted based on cancer type and ethnicity.

The I^2 statistic was used to analyze heterogeneity. If $I^2 > 50\%$, the random-effects model was applied to analysis, otherwise, a random fixed effects model was used [11-13]. Sensitivity analysis was also conducted to make sure the reliability of the results in order to identify whether the heterogeneity among these studies was from some individual studies. The pooled OR was assessed using Z test and HWE evaluation was performed with chi-square test in control groups [14]. Both Egger's test and Begg's test funnel plots were utilized to detect the potential publication bias among the included studies [15]. $P < 0.05$ was considered to be statistically significant. All statistical analyses were performed with STATA 12.0 (Stata Corp, College Station, TX, USA).

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

First Author	#*	Year	Country	Ethnicity	Number		Male		Age (year)		Source of Controls	Cancer Type	Genotyping Method	HWE	Published Language	Study Design	NOS Score
					Cases	Control	Case	Control	Case	Control							
Andriel E [29]	1	2009	Greek	Caucasian	37	83	24	61	< 14		HB	Hodgkin's lymphomas	PCR	YES	English	Retrospective	7
Andriel E [29]	2	2009	Greek	Caucasian	46	83	24	61	< 14		HB	Non-Hodgkin lymphomas	PCR-RFLP	YES	English	Retrospective	7
Castano-Rod [30]		2013	Australia	Asian	70	214	42	95	65.8 + 13.8	54.2 + 13	HB	Gastric cancer	PCR	YES	English	Retrospective	6
Castano-Rod [31]		2014	Australia	Asian	87	222	55	99	65.3 + 13.2	54.3 + 12.8	HB	Gastric cancer	PCR	YES	English	Retrospective	6
Chao YC [32]		2005	China	Asian	82	117	82	75	64.4 + 12.7	60.6 + 18.3	HB	Esophageal cancer	PCR-RFLP	NA	English	Retrospective	7
Companioni O [33]		2014	Spain	Caucasian	352	1192	214	759	58.4 + 7.9	58.4 + 7.7	PB	Gastric cancer	NA	YES	English	Retrospective	8
Gong AM [24]		2016	China	Asian	164	169	/	/	/	/	PB	Gastric cancer	PCR	YES	English	Retrospective	5
Guo Q [34]		2006	China	Asian	110	160	64	/	53.71 + 13.27	/	HB	Colorectal cancer	PCR	YES	English	Retrospective	7
Kim J [35]	1	2013	Korea	Asian	244	387	333	333	54.8 + 8.4	54.3 + 7.4	HB	Gastric cancer (intestinal-type)	PCR	YES	English	Retrospective	7
Kim J [35]	2	2013	Korea	Asian	215	387	333	333	54.8 + 8.4	54.3 + 7.4	HB	Gastric cancer (diffuse-type)	PCR	YES	English	Retrospective	7
Landi S [36]		2006	Italy	Caucasian	281	265	/	/	/	/	HB	Colorectal cancer	PCR	YES	English	Retrospective	6
Li K [37]		2014	China	Asian	225	237	172	175	54.0 + 12.3	54.8 + 11.2	HB	Gastric cancer	PCR	YES	English	Retrospective	7
Mason TE [38]		2010	America	African-American	204	139	254	188	68.95 + 9.73	57.33 + 11.3	PB	Prostate cancer	PCR	YES	English	Retrospective	7
Miedema KG [39]		2012	Netherlands	Mixed	180	180	115	88	4.4	8	PB	ALL	PCR	YES	English	Prospective	7
Min ZC [40]		2012	China	Asian	168	208	168	208	/	/	HB	Prostate cancer	PCR-LDR	YES	Chinese	Retrospective	6
Su J [41]		2017	China	Asian	406	893	229	533	/	/	HB	Laryngeal cancer	PCR	YES	English	Retrospective	6
Tahara T [10]		2009	Japan	Asian	149	94	109	65	64 + 12.4	64.1 + 12.3	HB	Gastric cancer	PCR	YES	English	Retrospective	6
Ture-Ozdemir F [42]		2008	Turkey	Caucasian	56	51	30	30	61	56	HB	MALT lymphoma	PCR-RFLP	YES	English	Retrospective	5
Yang L [43]		2016	China	Asian	163	326	140	280	62.15	60.55	HB	Laryngeal cancer	PCR-RFLP	YES	Chinese	Retrospective	8
Yu X [44]	1	2011	China	Asian	53	539	105	349	32	33	HB	ALL (T)	PCR	YES	English	Retrospective	8
Yu X [44]	2	2011	China	Asian	121	539	105	349	32	33	HB	ALL (B)	PCR	YES	English	Retrospective	8
Zeljic K [45]		2014	Serbia	Caucasian	93	104	68	76	/	/	HB	Oral cancer	PCR or PCR-RFLP	YES	English	Retrospective	6
Zhang L [46]		2011	China	Asian	160	296	192	122	/	/	HB	Gastric cancer	PCR-RFLP	YES	Chinese	Retrospective	5
Zhao D [47]		2007	China	Asian	470	470	330	342	/	/	PB	Gastric cancer	PCR-RFLP	YES	English	Retrospective	7

