Int J Clin Exp Med 2019;12(3):2216-2229
www.ijcem.com /ISSN:1940-5901/IJCEM0078172

Original Article

TLR-4 rs4986790 polymorphism contributes to cancer risk: an updated meta-analysis

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Received February 28, 2018; Accepted October 30, 2018; Epub March 15, 2019; Published March 30, 2019

Abstract: The association of toll-like receptor 4 (*TLR4*) gene Asp299Gly (+896A/G, rs4986790) polymorphism with cancer risk, many studies have been revealed. However, the result is still uncertain. We carried out an updated meta-analysis of 44 studies that contained 13667 cases and 17115 controls to verify the degree of association. Evaluating the degree of association was using Odds ratio (OR) and 95% confidence intervals (95% CI). In total, we found a distinct increased risk of cancer susceptibility when all qualified studies were collected (G versus A:OR=1.115, 95% CI: 1.039-1.197, P=0.002; GG+AG versus AA:OR=1.125, 95% CI: 1.044-1.212, P=0.002; AG versus AA:OR=1.126, 95% CI: 1.044-1.215, P=0.002). Sub-group analysis suggested that *TLR4* rs4986790 was associated with an increased risk of gastric cancer (G versus A:OR=1.587, 95% CI: 1.332-1.905, P=0.000; GG+AG versus AA:OR=1.625, 95% CI: 1.343-1.966, P=0.000; AG versus AA:OR=1.615, 95% CI: 1.332-1.958, P=0.000) and colorectal cancer (CRC) (G vs A: OR=1.238, 95% CI: 1.035-1.481, P=0.020; GG+AG versus AA:OR=1.217, 95% CI: 1.004-1.475, P=0.046). However, there were not enough evidence and data to assess the association of Asp299Gly between *TLR*4 gene and other cancers risk. The results of this meta-analysis indicated that *TLR*-4 Asp299Gly Polymorphism was correlated with an increased risk of cancer, particularly, gastric cancer and colorectal cancer (CRC).

Keywords: *TLR-4,* rs4986790, polymorphism, cancer, risk

Introduction

The first identified member of the toll-like receptor family is the toll-like receptor 4 (*TLR*4), which can identify pathogen-associated molecular patterns (PAMPs) and damage-associated molecular pattern (DAMPs). The gene locus of human *TLR*4 is chromosome 9q32-q33 and includes four exons gene. *TLR*-4 encodes an important endotoxin signaling receptor, which exerts an enormous function on pathogen recognition and activation of innate immunity. *TLR*4 widely expresses in different tissues and cells, such as: macrophages, cardiomyocytes, airway epithelial, adipose tissue, skeletal muscle, stromal cells, immune cells and so on [1] {Zhang, 2013 #5}. The Asp299Gly is in the position of the coding sequence and affect the *TLR*4 extracellular domain. Previously, many studies have been published about the correlation of *TLR*4 rs4986790 polymorphism with different cancer risk. Such as: gastric cancer [2-10], colorectal cancer [7, 11-16], prostate cancer [17-22], cervical cancer [23, 24], lung cancer [25] and so on. However, the fields of these studies were different and even the result was the opposite. For instance, Davoodi et al. [14] found that *TLR4* rs4986790 polymorphism was not associated with the risk of colorectal cancer in 2013. Whereas, a study published by Om-rane et al. [11] in 2014 about the association of *TLR*4 rs 4986790 with colorectal cancer, which suggest that the *TLR*4 Asp299Gly was correlated with an increased risk of gastric cancer risk. Furthermore, Yang et al. [40] made an accumulative meta-analysis about this topic in 2016, the results of the meta-analysis suggested *TLR*4 Asp299Gly variants are strongly associated with increasing cancer risk, especially gastric cancer. However, no association was observed in other cancers (containing colorectal cancer (CRC), prostate cancer, and lymphoma and so on).

In order to verify the association between *TLR*-4 rs4986790 polymorphism and cancer risk (especially CRC) and assess the influence of different tumor types more accurately. We selected several paper [2-10, 17-38, 47, 48] and several new published studies [16, 39] then carried out an update meta-analysis to confirm the correlation of *TLR4* rs4986790 polymorphism with cancer risk in accordance with 13667 cases and 17115 controls of 44 studies in 40 articles.

Materials and methods

Identification of eligible studies

For the reliability of the results, The eligible studies was collected through researching from Embase, PubMed, Google Scholar Search and China National Knowledge Infrastructure (CNKI), with key words "*TLR*4 Asp299Gly" or "*TLR*4 +896A/G", or "*TLR*4 rs4986790" or "toll-like receptor 4 rs4986790 (Asp299Gly, +896A/G)", "polymorphism" or "genetic variants" or "single nucleotide" or "SNP", "cancer" or "carcinoma" or "tumour" and "risk" as well as their combinations (from 2004 to 2017). There was no any restriction on studies and the last study was published on February 24, 2017. Two reviewers screened independently all references of the retrieved articles and reviews for original studies.

The studies of Inclusion and exclusion criteria

The following is inclusion criteria that the included studies need to meet: (1) Case-control studies; (2) Research the correlation between *TLR4* Asp299Gly (+896A/G, rs4986790) and cancer risks; (3) Histopathologic examination of the diagnosis of cancer; (4) Offering precise genotype frequencies to calculate the value of odds ratios (ORs) and 95% confidence intervals. No detailed gene frequencies were omitted. The data was different when two published studies were from the same paper, using the original dates from the initial studies. Letter, meta-analysis comment, review and editorial were deleted. Titles and abstracts were viewed and full articles were further estimated to verify feasibility on the basis of inclusion and exclusion criteria, all questions were discussed and handled by three reviewers.

Data extraction

Two authors (Zhu and Ye) extracted the data of eligible studies lonely and used a standard data extraction form. We collected the following contents: the first name of author, the year of publication, country of research, method of genotyping, type of cancer, value of Hardy-Winberg equilibrium, number of cases and controls genotype (AA, AG, GG) frequency in cases and controls of every eligible study. If there was a dispute, the original data of the included studies would be recheck and come to an agreement. If the dispute remained unresolved, the third investigators would be take part in to adjudicate the disagreements (Zeng).

Statistics analysis

Estimating the correlation level between *TLR4* rs4986790 polymorphism and cancer risks is using the value of Odds ratio (OR) and 95% confidence intervals (95% CI). The pooled ORs were calculated by Z test for dominant model (AG+GG vs AA), recessive models (GG vs AG+AA), homozygote model (GG vs AA), heterozygote model (AG vs AA) and additive model (G vs A). The influence of cancer type was explored by conducting subgroup analyses. The Hardy-Weinberg equilibrium (HWE) was applied to test the controls of every study.

Q-test and I-squared (I^2) was performed for evaluating the heterogeneity by the chi-square test. And the heterogeneity was deemed obvious and using random-effects model to pool the data from different studies when $P<0.10$ and $I^2>50\%$. On the contrary, a significant heterogeneity didn't exist and the fixed-effect model was applied when $P>0.10$ and $I^2<50\%$.

Begg's funnel plot was applicable to check the publication bias, and $P<0.05$ was deem to have distinct publication bias. Calculating all statistical analyses were using STATA software (version 11.0, Stata Corporation, College Station, TX). All values of test were two sided.

