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Original Article

The receptor for advanced glycation end products gene polymorphisms contribute to cancer susceptibility: evidence from meta-analysis

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Abstract: Background: The receptor for advanced glycation end products (*RAGE*) gene polymorphisms, especially the *RAGE* Gly82Ser, -374T/A and -429T/C polymorphisms have been suggested as risk factors for cancer with inconclusive results. The aim of the current study is to investigate the associations between these polymorphisms and cancer risk by meta-analysis. Methods: A search was performed in PubMed, Embase, China National Knowledge Internet (CNKI), Wangfang, and Weipu database up to September 15, 2015. The pooled odds ratio (OR) with 95% confidence interval (CI) was calculated to evaluate the associations between the polymorphisms and cancer risk. We also calculated the false positive report probabilities (FPRPs) for the statistically significant association (*P* value < 0.05) to evaluate whether an association is noteworthy. Results: A total of 19 case-control studies including 5,377 cases and 5,690 controls were identified. Overall, the *RAGE* Gly82Ser polymorphism was found to contribute to the increased cancer risk (AA vs. GA+GG: OR = 1.360, 95% CI = 1.191-1.554, I^2 = 27.4% and P_H = 0.175 for heterogeneity; AA vs. GG: OR = 1.735, 95% CI = 1.483-2.029, I^2 = 10.1% and P_H = 0.346 for heterogeneity; A vs. G: OR = 1.231, 95% CI = 1.110-1.367, I^2 = 43.8% and P_H = 0.031 for heterogeneity). In Asian populations, the *RAGE* Gly82Ser (AA vs. GG: OR = 1.742, 95% CI = 1.488-2.038, I^2 = 23.4% and P_H = 0.228 for heterogeneity) and the *RAGE* -374T/A (AA vs. TT: OR = 1.449, 95% CI = 1.220-1.721, I^2 = 6.2% and P_H = 0.382 for heterogeneity) polymorphisms were associated with increased cancer risk. Subgroup analysis indicated that the *RAGE* Gly82Ser polymorphism was associated with lung cancer susceptibility (AA vs. GG: OR = 1.663, 95% CI = 1.316-2.102, I^2 = 0 and P_H = 0.418 for heterogeneity). Conclusions: The study suggested that the *RAGE* Gly82Ser and the *RAGE* -374T/A polymorphisms was associated with increased cancer risk, especially in Asians. Besides, the *RAGE* Gly82Ser polymorphism was associated with lung cancer susceptibility.

Keywords: Cancer, *RAGE*, meta-analysis, FPRP

Introduction

Cancer is a growing problem globe wide. A considerable increase in the absolute numbers of cancer cases and deaths is foreseen in the next decades [1]. The projected increase in global cancer burden from 12.7 million new cases in 2008 to 22.2 million by 2030 alarms us that urgent action is needed [2]. Cancer is a heterogeneous group of diseases with a variety of causes. Recently, an increasing number of studies were focused on the association between gene variants and malignant tumor. One type of the common genetic variations is the single nucleotide polymorphisms (SNPs), which is associated with population diversity, disease susceptibility, drug metabolism, and genome evolution [3].

As a cell surface molecule, the receptor for advanced glycation end products *(RAGE)* is a multi-ligand member of the immunoglobulin superfamily [4]. It is involved in the pathogenesis of different kinds of diseases, including Alzheimer's disease (AD), diabetes mellitus (DM), cardiovascular disease, inflammation, and cancer [5-9]. RAGE and its ligands are commonly over-expressed in most types of solid tumors. The gene for *RAGE* is located on chromosome 6p21.3 at the major histocompatibility

Table 1. Characteristics of case-control studies of *RAGE* polymorphisms

First author	Year	Country	Ethnicity	Types	Case age	Sample size		Methods
						case	control	
Chocholatý M	2014	Czech	Caucasian	Clear cell renal cancer	63±11	214	154	PCR-RFLP[a]
Duan Z	2014	Finland	Caucasian	Pancreatic cancer	57.6±4.6	141	141	Illumina Infinium Assay
Feng LJ	2015	China	Asian	Breast cancer	-	188	210	PCR-RFLP
Gu H	2008	China	Asian	Gastric cancer	59 (51-66)	283	283	PCR-RFLP
Hashemi M	2012	Iran	Caucasian	Breast cancer	-	71	93	ARMS-PCR[b]
Hoff E (C)	2009	Netherlands	Caucasian	Colorectal cancer	-	235	165	PCR-RFLP
Hoff E (G)	2009	Netherlands	Caucasian	Gastric cancer	-	75	165	PCR-RFLP
Krechler T	2010	Czech	Caucasian	Pancreas cancer	64±11	51	154	PCR-RFLP
Pan H	2013	China	Asian	Lung cancer	57.4±10.5	819	803	PCR-LDR[c]
Pan H	2014	China	Asian	Breast cancer	55.6±10.1	509	504	PCR-LDR
Qian F	2014	China	Asian	Colorectal cancer	58.5 (27-84)	90	78	PCR-RFLP
Su S	2015	China	Asian	Oral cancer	54.29±11.28	618	592	TaqMan
Su SC	2015	China	Asian	Hepatocellular carcinoma	62.99±11.97	265	300	TaqMan
Tesarova P	2007	Czech	Caucasian	Breast cancer	61.2±11.9	120	92	PCR-RFLP
Tóth É K	2007	Hungary	Caucasian	Colorectal cancer	65.7±10.5	183	141	PCR-RFLP
Wang H	2015	China	Asian	Lung cancer	59.8±10.4	275	126	PCR-RFLP
Wang X	2012	China	Asian	Non-samll cell lung cancer	-	562	764	PCR-RFLP
Xu Q	2012	China	Asian	Cervical squamous cell carcinoma	54.6±5.7	488	715	TaqMan
Zhang S	2013	China	Asian	Epithelial ovarian cancer	53.6±3.8	190	210	PCR-RFLP