Abbreviations: *Number of data separately reported by articles. HB, hospital-based; PB, population-based; ALL, acute lymphatic leukemia; MALT, mucosa-associated lymphoid tissue; PCR, polymerase chain reaction; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; PCR-LDR, polymerase chain reaction-ligase detection reaction.

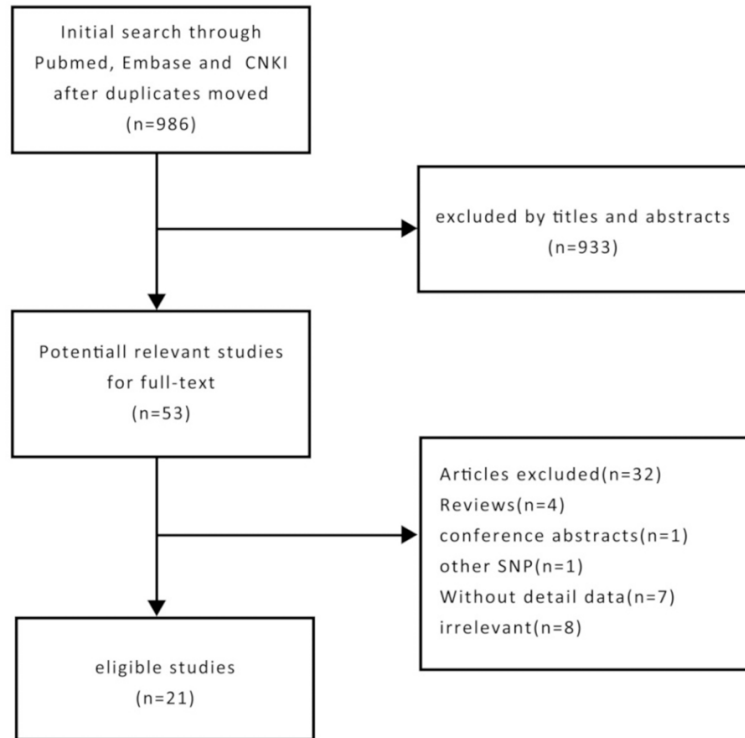


Figure 1. Flow chart of study selection in this meta-analysis.

Results

Study selection and characteristics

We performed an initial search and obtained 986 articles through the databases of Pubmed, Embase and CNKI. Based on the titles and abstracts, 53 potentially relevant articles were retrieved for full-text evaluation. 32 articles were excluded, including 4 reviews, 1 conference abstracts, 1 article about other SNP, 7 articles without detail data, 8 irrelevant articles. Finally, a total of 21 articles published from 2005-2017 were included in our meta-analysis (**Table 1; Figure 1**).

The 21 included articles consisted of 4136 cases and 7105 controls. And the total sample size of patient was 11241, ranging from 107 to 1544 per cohort. Because three articles had two cohorts and ethnicities, there were 24 cohorts. 6 cohorts were conducted in Caucasian, 16 in Asian, 1 in African American and 1 in mixed races. The controls were healthy or free of cancer, and matched for age, ethnicity or area to cases. Most of the cohorts examined the blood sample using PCR genotyping method.