Results

Characteristics of contained studies

A total of 40 articles and 44 studies were contained on the basis of the inclusion and exclusion criteria with 13667 cases and 17115

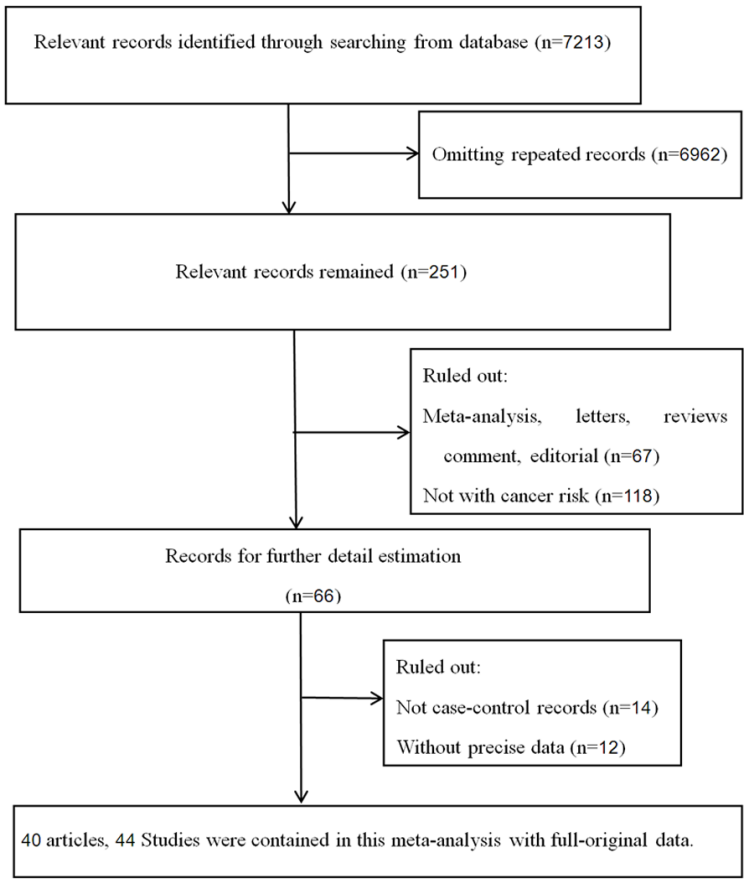

Figure 1. The detailed process of searching for appropriate studies. A total of 40 articles were identified and two articles contained three studies respectively. So, there were 44 studies included in our meta analysis.

controls. **Figure 1** has list the detailed screening process. The studies and main characteristics in the meta-analysis were presented in **Table 1** There were nine concerned with gastric cancer studies [2-10], seven concerned with colorectal cancer studies [7, 11-16], six concerned with Prostate cancer studies [17-22], six concerned with lymphoma studies [28-33], three concerned with breast cancer studies [26, 27, 39], two concerned with cervical cancer studies [23, 24], one concerned with lung cancer study [25], one concerned with ovarian cancer study [7], one concerned with bladder cancer study [38], one concerned with oesophageal cancer study [2], one concerned with leukaemia study [37], one concerned with endometrial study [36], one concerned with nasopharyngeal study [35], one concerned with malignant melanoma study [34] in this meta-analysis. **Table 1** revealed the results of Hardy-Weinberg equilibrium test for the distribution of the genotype in control population and the genotype distribution of the controls of six studies [14, 15, 17, 19, 38, 47] wasn't line in HWE.

Meta-analysis results

Gathering 13667 cases and 17115 controls in this updated meta-analysis, the significance correlation between the *TLR4* rs4986790 polymorphism and cancer risk was found in the three genetic models (G versus A:OR=1.115, 95% CI: 1.039-1.197, P=0.002; GG+AG versus AA:OR=1.125, 95% CI: 1.044-1.212, P=0.002; AG versus AA:OR=1.126, 95% CI: 1.044-1.215, P=0.002) (**Table 2**). Sub-group analysis suggested that *TLR*4 rs4986790 was associated with an increase risk of gastric cancer (G versus A:OR=1.587, 95% CI: 1.332-1.905, P=0.000; GG+AG versus AA:OR=1.625, 95% CI: 1.343-1.966, P=0.000; AG versus AA:OR=1.615, 95% CI: 1.332-1.958, P=0.000) and colorectal cancer (CRC) (G vs A: OR=1.238, 95% CI: 1.035-1.481, P=0.020; GG+AG versus AA:OR=1.217, 95% CI: 1.004-1.475, P=0.046) (**Table 2**).

No correlation was observed in prostate cancer, lymphoma, breast cancer, and cervical cancer. So far, there have been not enough studies to estimate the correlation between *TLR4* rs4986790 Polymorphism and other cancer risk, which included lung cancer, ovarian cancer, endometrial cancer, oesophageal cancer, bladder cancer and nasopharyngeal cancer.

Heterogeneity

The *P* value is Cochran's Q test for between-study heterogeneity in each genetic comparison model. When pheterogeneity >0.1 and I-squared <50%, A fixed effects model was applied, Otherwise, a random effects model was applied. As were shown in the figures that obvious heterogeneities existed in Overall

Table 1. General information of selected studies on the association between *TLR-4* rs4986790 polymorphisms and cancer risk in this meta-analysis

Authors' name	Year	Country	Tumor type	Case			Control			*P* value of HWE
				AA	AG	GG	AA	AG	GG	
Zheng SL	2004	Sweden	Prostate	1241	136	1	693	79	5	0.26
Hellmig S	2005	Germany/Australia	Gastric MALT lymphoma	83	4	0	313	45	0	0.44
Chen YC	2005	USA	Prostate	588	66	3	605	59	5	0.04
Nieters A	2006	Germany	Lymphoma	590	84	1	596	71	1	0.76
Boraska Jelavic T	2006	Croatia	Colorectal	77	10	2	84	4	0	0.98
Forrest MS	2006	USA/UK	Non-Hodgkin lymphoma	794	106	3	1254	172	6	0.99
Garza-Gonzalez E	2007	Mexico	Gastric	72	6	0	175	14	0	0.87
Hold GL	2007	Poland	Gastric	258	51	3	387	31	1	0.90
Hold GL	2007	USA	Gastric	266	38	3	194	16	1	0.58
Hold GL	2007	USA	Oesophageal	148	11	0	194	16	1	0.58
Cheng I	2007	USA	Prostate	439	66	1	456	48	2	0.83
Trejo-de la OA	2008	Mexico	Gastric	34	4	0	138	6	0	0.97
Ture-Ozdemir F	2008	Greece	Gastric MALT lymphoma	38	18	0	39	12	0	0.64
Santini D	2008	Italy	Gastric	159	11	1	140	11	0	0.89
Etokebe GE	2009	Croatia	Breast	110	20	0	84	15	0	0.72
Pandey S	2009	India	Cervical	114	35	1	123	26	1	0.96
Purdue MP	2009	USA	Non-Hodgkin lymphoma	1195	133	6	1126	131	8	0.16
Wang MH	2009	USA	Prostate	230	24	0	216	35	0	0.49
Ashton KA	2010	Australia	Endometrial	163	25	3	258	31	2	0.62
Balistreri CR	2010	Italy	Prostate	49	1	0	111	13	1	0.68
Rigoli L	2010	Italy	Gastric	42	18	0	80	7	0	0.3
Davoodi	2011	Iran	Colorectal	58	2	0	50	0	0	-
Yang	2011	China	Colorectal	96	4	2	84	2	1	0.00
Gast A	2011	Germany	Malignant melanoma	665	91	0	659	73	3	0.82
Miedema KG	2012	Netherlands	Leukaemia	168	20	0	151	28	0	0.35
Theodoropoulos GE	2012	Greece	Breast	201	57	3	412	63	5	0.35
Yang ZH	2012	China	Nasopharyngeal	205	29	2	250	33	4	0.08
Dai	2012	China	Colorectal	219	44	5	228	38	2	0.62
Primentel-Nunes	2013	Portugal	Colorectal	169	0	15	186	0	5	0.00
Shen Y	2013	China	Bladder	431	2	3	519	1	2	0.00
De Oliveiro JG	2013	Brazil	Gastric	174	26	0	224	16	0	0.87
Omrane I	2013	Tunisia	Colorectal	87	13	0	120	18	2	0.42
Qadri Q	2014	India	Gastric	107	23	0	169	31	0	0.49
Gu X	2014	China	Non-Hodgkin lymphoma	149	7	1	413	21	1	0.43
Companioni O	2014	Italy	Gastric	316	45	0	1134	133	3	0.91
Kutikhin AG	2014	Russian	Gastric	46	11	0	258	39	0	0.48
Kutikhin AG	2014	Russian	Colorectal	173	40	0	258	39	3	0.55
Kutikhin AG	2014	Russian	Ovarian	57	7	0	144	24	0	0.61
Zidi S	2015	Tunisia	Cervical	116	6	8	207	46	7	0.09
Kurt H	2015	Turkey	Lung	159	1	0	99	1	0	0.99
Kopp TI	2015	Danish	Colorectal	839	76	0	1577	141	1	0.49
Winchester DA	2015	USA	Prostate	768	94	5	741	82	7	0.03
Semlali	2016	Saudi Arabian	Colon	106	7	1	92	7	1	0.19
Semlali	2017	Saudi Arabian	Breast	115	8	0	101	14	0	0.80