a: Polymerase chain reaction-Restriction fragment length polymorphism; b: Amplification refractory mutation system Polymerase chain reaction; c: Polymerase chain reaction-Ligase detection reaction.

complex (MHC) locus in the class II/III junction and is composed of a 1.7-kb 5' flanking region and 11 exons [10]. Presently, several SNPs of the *RAGE* gene have been identified. Among them, the *RAGE* Gly82Ser (557G/A, rs2070600), -374T/A (rs1800624) and -429T/C (rs1800625) have been most investigated [11].

Growing studies indicated that these polymorphisms were implicated in various cancers. A recent study suggested that the *RAGE* Gly82Ser and -429T/C polymorphisms were associated with the increased breast cancer risk [12]. Gu et al. found that the *RAGE* Gly82Ser polymorphism contributed to an increased risk of gastric cancer in the Chinese population [13]. However, some other studies reported contrary outcomes [14, 15]. For lung cancers, Wang X [16] found that there were significant differences for all the three *RAGE* polymorphisms between cases and controls, while Pan H [17] and Wang H [18] observed significant difference merely in the -429T/C polymorphism. Besides, two meta-analyses were performed to investigate the associations between these polymorphisms and cancer risk. According to Zhao D's meta-analysis [19], the *RAGE* Gly82Ser may increase the susceptibility to cancer, while the *RAGE* -374T/A contributes to decreased susceptibility to breast cancer but to increased susceptibility to lung cancer. According to Xia W's meta-analysis [20], the *RAGE* Gly82Ser was associated with increased risk of cancer, while -374T/A polymorphism was associated with reduced risk of cancer as breast cancer and lung cancer.

Due to these inconclusive reports, we thus performed the current meta-analysis to investigate the relationship between the *RAGE* Gly82Ser, -374T/A and -429T/C polymorphisms and cancer susceptibility. To our knowledge, this is the most comprehensive meta-analysis to investigate the associations of the *RAGE* polymorphisms and malignant tumor risk.

Materials and methods

Study selection

A literature search in PubMed, Embase, China National Knowledge Internet (CNKI), Wanfang and Weipu databases was carried out to identify studies investigating the association between the *RAGE* polymorphisms and malignancies susceptibility up to September 15, 2015. The search terms were used as follows: 'cancer' or 'carcinoma' in combination with 'gene polymorphism' or 'variant' or 'mutation' in combination with '*RAGE*' or 'the receptor for advanced glycation end products'. There is no language restriction. The following inclusive crite-

Table 2. The genotype distributions of *RAGE* polymorphisms among cases and controls

First author	Year	Gly82Ser							-374T/A							-429T/C						
		Cases			Controls			HWE[d]	Cases			Controls			HWE	Cases			Controls			HWE
		GG	GA	AA	GG	GA	AA		TT	TA	AA	TT	TA	AA		TT	TC	CC	TT	TC	CC	
Chocholatý M	2014	200	13	1	144	9	1	0.06	94	97	23	69	60	25	0.06	142	57	15	109	39	6	0.3
Duan Z	2014	126	15	0	130	11	0	0.629														
Feng LJ	2015								51	66	71	92	59	59	<0.001							
Gu H	2008	142	126	15	170	105	8	0.081														
Hashemi M	2012								49	17	3	51	33	5	0.911	59	11	1	85	8	0	0.665
Hoff E (C)	2009	221	14	0	158	7	0	0.781														
Hoff E (G)	2009	72	3	0	158	7	0	0.781														
Krechler T	2010	47	4	0	144	9	1	0.06	24	21	6	69	60	25	0.06	37	13	1	109	39	6	0.3
Pan H	2013	321	382	116	352	377	74	0.058	471	289	59	472	287	44	0.966	447	303	69	485	289	29	0.077
Pan H	2014	313	164	32	310	168	26	0.603	382	119	8	354	143	7	0.077	379	124	6	365	130	9	0.507
Qian F	2014	48	33	9	60	15	3	0.123														
Su S	2015	373	223	22	361	209	22	0.218	461	136	21	435	136	21	0.014	509	102	7	532	57	3	0.28
Su SC	2015	160	88	17	179	112	9	0.084	210	49	6	220	72	8	0.476	216	44	5	277	22	1	0.434
Tesarova P	2007	115	5	0	86	6	0	0.746	63	44	13	41	39	12	0.574	85	32	3	63	26	3	0.875
Tóth É K	2007															4	44	135	5	35	101	0.376
Wang H	2015	193	73	9	85	36	5	0.632	178	82	15	92	31	3	0.84	195	76	4	100	26	0	0.197
Wang X	2012	84	360	118	197	406	161	0.072	93	330	139	188	399	177	0.216	201	274	87	229	387	148	0.496
Xu Q	2012	88	247	153	199	341	175	0.228	105	233	150	165	377	173	0.144	129	188	171	182	344	189	0.314
Zhang S	2013	36	82	72	65	96	49	0.244														

d: Hardy-Weinberg equilibrium.