Meta-analysis results

To estimate the association between the cancer risk and CD14-159C/T polymorphism, we pooled the ORs and their corresponding 95% CIs. However, no significant associations between the CD14 159C/T polymorphism and cancer risk were found (TT + CT vs. CC: OR = 0.98, 95% CI = 0.83-1.16, P = 0.81; TT vs. CT + CC: OR = 1.13, 95% CI = 0.87-1.46, P = 0.37; TT vs. CC: OR = 1.03, 95% CI = 0.73-1.44, P = 0.87; CT vs. CC: OR = 0.91, 95% CI = 0.75-1.09, P = 0.29; C vs. T: OR = 0.97, 95% CI = 0.87-1.09, P = 0.66).

In the subgroup analysis by cancer type, there was a significant association between the CD14 159C/T polymorphism and risk of acute lymphoblastic leukemia (TT vs. CT + CC: OR = 1.80, 95% CI = 1.37-2.38, P < 0.001; C vs. T: OR = 0.81, 95% CI = 0.67-0.98, P = 0.03). Meanwhile, the association between the polymorphism of CD14 159C/T gene and prostate cancer risk was also confirmed (TT vs. CC: OR = 0.62, 95% CI = 0.39-0.99, P = 0.04). However, we failed to detect any association between the 159C/T polymorphism and gastric, colorectal or laryngeal cancers. Due to the limited number of included studies, we didn't perform a subgroup analysis of other cancer types. Furthermore, when stratified by ethnicity and language, no significant association was found in all genetic models (**Table 2; Figure 2**).

Publication bias and sensitivity analysis

Begg' test ($P > |z| = 0.135$) or Egger' test ($P > |t| = 0.625$) didn't show argument for publication bias (**Figure 3**). Besides, no significant change was detected in sensitivity analysis. Therefore, the results of current study were reliable and stable.

Discussion

CD14 is a kind of lipopolysaccharide (LPS) receptor, made up of glycoprotein [16] and

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Table 2. Summary of results from different comparative genetic models