Meta-analysis about the *TLR*-4 rs4986790 Polymorphism and Cancer Risk (**Figures 2**-**4**). The pheterogeneity value of gene models (GA+GG versus AA, GA versus AA, G versus A) are all 0.000, Heterogeneity didn't disappear when deleting articles with larger difference. He-

Table 2. Main results of the updated meta-analysis of the pooled OR

Genotype	Number of studies	Cumulative OR (95% CI)	Hypothesis test		Pheterogeneity	I-squared (%)
			Z	p		
Overall						
GG+AG/AA	44	1.125 (1.044, 1.212)	3.10	0.002	0.000	48.1
GG/AA+AG	44	1.092 (0.800, 1.492)	0.55	0.579	0.687	0.00
GG/AA	44	1.097 (0.803, 1.498)	0.58	0.561	0.771	0.00
AG/AA	44	1.126 (1.044, 1.215)	3.06	0.002	0.000	47.4
G/A	44	1.115 (1.039, 1.197)	3.03	0.002	0.000	48.6
Tumour type Colorectal cancer						
GG+AG/AA	9	1.217 (1.004, 1.475)	2.00	0.046	0.241	22.7
GG/AA+AG	9	1.671 (0.905, 3.085)	1.64	0.101	0.533	0.00
GG/AA	9	1.702 (0.921, 3.145)	1.70	0.089	0.541	0.00
AG/AA	9	0.853 (0.698, 1.034)	1.55	0.120	0.608	0.00
G/A	9	1.238 (1.035, 1.481)	2.33	0.020	0.051	48.3
Gastric cancer						
GG+AG/AA	10	1.625 (1.343, 1.966)	4.99	0.000	0.062	44.6
GG/AA+AG	10	1.964 (0.612, 6.307)	1.13	0.257	0.742	0.00
GG/AA	10	2.069 (0.646, 6.630)	1.22	0.221	0.723	0.00
AG/AA	10	1.615 (1.332, 1.958)	4.88	0.000	0.073	42.8
G/A	10	1.587 (1.322, 1.905)	4.95	0.000	0.074	42.6
Prostate cancer						
GG+AG/AA	6	1.008 (0.863, 1.177)	0.10	0.920	0.104	45.3
GG/AA+AG	6	0.483 (0.230, 1.011)	1.93	0.053	0.676	0.00
GG/AA	6	0.486 (0.232, 1.017)	1.91	0.056	0.675	0.00
AG/AA	6	1.043 (0.890, 1.222)	0.52	0.604	0.110	44.3
G/A	6	0.975 (0.841, 1.130)	0.34	0.737	0.113	43.9
Lymphoma						
GG+AG/AA	6	0.984 (0.847, 1.142)	0.21	0.830	0.261	23.0
GG/AA+AG	6	1.089 (0.443, 2.741)	0.18	0.856	0.680	0.00
GG/AA	6	1.109 (0.441, 2.792)	0.22	0.826	0.678	0.00
AG/AA	6	0.989 (0.850, 1.151)	0.14	0891	0.267	22.1
G/A	6	0.979 (0.849, 1.129)	0.29	0.770	0.287	19.3
Breast cancer						
GG+AG/AA	3	1.213 (0.956, 1.539)	1.59	0.112	0.223	33.3
GG/AA+AG	3	1.007 (0.338, 3.000)	0.01	0.990	0.462	0.00
GG/AA	3	1.036 (0.348, 3.079)	0.06	0.950	0.441	0.00
AG/AA	3	1.221 (0.958, 1.556)	1.61	0.107	0.399	0.00
G/A	3	1.259 (0.859, 1.847)	1.18	0.238	0.121	52.6
Cervical cancer						
GG+AG/AA	2	0.925 (0.737, 1.162)	0.67	0.503	0.444	0.00
GG/AA+AG	2	0.792 (0.195, 3.176)	0.33	0.742	-	-
GG/AA	2	0.790 (0.197, 3.166)	0.33	0.739	-	-
AG/AA	2	0.929 (0.738, 1.169)	0.63	0.530	0.433	0.00
G/A	2	1.926 (0.745, 1.151)	0.69	0.489	0.473	0.00

The *P* value is Cochran's Q test for between-study heterogeneity in each genetic comparison model.

terogeneity may be drive from race, cancer type, lifestyle, environment and sample capacity. In order to find the source of heterogeneity, we further carried out subgroup analysis. The

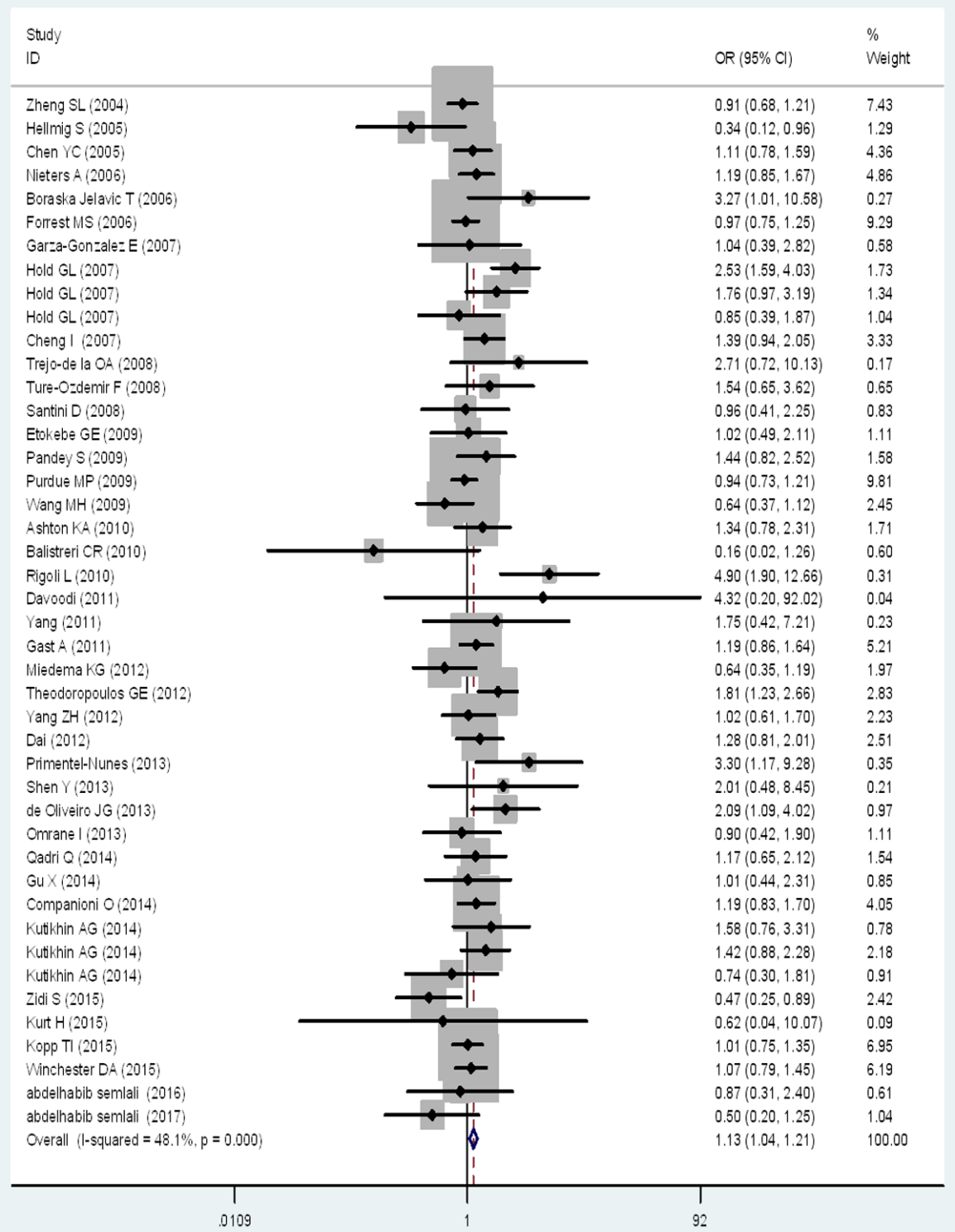

Figure 2. Overall meta-analysis of the *TLR-4* rs4986790 polymorphism and cancer risk in the dominate genetic model.

results of subgroup analysis not only revealed that the rs4986790 was associated with an increased risk of gastric cancer and colorectal cancer, but also eliminated heterogeneity, which suggested that cancer type was a source of heterogeneity.