Table 3. Summary of different comparative results

Polymorphisms	N[e]	OR[f] (95% CI[g])	POR[h]	I-square[i]	P_H[j]	OR (95% CI)	POR	I-square	P_H	OR (95% CI)	POR	I-square	P_H	OR (95% CI)	POR	I-square	P_H	OR (95% CI)	POR	I-square	P_H
Gly82Ser			GA+AA vs. GG			AA vs. GA+GG				AA vs. GG				GA vs. GG				A vs. G			
Total	16	1.313 (1.109-1.555)	0.002	0.605	0.001	1.360 (1.191-1.554)	< 0.001	0.274	0.175	1.735 (1.483-2.029)	< 0.001	0.101	0.346	1.259 (1.062-1.492)	0.008	0.577	0.002	1.231 (1.110-1.367)	< 0.001	0.438	0.031
Lung cancer	3	1.315 (0.872-1.982)	0.192	0.827	0.003	1.203 (0.794-1.823)	0.384	0.668	0.049	1.663 (1.316-2.102)	< 0.001	0	0.418	1.296 (0.803-2.092)	0.288	0.862	0.001	1.210 (1.093-1.340)	< 0.001	0.226	0.275
Breast caner	2	0.981 (0.766-1.257)	0.881	0	0.456	-	-	-	-	-	-	-	-	0.948 (0.731-1.229)	0.685	0	0.49	1.019 (0.829-1.253)	0.86	0	0.428
Gastric cancer	2	1.456 (1.054-2.010)	0.023	0	0.523	-	-	-	-	-	-	-	-	1.401 (1.007-1.951)	0.046	0	0.559	1.378 (1.055-1.800)	0.019	0	0.577
Colorectal cancer	2	2.278 (1.323-3.925)	0.003	0.327	0.223	-	-	-	-	-	-	-	-	2.148 (1.216-3.795)	0.008	0.159	0.275	2.169 (1.343-3.503)	0.002	0.116	0.288
Pancreatic cancer	2	1.349 (0.688-2.645)	0.383	0	0.852	-	-	-	-	-	-	-	-	1.394 (0.707-2.746)	0.338	0	0.965	1.289 (0.671-2.478)	0.446	0	0.752
Asian	10	1.352 (1.110-1.648)	0.003	0.75	< 0.001	1.398 (1.146-1.704)	0.001	0.397	0.093	1.742 (1.488-2.038)	< 0.001	0.234	0.228	1.238 (1.051-1.568)	0.015	0.733	< 0.001	1.244 (1.104-1.402)	< 0.001	0.638	0.003
Caucasian	6	1.131 (0.753-1.699)	0.552	0	0.902	0.826 (0.099-6.908)	0.86	0	0.881	0.834 (0.100-6.986)	0.867	0	0.875	1.154 (0.765-1.742)	0.495	0	0.899	1.105 (0.744-1.640)	0.621	0	0.906
-374T/A			TA+AA vs. TT			AA vs. TA+TT				AA vs. TT				TA vs. TT				A vs. T			
Total	12	1.944 (0.866-1.258)	0.652	0.699	< 0.001	1.182 (1.031-1.355)	0.016	0.124	0.323	1.310 (1.117-1.536)	0.001	0.36	0.102	1.029 (0.855-1.239)	0.761	0.657	0.001	1.031 (0.903-1.178)	0.652	0.668	0.001
Lung cancer	3	1.338 (0.969-1.847)	0.077	0.721	0.028	1.186 (0.960-1.465)	0.113	0	0.381	1.527 (1.186-1.966)	0.001	0	0.58	1.301 (0.911-1.858)	0.148	0.751	0.018	1.172 (1.053-1.305)	0.004	0.158	0.305
Breast caner	4	0.923 (0.525-1.622)	0.78	0.841	< 0.001	1.291 (0.917-1.816)	0.144	0	0.478	1.156 (0.590-2.265)	0.672	0.561	0.077	0.905 (0.533-1.537)	0.711	0.787	0.003	0.941 (0.602-1.472)	0.791	0.848	< 0.001
Asian	8	1.133 (0.908-1.413)	0.268	0.77	< 0.001	1.263 (1.093-1.460)	0.002	0	0.642	1.449 (1.220-1.721)	< 0.001	0.062	0.382	1.086 (0.872-1.353)	0.463	0.741	< 0.001	1.108 (0.956-1.285)	0.173	0.713	0.001
Caucasian	4	0.837 (0.641-1.094)	0.194	0	0.41	0.689 (0.453-1.048)	0.082	0	0.965	0.681(0.438-1.058)	0.087	0	0.999	0.897 (0.674-1.193)	0.454	0.271	0.249	0.825 (0.673-1.012)	0.065	0	0.728
-429T/C			TC+CC vs. TT			CC vs. TC+TT				CC vs. TT				TC vs. TT				C vs. T			
Total	12	1.229 (0.986-1.531)	0.066	0.731	< 0.001	1.344 (0.941-1.921)	0.104	0.624	0.002	1.382 (0.892-2.140)	0.147	0.654	0.001	1.169 (0.944-1.449)	0.153	0.69	< 0.001	1.243 (1.028-1.502)	0.025	0.784	< 0.001