Variables	N	Number		Dominant model (TT + CT vs. CC)			Recessive model (TT vs. CT + CC)			Homozygote model (TT vs. CC)			Heterozygote model (CT vs. CC)			Allele contrast model (C vs. T)			
		Study	Case	Control	OR (95% CI)	P	I ² (%)	OR (95% CI)	P	I ² (%)	OR (95% CI)	P	I ² (%)	OR (95% CI)	P	I ² (%)	OR (95% CI)	P	I ² (%)
All	24	4136	7105	0.98 (0.83-1.16)	0.81	65.8	1.13 (0.87-1.46)	0.37	84.7	1.03 (0.73-1.44)	0.87	84.7	0.91 (0.75-1.09)	0.29	64.1	0.97 (0.87-1.09)	0.66	73.1	
By cancer type																			
Gastric cancer	10	2136	3418	1.05 (0.81-1.36)	0.74	70.0	1.28 (0.77-2.13)	0.35	92.2	1.26 (0.64-2.48)	0.50	91.7	0.97 (0.75-1.27)	0.85	63.7	0.95 (0.79-1.15)	0.59	81.2	
Acute lymphoblastic leukemia	3	354	1258	0.83 (0.51-1.33)	0.43	54.2	1.80 (1.37-2.38)	< 0.001	0.0	1.30 (0.90-1.88)	0.16	47.0	0.61 (0.36-1.03)	0.06	53.6	0.81 (0.67-0.98)	0.03	45.0	
Colorectal cancer	2	391	425	0.69 (0.24-1.95)	0.48	88.4	1.03 (0.76-1.41)	0.84	0.0	0.78 (0.35-1.71)	0.53	73.5	0.62 (0.17-2.21)	0.46	90.7	1.11 (0.78-1.58)	0.57	65.9	
Laryngeal cancer	2	569	1219	0.94 (0.57-1.55)	0.80	70.3	1.13 (0.75-1.70)	0.56	63.6	1.02 (0.50-2.09)	0.95	79.7	0.92 (0.61-1.39)	0.68	53.0	0.98 (0.72-1.34)	0.90	74.2	
Prostate cancer	2	372	347	0.99 (0.70-1.40)	0.95	0.0	0.61 (0.32-1.14)	0.12	63.6	0.62 (0.39-0.99)	0.04	2.3	1.22 (0.84-1.79)	0.30	0.0	1.19 (0.95-1.49)	0.12	0.0	
By ethnicity																			
Non-caucasian	6	865	1528	1.16 (0.74-1.57)	0.70	64.2	1.28 (0.33-5.05)	0.72	95.4	1.21 (0.29-5.05)	0.79	94.4	0.94 (0.64-1.38)	0.75	59.3	0.94 (0.66-1.35)	0.75	82.8	
Caucasian	18	3271	5577	0.95 (0.78-1.16)	0.62	67.4	1.07 (0.89-1.27)	0.49	62.7	0.96 (0.74-1.25)	0.78	70.0	0.89 (0.72-1.11)	0.31	67.1	0.98 (0.88-1.10)	0.79	66.1	
By language																			
English	21	3645	6275	1.01 (0.84-1.22)	0.90	67.6	1.15 (0.86-1.55)	0.35	86.3	1.06 (0.72-1.55)	0.77	86.3	0.92 (0.75-1.14)	0.46	67.6	0.95 (0.84-1.08)	0.43	74.1	
Chinese	3	491	830	0.78 (0.59-1.02)	0.70	0.0	0.90 (0.69-1.17)	0.44	0.0	0.81 (0.56-1.17)	0.26	0.0	0.77 (0.58-1.03)	0.08	0.0	1.15 (0.97-1.36)	0.11	0.0	

Abbreviations: OR, odds ratio; P, P-value of Z-test to evaluate the significance of the ORs; CI, confidence interval; I², I-squared (variation in OR attributable to heterogeneity).