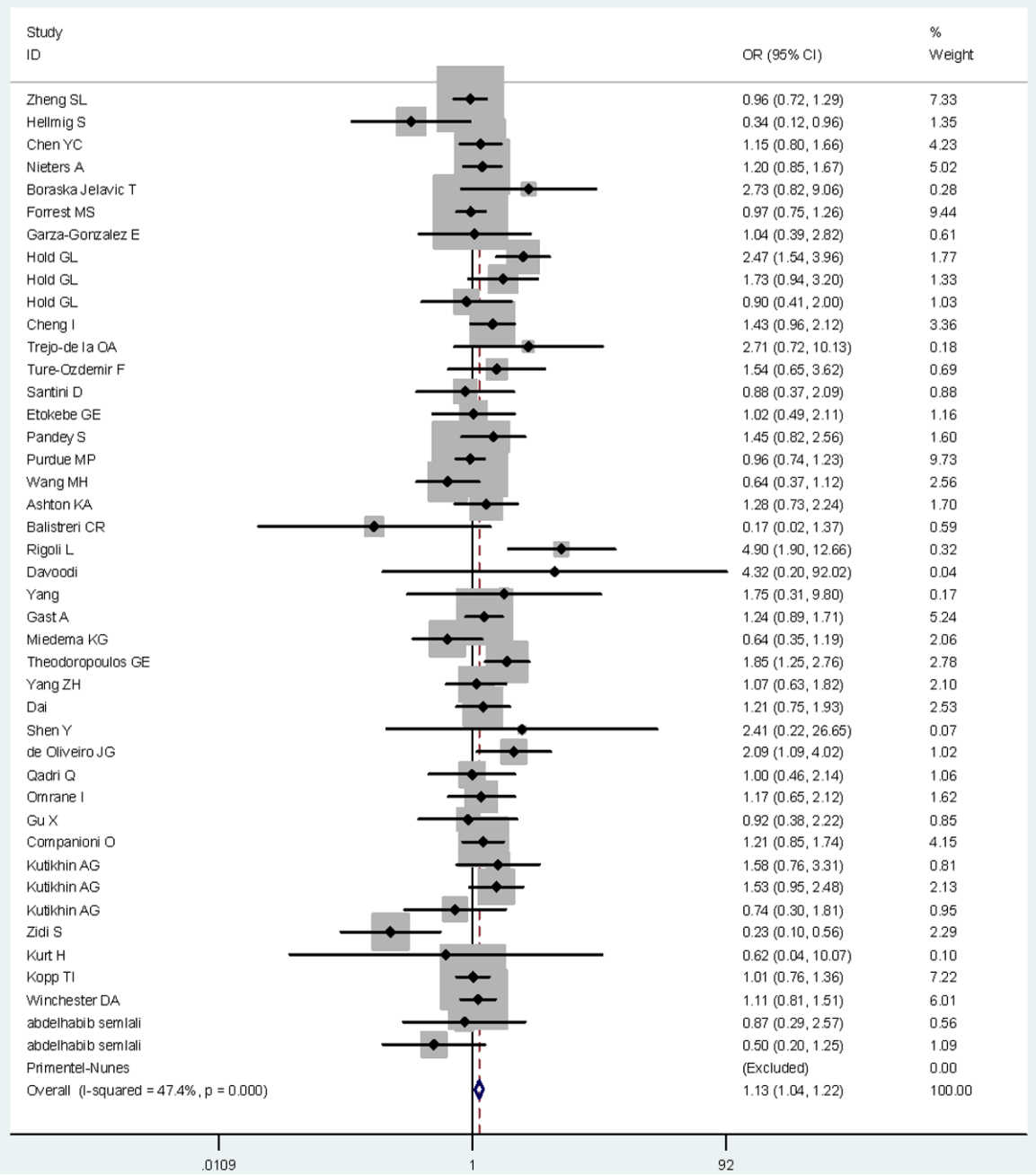

Figure 3. Overall Meta-analysis of the *TLR-4* rs*4986790* polymorphism and cancer risk in the heterozygous genetic mode.

Sensitivity analysis

The effects of the individual data on the pooled OR are using a sensitivity to estimate by continuously canceling each eligible study from amalgamative analysis. The results suggested that no single study influenced the pooled OR for three gene model (GA+GG versus AA, GA versus AA, G versus A) obviously, Because no substantial change was found. (Didn't present in the figure).

Publication bias

The publication bias is using the Begg's funnel plot to estimate. The shape of funnel plot (**Figures 5-7**) was symmetric and didn't show distinct publication bias in all the studies.