Lung cancer	3	1.117 (0.741-1.683)	0.598	0.846	0.002	1.519 (0.522-4.419)	0.443	0.897	< 0.001	1.527 (0.451-5.176)	0.497	0.915	< 0.001	1.059 (0.777-1.444)	0.716	0.707	0.033	1.161 (0.776-1.737)	0.468	0.905	< 0.001
Breast caner	3	0.954 (0.748-1.217)	0.705	0.34	0.22	0.795 (0.348-1.815)	0.586	0	0.578	0.785 (0.343-1.796)	0.566	0	0.542	0.966 (0.753-1.240)	0.788	0.116	0.323	0.947 (0.761-1.178)	0.623	0.457	0.158
Asian	7	1.256 (0.947-1.667)	0.114	0.841	< 0.001	1.446 (0.880-2.377)	0.146	0.776	< 0.001	1.416 (0.808-2.482)	0.225	0.793	< 0.001	1.187 (0.899-1.567)	0.226	0.82	< 0.001	1.299 (1.014-1.664)	0.039	0.872	< 0.001
Caucasian	5	1.156 (0.862-1.549)	0.333	0	0.536	1.185 (0.791-1.776)	0.411	0	0.669	1.431 (0.760-2.696)	0.267	0	0.659	1.120 (0.824-1.523)	0.469	0	0.715	1.145 (0.916-1.431)	0.236	0.022	0.394

e: Numbers of case-control studies; f: Odds ratio; g: Confidence interval; h: Value for OR; i: I-square of heterogeneity test; j: *P* value of heterogeneity test.

ria were adopted: (1) a case-control study; (2) articles evaluating the relationship between the *RAGE* polymorphisms and malignant tumor risk; (3) genotype distributions in both cases and controls were available for calculating the odds ratio (OR) and 95% confidence interval (CI). The following exclusive criteria were also used: (1) the studied population was based on family or sibling pairs; (2) reviews, case reports, meta-analyses, or systematic reviews; (3) genotype frequencies or numbers were not reported. In case the overlapped publications exist, the study with largest sample size or the latest publication date was included.

Date extraction

Information was independently collected by two reviewers (Sitong Liu and Xiang Tong) according to the inclusive criteria. In case of disagreement, a third author (Maoying He) would assess these articles. The following items were extracted from each study: first author, year of publication, country, ethnicity, type of cancer, genotype distributions, and genotyping methods.

Statistical method

Statistical analysis was performed using Stata 12.0 software. Hardy-Weinberg equilibrium (HWE) in the control groups was tested by Pearson's χ^2 test. The OR and 95% CI were used to assess the strength of the association between the *RAGE* polymorphisms and malignant tumor susceptibility. Heterogeneity was evaluated by the χ^2 based Q-test and I-squared (I^2) statistics test. It was considered statistically significant at *P* value < 0.10. When P > 0.10, the OR was calculated by the fixed-effects model; otherwise, the random-effect model was adopted. The genetic models were mainly evaluated by the pooled ORs of the polymorphisms in dominant models (Gly82Ser: GA+AA vs. GG; *RAGE* -374T/A: TA+AA vs. TT; *RAGE* -429T/C: TC+CC vs. TT). Additionally, we also estimated other genetic models (Gly82Ser: AA vs. GA+GG, AA vs. GG, GA vs. GG and A vs. G; *RAGE* -374T/A: AA vs. TA+TT, AA vs. TT, TA vs. TT and A vs. T; *RAGE* -429T/C: CC vs. TC+TT, CC vs. TT, TC vs. TT and C vs. T). Furthermore, to investigate the ethnic-specific and cancer type-specific effects, the subgroup analysis was performed after stratification of the data by ethnicity and cancer type.

In addition, to evaluate whether an association was "noteworthy", we also calculated the false positive report probabilities (FPRPs) for the statistically significant association (*P* value < 0.05) by prior probabilities of 0.001. In the test, as suggested by the previous study [21], we set a FPRP cut-off value of 0.2, and only the results with FPRP < 0.2 were considered as significant association.

To assess the quality and consistency of the results, sensitivity was carried out by excluding studies one by one. Publication bias was assessed by visual inspection of asymmetry in Begg's funnel plots and Egger's test and it was regarded as statistically significant when *P* value < 0.05.

Results

The characteristics of each case-control study are summarized in **Table 1**. The genotype distributions are summarized in **Table 2**. Summary of different comparative results for this meta-analysis was listed in **Table 3**. The FPRP values for significant findings were shown in **Table 4**.