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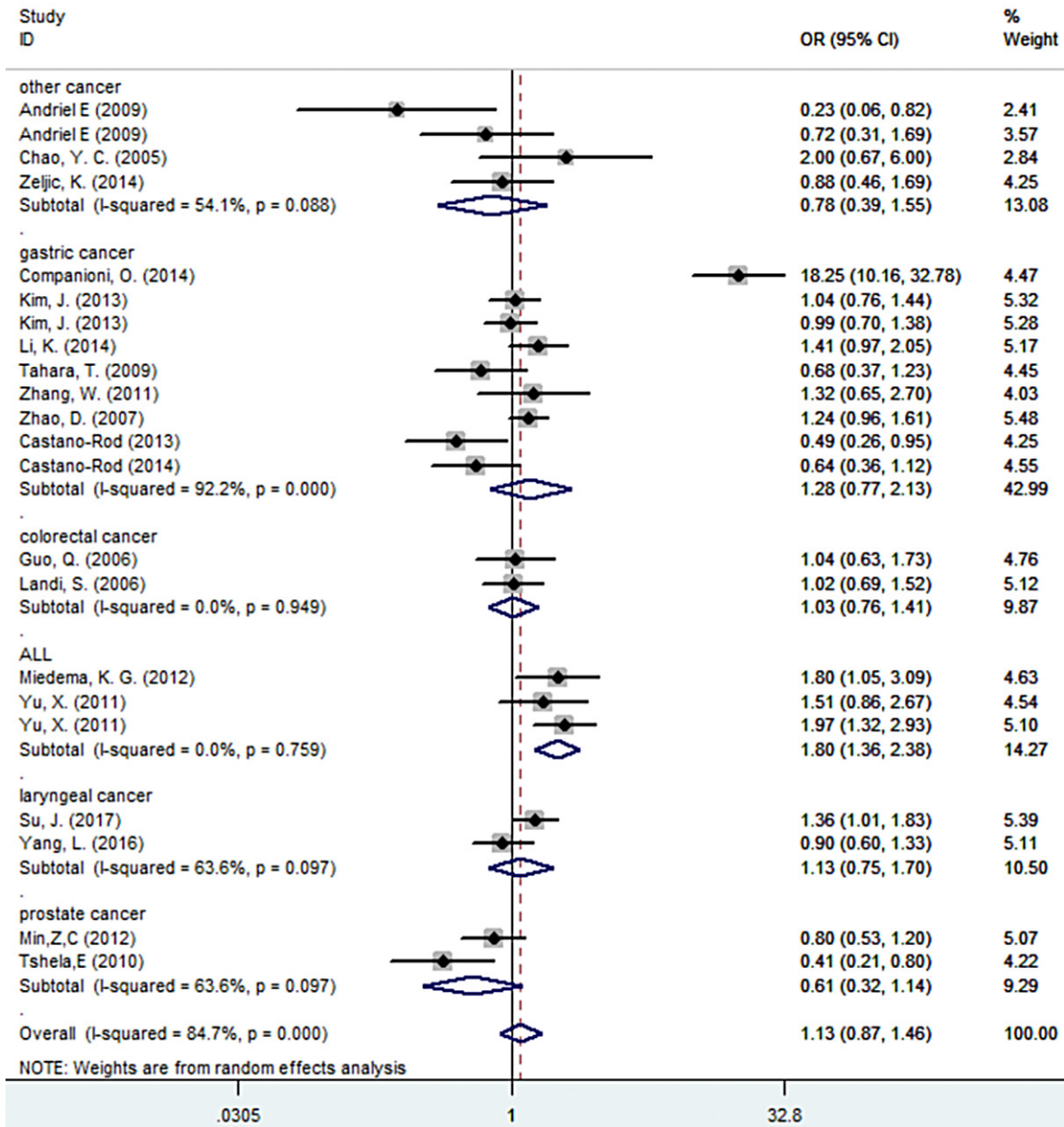


Figure 2. Meta-analysis of the association between CD14-159C/T polymorphisms and susceptibility to cancer.

existing in two distinct forms: mCD14 and sCD14 [17]. Along with LPS-binding protein, CD14 acts to transfer LPS to the Toll-like receptor 4/MD-2 signaling complex [18, 19]. It mediates and initiates many inflammatory responses leading to the increasing of pro-inflammatory cytokines and aggravation of inflammation, which will finally result in many pathological responses including toxemia, endotoxin shock and mucosal damage [20]. For example, the expression of mCD14 in bladder cancer cell lines could induce interleukin-8 which will pro-

mote angiogenesis in tumors and stimulate endothelial cell growth. Hence, increasing CD14 may reinforce all these responses, result in exacerbations, carcinogenesis or cancer progression [21, 22]. CD14 159C/T is located in the promoter region of CD14 gene, surrounded by cytokine gene cluster. The T allele carriers will have higher expression of CD14 on peripheral blood monocytes, especially TT homozygotes [23] Consequently, this polymorphism is likely to play a key role in the pathogenesis of cancer.