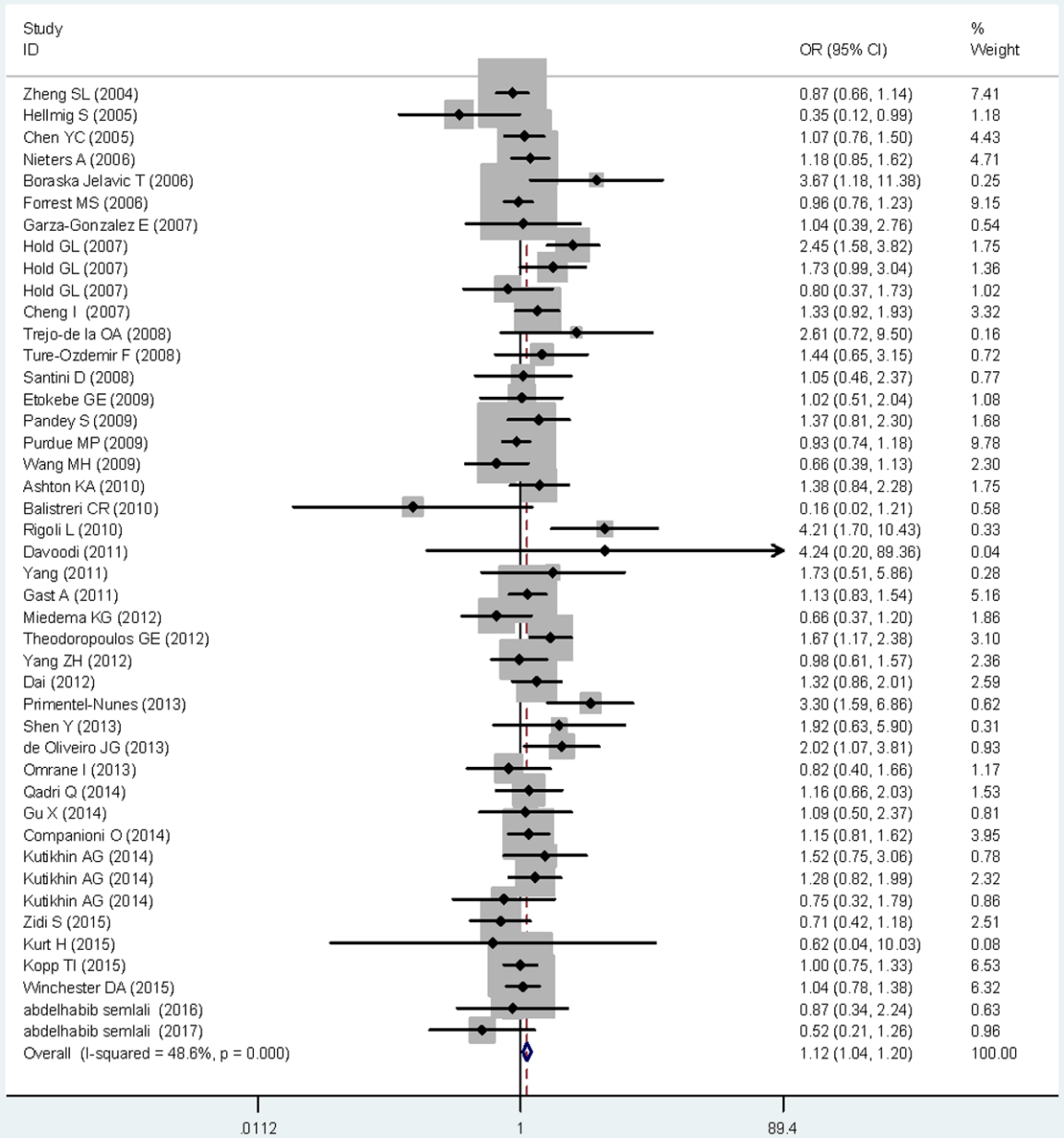

Figure 4. Overall Meta-analysis of the *TLR*-4 rs4986790 polymorphism and cancer risk in the additive genetic model.

Furthermore, the Begg's regression test's results of three genetic models were P=0.412, 95% CI: -0.520-1.246 for the dominant model; P=0.867, 95% CI: -0.809-0.956 for the heterozygous genetic model; P=0.278, 95% CI: -0.407-1.382 for the additive model respectively, which implied that no publication bias existed.

Discussion

According to 44 studies with 13667 cases and 17115 controls about the correlation of TLR4 rs4986790 polymorphism with cancer risk, this meta-analysis offered strong evidence of association between *TLR*4 rs4986790 polymorphism and cancers risk. These evidences indicated *TLR*4 rs4986790 was a risk factor for cancer, especially gastric cancer and colorectal cancer. It wasn't found that *TLR*4 rs4986790 was associated with an increased the risk of other cancers.

*TLR*s were classified as a class of transmembrane glycoprotein family, which was an impor-

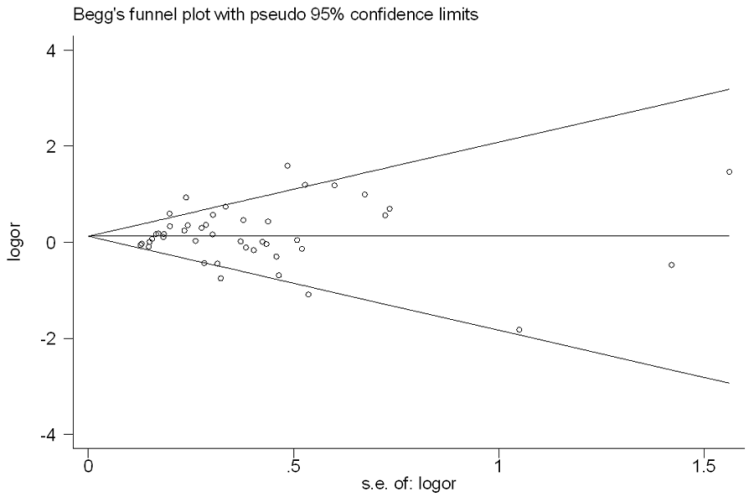

Figure 5. Funnel plot analysis to detect publication bias for *TLR4* rs4986790 GG+AG vs AA polymorphism associated with cancer risk.

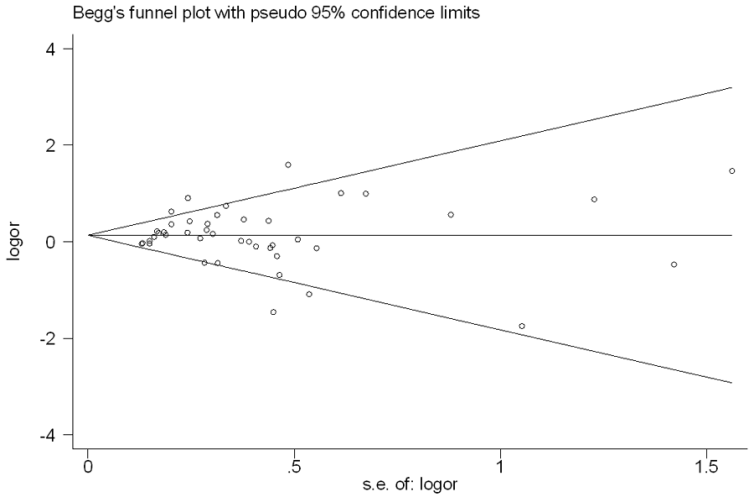

Figure 6. Funnel plot analysis to detect publication bias for *TLR4* rsrs4986790 AG vs AA polymorphism associated with cancer risk.

tant guarantee of the natural immunity of human beings against the invasion of microbes. *TLR*s also were receptors that recognize bioactive molecules and participates in the inflammatory response and actives a variety of inflammatory mediators. Such as, TNF-α, IL-6, and IL-1β and so on. *TLR*4 is the main one of the *TLR*s and played a key role in the inflammatory response of the infected Gram-negative bacteria. *TLR4* rs4986790 variant was situated in a coding region and turned amino acid 299 glycine into asparagine (Asp299Gly). The influence of *TLR*4 rs4986790 polymorphisms on various types of cancer has been focused. In recent years, lots of studies of the correlation between *TLR*4 rs4986790 and cancer risk have been published. Garza-Gonzalez et al. [8] and Qurteeba Qadri et al. [5] indicated no correlation of *TLR4* rs4986790 polymorphisms with gastric cancer risk, In contrast, De Oliveira et al. [10] found that *TLR*4 rs4986790 was associated with an increased in the risk of gastric cancer. Besides the study of the correlation between *TLR*4 rs4986790 polymorphisms and gastric cancer, many researchers also focused on the association of other cancers with *TLR*4 rs4986790, such as: colorectal cancer, breast cancer, lung cancer and so on. Kopp et al. [12] found that TLR4 rs4986790 polymorphism was not associated with an increased the risk of colorectal cancer. Semlali et al. [39] indicated that *TLR*4 rs4986790 polymorphism was not correlated with breast cancer risk. Hulyam Kurt et al. [25] suggested that *TLR*4 rs4986790 polymorphism was not a risk factor of lung cancer. Except for the study of the link between single cancer and *TLR*4 rs4986790 polymorphism, Yang et al. [40] made an accumulative meta-analysis to assess the link between *TLR*4 rs4986790 polymorphism and cancer risk. Their results were that *TLR*4 rs4986790 polymorphism contributed to cancer, particularly gastric cancer. No association has been found in other cancers. We made this meta-analysis for the association of *TLR*4 rs4986790 polymorphism with cancer risk and found that *TLR*4 rs4986790 polymorphism increased cancer risk, which was in line with the previous meta analysis [40]. However, in the sub-group analysis, not only have we found that *TLR*4 rs4986790 polymorphism was associated with gastric cancer, but also it has been found to contribute to colorectal cancer.