Study characteristics

Totally, 351 articles were in accord with the searching strategies (**Figure 1**). Finally, 19 case-control studies from 18 articles were identified in the present meta-analysis study [12-18, 22-32]. A total of 4935 cases and 5246 controls from 16 case-control studies were included for the Gly82Ser polymorphism, 4180 cases and 4507 controls from 12 case-control studies were included for the -374T/A polymorphism, and 4175 cases and 4438 controls from 12 case-control studies were included for the -429T/C polymorphism. These studies were conducted among Asians (11 studies) or Caucasians (8 studies), including 10 cancer types: breast cancer (4 studies), lung cancer (3 studies), colorectal cancer (3 studies), gastric cancer (2 studies), pancreatic cancer (2 studies), clear cell renal cancer (1 study), oral cancer (1 study), hepatocellular carcinoma (1 study), cervical squamous cell carcinoma (1 study), epithelial ovarian cancer (1 study). Hardy-Weinberg equilibrium (HWE) was calculated

Table 4. The results of FPRP test of all significant associations observed in the meta-analysis

Polymorphisms	Gene models	OR	95% CI	*P* value	Power OR = 1.50	FPRP P = 0.001
Gly82Ser	GA+AA vs. GG					
	Total	1.313	1.109-1.555	0.002	0.939	0.631
	Gastric cancer	1.456	1.054-2.010	0.023	0.572	0.975
	Colorectal cancer	2.278	1.323-3.925	0.003	0.066	0.979
	Asian	1.352	1.110-1.648	0.003	0.848	0.769
	AA vs. GA+GG					
	Total	1.36	1.191-1.554	< 0.001	0.925	0.007
	Asian	1.398	1.146-1.704	0.001	0.757	0.545
	AA vs. GG					
	Total	1.735	1.483-2.029	< 0.001	0.018	< 0.001
	Lung cancer	1.663	1.316-2.102	< 0.001	0.194	0.097
	Asian	1.742	1.488-2.038	< 0.001	0.031	< 0.001
	GA vs. GG					
	Total	1.259	1.062-1.492	0.008	0.978	0.889
	Gastric cancer	1.401	1.007-1.951	0.046	0.657	0.986
	Colorectal cancer	2.148	1.216-3.795	0.008	0.108	0.987
	Asian	1.238	1.051-1.568	0.015	0.944	0.988
	A vs. G					
	Total	1.231	1.110-1.367	< 0.001	1	0.092
	Lung cancer	1.21	1.093-1.340	< 0.001	1	0.201
	Gastric cancer	1.378	1.055-1.800	0.019	0.733	0.962
	Colorectal cancer	2.169	1.343-3.503	0.002	0.066	0.959
	Asian	1.244	1.104-1.402	< 0.001	0.999	0.256
-374T/A	AA vs. TA+TT					
	Total	1.182	1.031-1.355	0.016	1	0.943
	Asian	1.263	1.093-1.460	0.002	0.99	0.616
	AA vs. TT					
	Total	1.31	1.117-1.536	0.001	0.952	0.481
	Lung cancer	1.527	1.186-1.966	0.001	0.445	0.697
	Asian	1.449	1.220-1.721	< 0.001	0.653	0.035
	A vs. T					
	Lung cancer	1.172	1.053-1.305	0.004	1	0.792
-429T/C	C vs. T					
	Total	1.243	1.028-1.502	0.025	0.974	0.961
	Asian	1.299	1.014-1.664	0.039	0.873	0.847

with the genotypes of control population, and two studies on the *RAGE* -374T/A polymorphism did not fall into HWE.

The RAGE Gly82Ser polymorphism

A statistically significant association was identified on analyses of the dominant model and other gene models (**Figure 2**). (GA+AA vs. GG: OR = 1.313, 95% CI = 1.109-1.555, I^2 = 60.5%; AA vs. GA+GG: OR = 1.360, 95% CI = 1.191-1.554, I^2 = 27.4%; AA vs. GG: OR = 1.735, 95% CI = 1.483-2.029, I^2 = 10.1%; GA vs. GG: OR = 1.259, 95% CI = 1.062-1.492, I^2 = 57.7%; A vs. G: OR = 1.231, 95% CI = 1.110-1.367, I^2 = 43.8%).

Due to the existence of significant heterogeneities with overall analyses, subgroup analyses were performed by cancer type and ethnicity. In the subgroup analysis by cancer type, we observed that the *RAGE* Gly82Ser polymorphism have a significant association with lung cancer risk (AA vs. GG: OR = 1.663, 95% CI =