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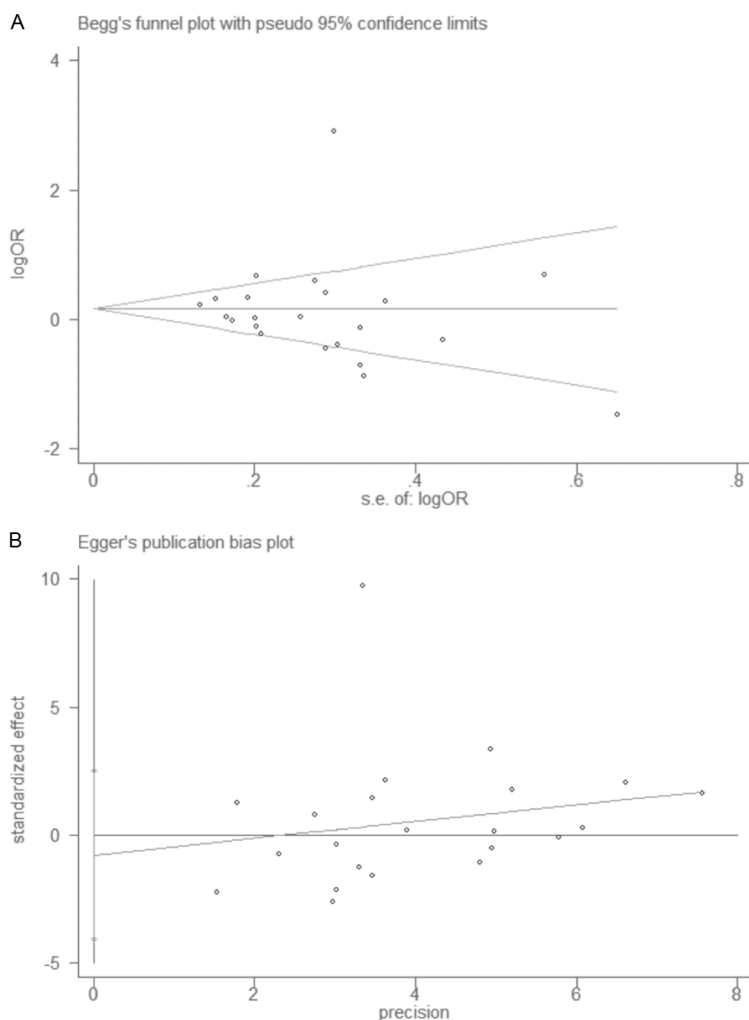


Figure 3. Assessment of publication bias by Begg's funnel plot and Egger's test.

Based on present study, including 4136 cancer patients and 7105 controls from 21 studies, no significant association was detected between CD14 159C/T and overall cancer risk. This was consistent with previous study carried out by Wei and colleagues [5]. Therefore, it seemed that the CD14 159C/T gene polymorphism may not be a risk factor for cancer. However, in the stratified analysis by cancer type, positive results were observed in the subgroup of acute lymphoblastic leukemia (ALL) and prostate cancer, which showed that CD14 159C/T polymorphism may be associated with ALL and prostate cancer. Unfortunately, we found no statistically significant association between CD14 159C/T variant and gastric cancer although previous studies indicate that there was a significant association between CD14 polymorphism with gastric cancer [24, 25]. However,

during subgroup analysis by cancer type, Wei and colleagues also didn't find any significant association when only analyzing gastric cancer type due to limited number of included studies [5]. Besides, the underlying genetic backgrounds and environmental may contribute to cancer risk, so we performed a subgroup analysis by ethnicity and language. However, no positive relationship was detected.

Despite interesting findings from the current meta-analysis, there are still some limitations needed to be acknowledged. Firstly, though a complete searching process was executed, the incorporated samples size was still limited. Some relevant studies, especially unpublished papers, might be missed [26]. Besides, due to limited sample size in a couple of subgroups, such as lymphoma, laryngeal cancer, oral cancer and so on, we failed to find the associations between the polymorphism of CD14 159C/T and some specific cancer types. Secondly, different subtypes of each cancer were not considered. As

mechanisms of different subtypes of the same cancer might be different, the polymorphism of CD14 may be associated with some specific subtypes of the cancer instead of the whole cancer [27]. Thirdly, controls of different studies were not defined uniformly. Controls of some studies were selected from the community while others were from hospitals [28]. Nevertheless, the current study also had some merits. On the one hand, a large number of included studies from different publications significantly increased statistical power of the analyses. On the other hand, based on results of our study, we found a novel mechanism to predict some cancer risk.

In conclusion, results from the current study suggested that the CD14 159C/T polymorphism may be associated with ALL and pros-

tate cancer, but no significant relationship has been found between overall cancer and CD14 159C/T polymorphism. Hence, more well-designed studies with larger sample size focusing on cancer types or ethnicities are needed to conduct a better comprehensive analysis about the association between CD14 159C/T polymorphism and cancer risk.

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Disclosure of conflict of interest

None.

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