The results of our research had the same and difference as the previous meta analysis [40]. The same point was that the conclusion of this

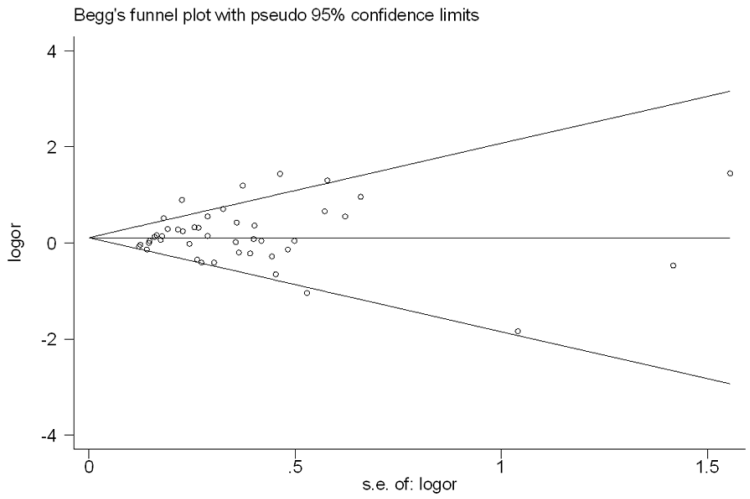

Figure 7. Funnel plot analysis to detect publication bias for *TLR4* rsrs4986790 G vs A polymorphism associated with cancer risk.

meta was consistent with the previous meta analysis for the correlation between *TLR*4 rs4986790 and cancer risk. The difference was that our result was opposite to the previous meta analysis about the correlation between *TLR*4 rs4986790 and colorectal cancer in sub-group analysis. We observed that *TLR*4 rs4986790 is a risk factor for colorectal cancer. Whereas, *TLR*4 rs4986790 was not correlated with increasing the risk of colorectal cancer in previous meta analysis. In addition, compared with the previous meta analysis, we included more related case-control studies in our meta analysis. Generally speaking, there were different conclusions between different studies about the same topic. On the one hand, as the distribution and expression were affected by geographical environment, sex, age, and so on. The subjects of some studies were different in countries, sex, races and ages, which may be affect the results. On the other hand, sufficient sample size was an important guarantee for the accuracy of the result, different sample sizes also could lead to different results in different studies, the larger the sample size, the more convincing results. What's more, methods of statistical analysis, methods of diagnostics of cancer, genotyping methods and the methods selected by the subjects could play a major role in result of each study. Utilizing different methods of study, the final results were different.

In sub-group analysis, we found *TLR*4 rs4986790 was closely linked to gastric cancer and colorectal cancer. No correlation has been found in other cancers in this meta analysis. The specific cause of cancer is not clear. Genetic inheritance, living habit, environmental pollution and chronic inflammation may lead to cancer. Studies have suggested that helicobacter pylori (H. pylori) was a parasitic on the digestive tract system. People infected with Helicobacter pylori (H. pylori) have much higher risk of chronic gastritis, intestinal metaplasia, peptic ulcer disease and gastric cancer [41]. In 2017, a study has been published about the link between *TLR*4 rs4986790 and chronic Helicobacter pylori infection. They founded that *TLR*4 rs4986790 increased the risk of chronic infection of Helicobacter pylori (H. pylori), the mechanism of which is likely to be the poor immune response of *TLR*4 rs4986790 polymorphism to the pathogen [42]. Hence, *TLR*4 rs4986790 promoted the occurrence of gastric cancer may be associated with increased the risk of chronic infection of Helicobacter pylori (H. pylori). In addition, Genetic inheritance, geographical environment, diet and so on may also be a risk factor for the occurrence of gastric cancer.

The mechanism of colorectal cancer is still unclear, but experimental research have proved that the inflammatory mediators in innate immune system and bacterial toxins are the main causes of colorectal cancer [43, 44]. When the *TLR*4 is activated, it can start to the MyD88 dependent pathway. MyD88 activates transcription factors nuclear factor-kappa B (NF-κB) and activator protein-1 (AP-1) through IκB kinase (IKK) and mitogen-activated protein kinase (MAPK) pathway, which promotes the occurrence of inflammation [45]. The inflammatory reaction promotes the activation of the innate immune system and induces a large number of proinflammatory cytokines and highly active chemicals. Such as IL1, IL6, TNFα, Lymphocytes, neutrophils, macrophages, and so on [45]. Proinflammatory cytokines and highly active chemicals increased intestinal epithelial cell injury, cell death and genotoxicity, which increased bacterial toxin. Bacterial toxin

could lead to DNA breakage and prevent DNA repair pathway. The combination of two mechanisms of DNA injury and cell replication increases the risk of cancer [44]. About TLR4 rs4986790 promoted the occurrence of colorectal cancer, we thought probably due to the over expression of *TLR*4 in colorectal cancer, resulting in inflammation and the increase of bacterial toxins, which lead to a decrease in intestinal mucosal resistance, and bacterial invasion into intestinal mucosa. It is well known that the gastrointestinal tract is rich in bacteria. Normally, the intestinal mucosa can resist the invasion of bacteria to maintain normal physiological function. However, Intestinal mucosal immune system damage causes intestinal mucosal resistance to weaken, bacterial invasion produces toxins and inflammatory reactions, activating the immune system to produce a series of chemical substances. If the intestinal epithelial cells are severely damaged by inflammatory mediators and bacterial toxins for a long time, which may cause chronic inflammatory bowel disease (IBD) and further developing to colorectal cancer [49]. The studies have proved that inflammatory bowel disease (IBD) increases the risk of colorectal cancer [46]. Except for the stimulation of inflammation and toxins, genetic, carcinogenic, living habits and gene-environment interactions may also be the risk factors for colorectal cancer. Moreover, the expression of *TLR*4 rs4986790 itself may promote the growth of cancer and restrains the apoptosis of the cells. Although we have not found *TLR*4 rs4986790 increases the risk of other cancers, this does not mean that *TLR*4 rs4986790 is not related to these cancers. The results may be affected by other related factors of the subject, which requires further research and more data to be confirmed.

There was an obvious heterogeneity in this meta analysis. Heterogeneity may come from many aspects. For example: cancer type, sample capacity, ethnicity, environment, lifestyle, age and so on. We made the subgroup analysis on basis of cancer type and sensitivity analysis to search the source of heterogeneity. According to the results of subgroup analysis, we found the disappearance of heterogeneity in the subgroup analysis on basis of cancer type, which revealed that cancer type was a source of the heterogeneity. Whereas, sensitivity analysis did not find any source of heterogeneity. In addition, the limitations of our meta-analysis our meta also existed. First of all, number of cancer samples was not enough big, which may affect validity and reliability of the result. Secondary, the controls for several studies didn't conform Hardy-Weinberg equilibrium, which may affect the results. However, when the studies that didn't satisfy the HWE were deleted from the meta-analysis, we still found that a significant correlation *TLR*4 rs4986790 with cancer risk. Thirdly, sub-group analysis is just according to the cancer type. The larger number of cancer types for searching just were gastric and colorectal cancer. The result is meaningless if the study was too little. Fourthly, the ethnic, life-style, dietary habit and environment may affect on the gene express and thus lead to different results. However, many studies didn't take these factors into account in this meta. Therefore, to get more precise results, more study of the association of *TLR*4 rs4986790 with cancer risk is needed about different ethnics, cancer types, life-style, dietary habit and environment.

Summed up, we demonstrated that *TLR*4 rs4986790 polymorphism contributed to cancer risk, especially in gastric and colorectal cancer, no correlation has been found in other cancers, which included lung cancer, breast cancer, Ovarian cancer, Lymphoma and so on. The more studies and larger scales of control-cases are essential to verify the correlation of *TLR*4 rs4986790 polymorphism with cancer risk.

Acknowledgements

This work was supported by Science Technology Department of Jiangxi provincial (20112BBG-70051) and Education Department of Jiangxi (GJJ14041).

Disclosure of conflict of interest

None.

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References

[1] Yin YW, Li JC, Li BH, Wang JZ, Liu Y, Liao SQ, Zhang MJ, Gao CY and Zhang LL. Toll-like re-

ceptor 4 gene Asp299Gly polymorphism in ischemic cerebrovascular disease: a meta-analysis. Int J Neurosci 2014; 124: 252-60.