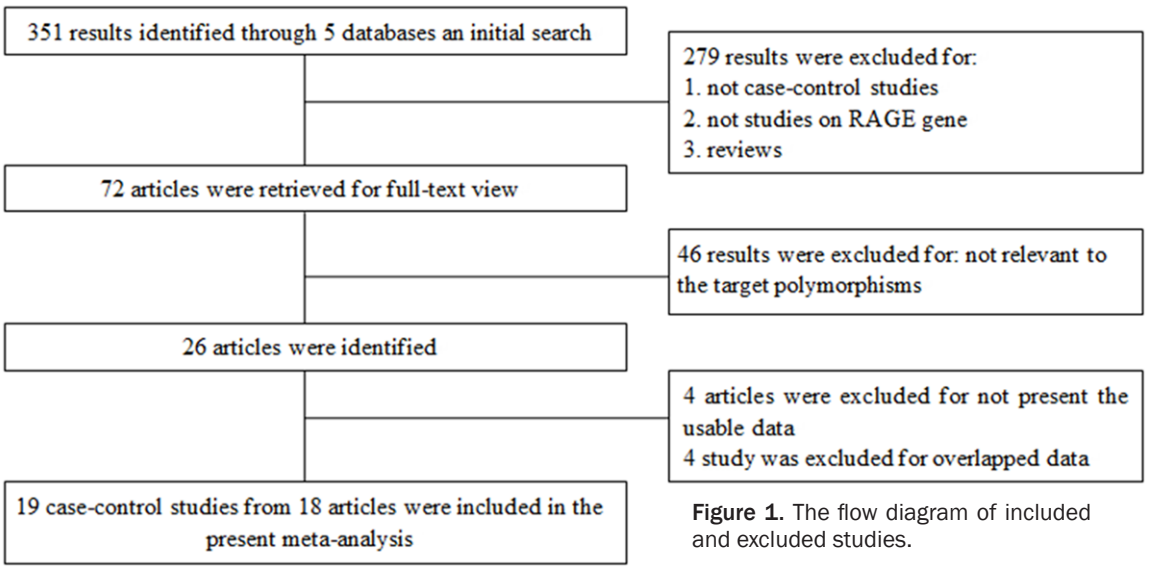

Figure 1. The flow diagram of included and excluded studies.

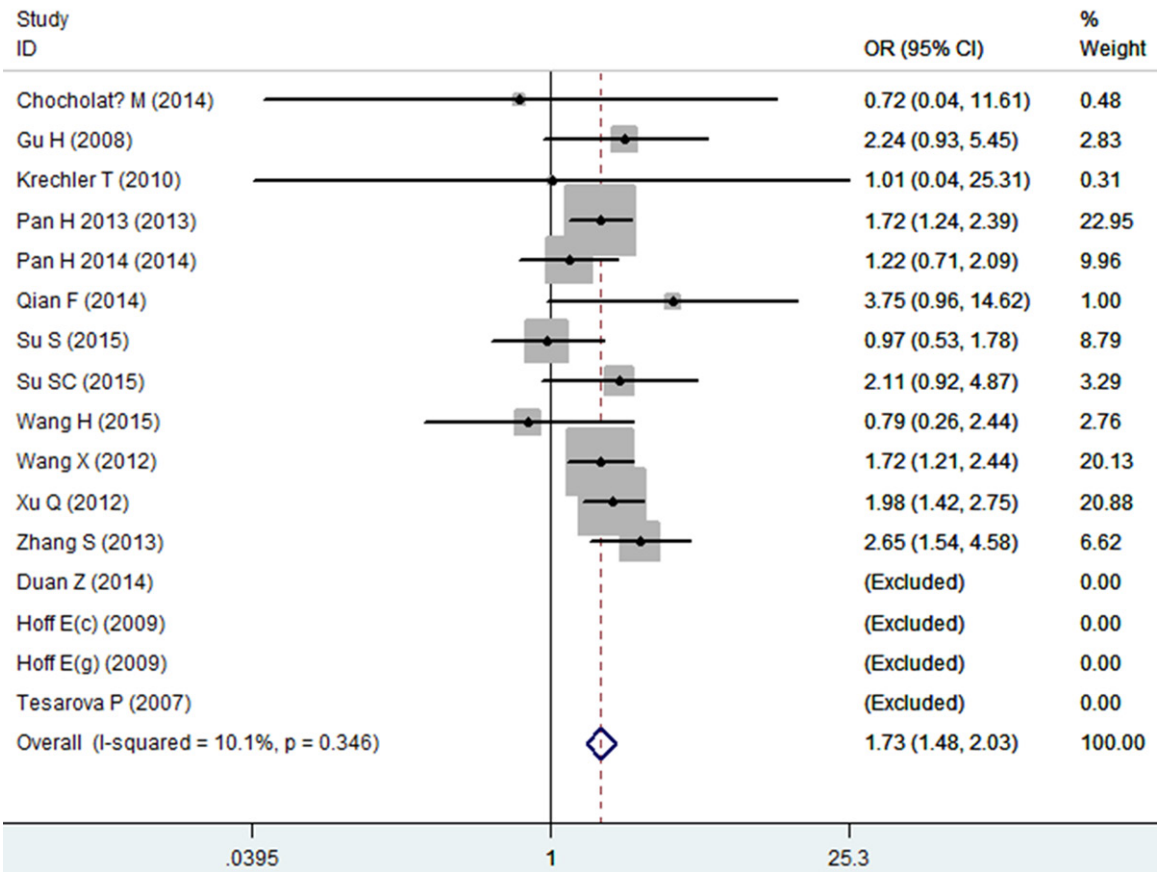

Figure 2. Meta-analysis of the *RAGE* Gly82Ser polymorphism and cancer risk (AA vs. GG).

1.316-2.102, I^2 = 0%; A vs. G: OR = 1.210, 95% CI = 1.093-1.340, I^2 = 22.6%), gastric cancer risk (GA+AA vs. GG: OR = 1.456, 95% CI = 1.054-2.010, I^2 = 0%; GA vs. GG: OR = 1.401, 95% CI = 1.007-1.951, I^2 = 0%; A vs. G: OR = 1.378, 95% CI = 1.055-1.800, I^2 = 0%), and colorectal cancer risk (GA+AA vs. GG: OR = 2.278, 95% CI = 1.323-3.925, I^2 = 32.7%; GA vs. GG: OR = 2.148, 95% CI = 1.216-3.795, I^2 = 15.9%; A vs. G: OR = 2.169, 95% CI = 1.343-