[2] Hold GL, Rabkin CS, Chow WH, Smith MG, Gammon MD, Risch HA, Vaughan TL, McColl KE, Lissowska J, Zatonski W, Schoenberg JB, Blot WJ, Mowat NA, Fraumeni JF Jr and El-Omar EM. A functional polymorphism of toll-like receptor 4 gene increases risk of gastric carcinoma and its precursors. Gastroenterology 2007; 132: 905-912.

[3] Rigoli L, Di Bella C, Fedele F, Procopio V, Amorini M, Lo Giudice G, Romeo P, Pugliatti F, Finocchiaro G, Luciano R and Caruso RA. TLR4 and NOD2/CARD15 genetic polymorphisms and their possible role in gastric carcinogenesis. Anticancer Res 2010; 30: 513-517.

[4] Trejo-de la OA, Torres J, Perez-Rodriguez M, Camorlinga-Ponce M, Luna LF, Abdo-Francis JM, Lazcano E and Maldonado-Bernal C. TLR4 single-nucleotide polymorphisms alter mucosal cytokine and chemokine patterns in mexican patients with Helicobacter pylori-associated gastroduodenal diseases. Clin Immunol 2008; 129: 333-340.

[5] Qadri Q, Rasool R, Afroze D, Naqash S, Gulzar GM, Yousuf A, Siddiqi MA and Shah ZA. Study of TLR4 and IL-8 gene polymorphisms in H. pylori-induced inflammation in gastric cancer in an ethnic kashmiri population. Immunol Invest 2014; 43: 324-336.

[6] Companioni O, Bonet C, Munoz X, Weiderpass E, Panico S, Tumino R, Palli D, Agnoli C, Vineis P, Boutron-Ruault MC, Racine A, Clavel-Chapelon F, Travis RC, Khaw KT, Riboli E, Murphy N, Vergnaud AC, Trichopoulou A, Benetou V, Trichopoulos D, Lund E, Johansen D, Lindkvist B, Johansson M, Sund M, Ardanaz E, Sanchez-Cantalejo E, Huerta JM, Dorronsoro M, Ramon Quiros J, Tjonneland A, Mortensen LM, Overvad K, Chang-Claude J, Rizzato C, Boeing H, Bueno-de-Mesquita HB, Siersema P, Peeters PH, Numans ME, Carneiro F, Licaj I, Freisling H, Sala N and Gonzalez CA. Polymorphisms of helicobacter pylori signaling pathway genes and gastric cancer risk in the european prospective investigation into cancer-eurgast cohort. Int J Cancer 2014; 134: 92-101.

[7] Kutikhin AG, Yuzhalin AE, Volkov AN, Zhivotovskiy AS and Brusina EB. Correlation between genetic polymorphisms within IL-1B and TLR4 genes and cancer risk in a Russian population: a case-control study. Tumour Biol 2014; 35: 4821-4830.

[8] Garza-Gonzalez E, Bosques-Padilla FJ, Mendoza-Ibarra SI, Flores-Gutierrez JP, Maldonado-Garza HJ and Perez-Perez GI. Assessment of the toll-like receptor 4 Asp299Gly, Thr399Ile and interleukin-8-251 polymorphisms in the risk for the development of distal gastric cancer. BMC Cancer 2007; 7: 70.

[9] Santini D, Angeletti S, Ruzzo A, Dicuonzo G, Galluzzo S, Vincenzi B, Calvieri A, Pizzagalli F, Graziano N, Ferraro E, Lorino G, Altomare A, Magnani M, Graziano F and Tonini G. Toll-like receptor 4 Asp299Gly and Thr399Ile polymorphisms in gastric cancer of intestinal and diffuse histotypes. Clin Exp Immunol 2008; 154: 360-364.

[10] de Oliveira JG, Rossi AF, Nizato DM, Miyasaki K and Silva AE. Profiles of gene polymorphisms in cytokines and toll-like receptors with higher risk for gastric cancer. Dig Dis Sci 2013; 58: 978-988.

[11] Omrane I, Baroudi O, Kourda N, Bignon YJ, Uhrhammer N, Desrichard A, Medimegh I, Ayari H, Stambouli N, Mezlini A, Bouzayenne H, Marrakchi R, Benammar-Elgaaid A and Bougatef K. Positive link between variant toll-like receptor 4 (Asp299Gly and Thr399Ile) and colorectal cancer patients with advanced stage and lymph node metastasis. Tumour Biol 2014; 35: 545-551.

[12] Kopp TI, Andersen V, Tjonneland A and Vogel U. Polymorphisms in NFKB1 and TLR4 and interaction with dietary and life style factors in relation to colorectal cancer in a danish prospective case-cohort study. PLoS One 2015; 10: e0116394.

[13] Boraska Jelavic T, Barisic M, Drmic Hofman I, Boraska V, Vrdoljak E, Peruzovic M, Hozo I, Puljiz Z and Terzic J. Microsatelite GT polymorphism in the toll-like receptor 2 is associated with colorectal cancer. Clin Genet 2006; 70: 156-160.

[14] Davoodi H and Seow HF. Variant Toll-like receptor4 (Asp299Gly and Thr399Ile alleles) and Toll-like receptor2 (Arg753Gln and Arg677Trp alleles) in colorectal cancer. Iran J Allergy Asthma Immunol 2011; 10: 91-99.

[15] Pimentel-Nunes P, Teixeira AL, Pereira C, Gomes M, Brandao C, Rodrigues C, Goncalves N, Boal-Carvalho I, Roncon-Albuquerque R Jr, Moreira-Dias L, Leite-Moreira AF, Medeiros R and Dinis-Ribeiro M. Functional polymorphisms of Toll-like receptors 2 and 4 alter the risk for colorectal carcinoma in europeans. Dig Liver Dis 2013; 45: 63-69.

[16] Semlali A, Reddy Parine N, Arafah M, Mansour L, Azzi A, Al Shahrani O, Al Amri A, Shaik JP, Aljebreen AM, Alharbi O, Almadi MA, Azzam NA, Kohailan M, Rouabhia M and Alanazi MS. Expression and polymorphism of toll-like receptor 4 and effect on NF-kappaB mediated inflammation in colon cancer patients. PLoS One 2016; 11: e0146333.

[17] Winchester DA, Till C, Goodman PJ, Tangen CM, Santella RM, Johnson-Pais TL, Leach RJ, Xu J, Zheng SL, Thompson IM, Lucia MS, Lippmann SM, Parnes HL, Dluzniewski PJ, Isaacs WB, De Marzo AM, Drake CG and Platz EA. Variation in genes involved in the immune response and prostate cancer risk in the placebo arm of the prostate cancer prevention trial. Prostate 2015; 75: 1403-1418.

[18] Zheng SL, Augustsson-Balter K, Chang B, Hedelin M, Li L, Adami HO, Bensen J, Li G, Johnasson JE, Turner AR, Adams TS, Meyers DA, Isaacs WB, Xu J and Gronberg H. Sequence variants of toll-like receptor 4 are associated with prostate cancer risk: results from the cancer prostate in sweden study. Cancer Res 2004; 64: 2918-2922.

[19] Chen YC, Giovannucci E, Lazarus R, Kraft P, Ketkar S and Hunter DJ. Sequence variants of toll-like receptor 4 and susceptibility to prostate cancer. Cancer Res 2005; 65: 11771-11778.

[20] Cheng I, Plummer SJ, Casey G and Witte JS. Toll-like receptor 4 genetic variation and advanced prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2007; 16: 352-355.

[21] Wang MH, Helzlsouer KJ, Smith MW, Hoffman-Bolton JA, Clipp SL, Grinberg V, De Marzo AM, Isaacs WB, Drake CG, Shugart YY and Platz EA. Association of IL10 and other immune response- and obesity-related genes with prostate cancer in CLUE II. Prostate 2009; 69: 874-885.

[22] Balistreri CR, Caruso C, Carruba G, Miceli V, Campisi I, Listi F, Lio D, Colonna-Romano G and Candore G. A pilot study on prostate cancer risk and pro-inflammatory genotypes: pathophysiology and therapeutic implications. Curr Pharm Des 2010; 16: 718-724.