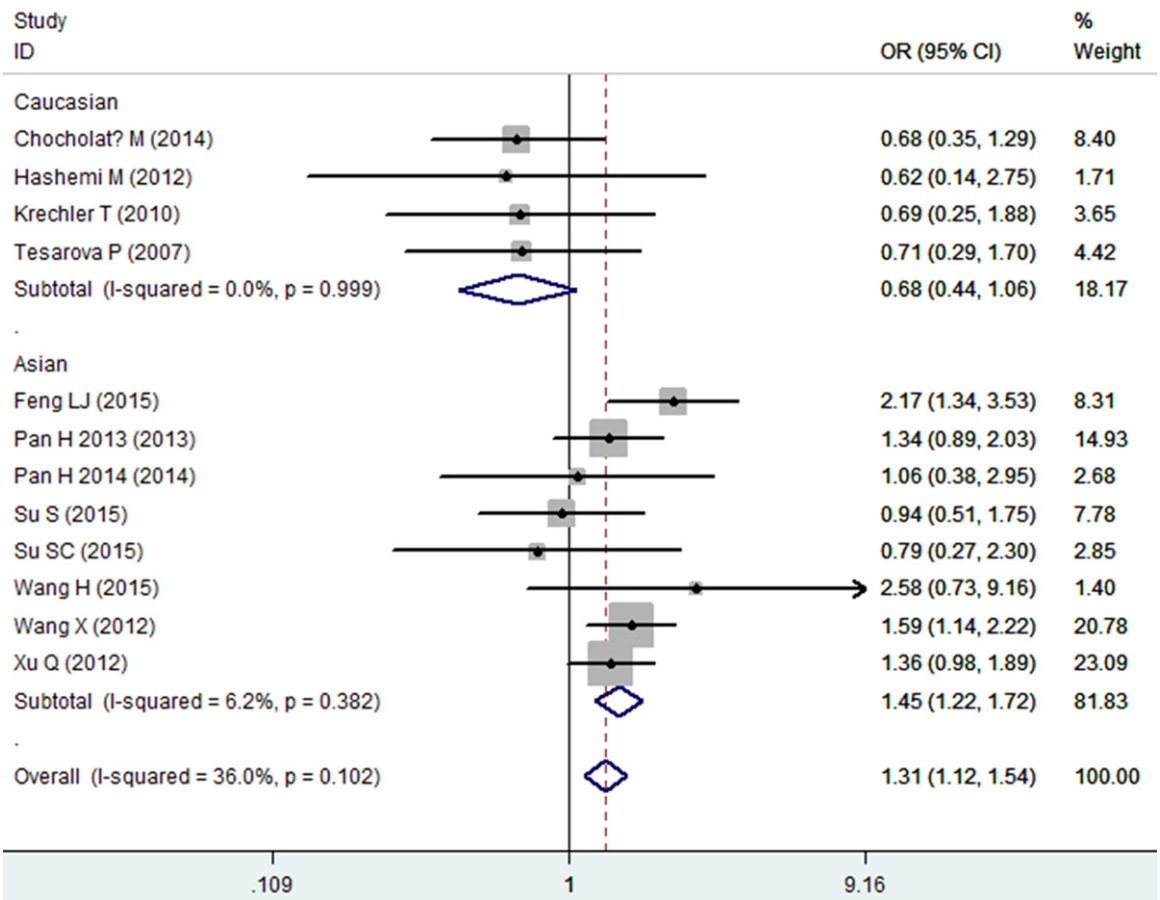

Figure 3. Meta-analysis of the *RAGE* -374T/A polymorphism and cancer risk (AA vs. TT) in Asians and Caucasians.

3.503, I^2 = 11.6%). In the analysis stratified by ethnicity, significant associations were observed in Asians in dominant model (GA+AA vs. GG: OR = 1.352, 95% CI = 1.110-1.648, I^2 = 75%) and other models but not in Caucasians.

As listed in the **Table 4**, for the total results, the FPRP test's results indicated that only three gene models (AA vs. GA+GG, AA vs. GG, A vs. G) of *RAGE* Gly82Ser polymorphism were truly associated with cancer risk (FPRP < 0.2) at the level of a prior probability of 0.001 and an OR of 1.5. In the subgroup analysis, the homozygote co-dominant model (AA vs. GG) was considered noteworthy in Asians and associated with lung cancer risk.

The RAGE -374T/A polymorphism

Overall, statistically significant associations were found between the *RAGE* -374T/A polymorphism and cancer risk in the recessive model (AA vs. TA+TT: OR = 1.182, 95% CI = 1.031-1.355, I^2 = 12.4%) and the homozygote co-dominant model (AA vs. TT: OR = 1.310, 95% CI = 1.117-1.536, I^2 = 36%).

In the subgroup analysis by cancer types, significant associations were found in lung cancer (AA vs. TT: OR = 1.527, 95% CI = 1.186-1.966, I^2 = 0%; A vs. T: OR = 1.172, 95% CI = 1.053-1.305, I^2 = 15.8%). In the subgroup analysis by ethnicity, statistically significant association was found in Asians (AA vs. TT: OR = 1.449, 95% CI = 1.220-1.721, I^2 = 6.2%) but not among Caucasians (**Figure 3**).

As listed in **Table 4**, only the homozygote co-dominant model (AA vs. TT) in Asians was considered truly associated with cancer risk at the level of a prior probability of 0.001.

The RAGE -429T/C polymorphism

In all, statistically significant associations were found between the *RAGE* -429T/C polymorphism and cancer risk in the allele model (C vs. T: OR = 1.243, 95% CI = 1.028-1.502, I^2 = 78.4%).