[23] Zidi S, Sghaier I, Gazouani E, Mezlini A and Yacoubi-Loueslati B. Evaluation of toll-like receptors 2/3/4/9 gene polymorphisms in cervical cancer evolution. Pathol Oncol Res 2016; 22: 323-330.

[24] Pandey S, Mittal RD, Srivastava M, Srivastava K, Singh S, Srivastava S and Mittal B. Impact of toll-like receptors [TLR] 2 (-196 to-174 del) and TLR 4 (Asp299Gly, Thr399Ile) in cervical cancer susceptibility in north indian women. Gynecol Oncol 2009; 114: 501-505.

[25] Kurt H, Ozbayer C, Bayramoglu A, Gunes HV, Degirmenci I, Oner KS and Metintas M. Determination of the relationship between rs4986790 and rs4986791 variants of TLR4 gene and lung cancer. Inflammation 2016; 39: 166-171.

[26] Theodoropoulos GE, Saridakis V, Karantanos T, Michalopoulos NV, Zagouri F, Kontogianni P, Lymperi M, Gazouli M and Zografos GC. Toll-like receptors gene polymorphisms may confer increased susceptibility to breast cancer development. Breast 2012; 21: 534-538.

[27] Etokebe GE, Knezevic J, Petricevic B, Pavelic J, Vrbanec D and Dembic Z. Single-nucleotide polymorphisms in genes encoding toll-like receptor -2, -3, -4, and -9 in case-control study with breast cancer. Genet Test Mol Biomarkers 2009; 13: 729-734.

[28] Hellmig S, Fischbach W, Goebeler-Kolve ME, Folsch UR, Hampe J and Schreiber S. Association study of a functional toll-like receptor 4 polymorphism with susceptibility to gastric mucosa-associated lymphoid tissue lymphoma. Leuk Lymphoma 2005; 46: 869-872.

[29] Nieters A, Beckmann L, Deeg E and Becker N. Gene polymorphisms in toll-like receptors, interleukin-10, and interleukin-10 receptor alpha and lymphoma risk. Genes Immun 2006; 7: 615-624.

[30] Purdue MP, Lan Q, Wang SS, Kricker A, Menashe I, Zheng TZ, Hartge P, Grulich AE, Zhang Y, Morton LM, Vajdic CM, Holford TR, Severson RK, Leaderer BP, Cerhan JR, Yeager M, Cozen W, Jacobs K, Davis S, Rothman N, Chanock SJ, Chatterjee N and Armstrong BK. A pooled investigation of toll-like receptor gene variants and risk of non-Hodgkin lymphoma. Carcinogenesis 2009; 30: 275-281.

[31] Gu X, Shen Y, Fu L, Zuo HY, Yasen H, He P, Guo XH, Shi YW and Yusufu M. Polymorphic variation of inflammation-related genes and risk of non-Hodgkin lymphoma for uygur and han chinese in Xinjiang. Asian Pac J Cancer Prev 2014; 15: 9177-9183.

[32] Forrest MS, Skibola CF, Lightfoot TJ, Bracci PM, Willett EV, Smith MT, Holly EA and Roman E. Polymorphisms in innate immunity genes and risk of non-Hodgkin lymphoma. Br J Haematol 2006; 134: 180-183.

[33] Ture-Ozdemir F, Gazouli M, Tzivras M, Panagos C, Bovaretos N, Petraki K, Giannakopoulos A, Korkolopoulou P and Mantzaris GJ. Association of polymorphisms of NOD2, TLR4 and CD14 genes with susceptibility to gastric mucosa-associated lymphoid tissue lymphoma. Anticancer Res 2008; 28: 3697-3700.

[34] Gast A, Bermejo JL, Claus R, Brandt A, Weires M, Weber A, Plass C, Sucker A, Hemminki K, Schadendorf D and Kumar R. Association of inherited variation in toll-like receptor genes with malignant melanoma susceptibility and survival. PLoS One 2011; 6: e24370.

[35] Yang ZH, Dai Q, Gu YJ, Guo QX and Gong L. Cytokine and chemokine modification by toll-like receptor polymorphisms is associated with nasopharyngeal carcinoma. Cancer Sci 2012; 103: 653-658.

[36] Ashton KA, Proietto A, Otton G, Symonds I, McEvoy M, Attia J and Scott RJ. Toll-like recep-

tor (TLR) and nucleosome-binding oligomerization domain (NOD) gene polymorphisms and endometrial cancer risk. BMC Cancer 2010; 10: 382.

[37] Miedema KG, Tissing WJ, Te Poele EM, Kamps WA, Alizadeh BZ, Kerkhof M, de Jongste JC, Smit HA, de Pagter AP, Bierings M, Boezen HM, Postma DS, de Bont ES and Koppelman GH. Polymorphisms in the TLR6 gene associated with the inverse association between childhood acute lymphoblastic leukemia and atopic disease. Leukemia 2012; 26: 1203-1210.

[38] Shen Y, Liu Y, Liu S and Zhang A. Toll-like receptor 4 gene polymorphisms and susceptibility to bladder cancer. Pathol Oncol Res 2013; 19: 275-280.

[39] Semlali A, Jalouli M, Parine NR, Al Amri A, Arafah M, Al Naeem A, Abdullah Ajaj S, Rouabhia M and Alanazi MS. Toll-like receptor 4 as a predictor of clinical outcomes of estrogen receptor-negative breast cancer in Saudi women. Onco Targets Ther 2017; 10: 1207-1216.

[40] Yang H, Pan T, Duan G and Wang Y. A cumulative meta-analysis on the association of toll-like receptor 4 gene Asp299Gly polymorphism with cancer risk. Eur J Cancer 2016; 58: 130-137.

[41] Sipponen P and Marshall BJ. Gastritis and gastric cancer. Western countries. Gastroenterol Clin North Am 2000; 29: 579-592, v-vi.

[42] Loganathan R, Nazeer M, Goda V, Devaraju P, Ali M, Karunakaran P and Jayaraman M. Genetic variants of TLR4 and TLR9 are risk factors for chronic helicobacter pylori infection in south indian tamils. Hum Immunol 2017; 78: 216-220.

[43] Mangerich A, Knutson CG, Parry NM, Muthupalani S, Ye W, Prestwich E, Cui L, McFaline JL, Mobley M, Ge Z, Taghizadeh K, Wishnok JS, Wogan GN, Fox JG, Tannenbaum SR and Dedon PC. Infection-induced colitis in mice causes dynamic and tissue-specific changes in stress response and DNA damage leading to colon cancer. Proc Natl Acad Sci U S A 2012; 109: E1820-1829.

[44] Wogan GN, Dedon PC, Tannenbaum SR and Fox JG. Infection, inflammation and colon carcinogenesis. Oncotarget 2012; 3: 737-738.

[45] Li J, Yang F, Wei F and Ren X. The role of toll-like receptor 4 in tumor microenvironment. Oncotarget 2017; 8: 66656-66667.

[46] Jewel Samadder N, Valentine JF, Guthery S, Singh H, Bernstein CN, Wan Y, Wong J, Boucher K, Pappas L, Rowe K, Bronner M, Ulrich CM, Burt RW, Curtin K and Smith KR. Colorectal cancer in inflammatory bowel diseases: a population-based study in utah. Dig Dis Sci 2017; 62: 2126-2132.

[47] Yang G, Qiu J, Wang X, Shen Z, Shao S and Li F. The single nucleotide polymorphisms of toll-like receptor 4 gene and colorectal cancer suscepti-bility. Chin J Gastrointest Surg 2011; 14: 814-815.

[48] Dai Q, Zhong L, Zhang X and Yang ZH. Expression of IL-alpha and TNF-alpha modified by toll-like receptor 4 genetic polymorphism is associated with colorectal carcinoma. Chin J Pathophysiol 2012; 28: 1976-8.

[49] Herszényi L, Barabás L, Miheller P and Tulassay Z. Colorectal cancer in patients with inflammatory bowel disease: the true impact of the risk. Dig Dis 2015; 33: 52-57.