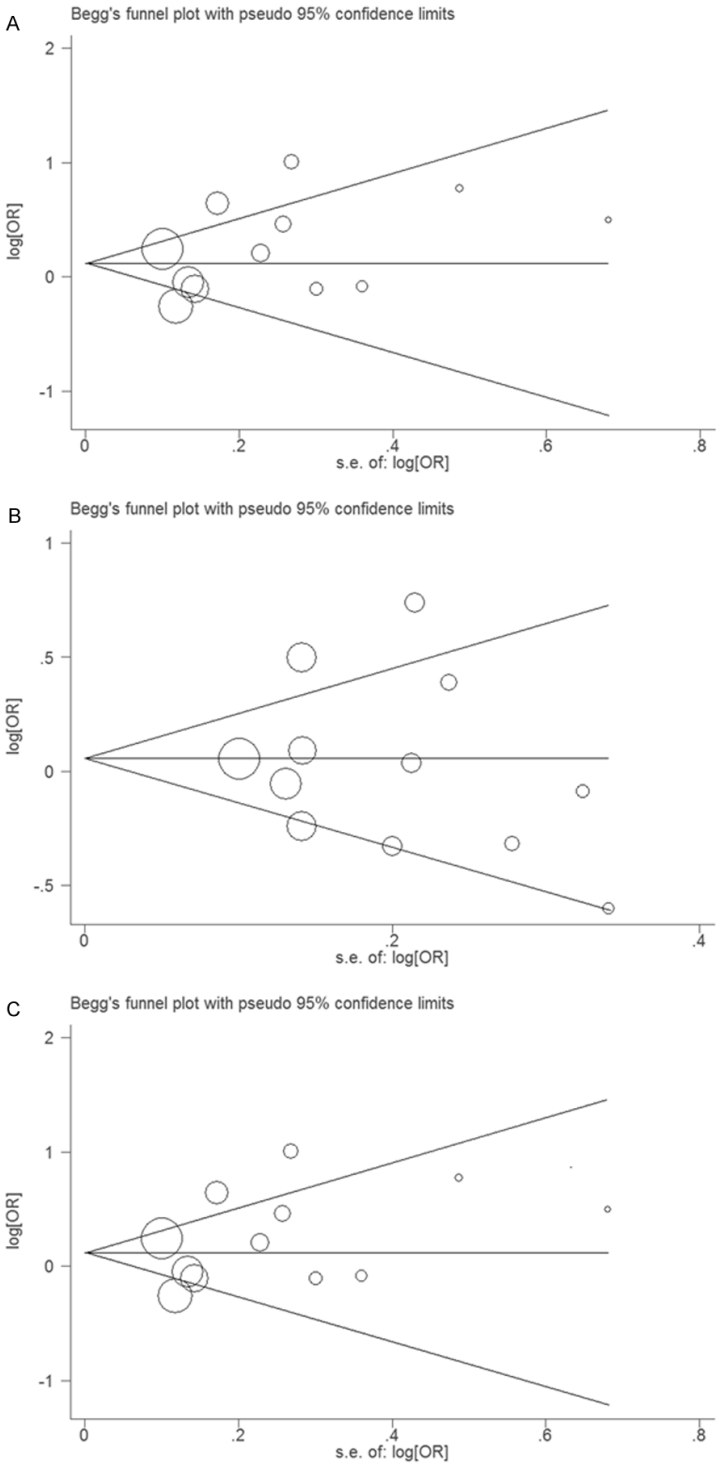

Figure 4. Publication bias in studies for the dominant models. a Gly82Ser, b -374T/A, c -429T/C.

In the subgroup analysis by cancer types, we did not find any association. In the subgroup analysis by ethnicity, a significant association was found among Asians in the allele model (C vs. T: OR = 1.299, 95% CI = 1.014-1.664, I^2 = 87.2%) but not in Caucasians.

As listed in **Table 4**, however, for a prior probability of 0.001, no one FPRP value was less than 0.2, which suggested the association between *RAGE* -429T/C polymorphism and tumor risk was not noteworthy.

Sensitivity analysis

The control groups in Feng LJ's [31] and Su S's [29] studies on the *RAGE* -374T/A polymorphism were out of HWE (**Table 2**). In order to avoid misleading results, these two studies were excluded for the *RAGE* -374T/A polymorphism to the pooled ORs. The results indicated that the significance of overall ORs did not change. Therefore, our conclusion was robust.

We further performed sensitivity analysis through omitting the studies one by one each time for all polymorphisms. The results showed the pooled ORs of these three polymorphisms were not materially altered by the contribution of any individual study, thus confirming the results of this meta-analysis were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to evaluate the publication bias. The shapes of the funnel plots did not show any evidence of obvious asymmetries (**Figure 4**). Similarly, the results of Egger's test demonstrated that there was no obvious evidence of publication bias (Gly82Ser: P = 0.796, -374T/A: P = 0.695; -429T/C: P = 0.242).

Discussion

The current meta-analysis was performed to investigate the relationship between the *RAGE* Gly82Ser, -374T/A and -429T/C polymorphisms and cancer susceptibility. Our study showed that the *RAGE* Gly82Ser polymorphism increased the risk of cancer in the co-dominant

model (AA vs. GG), the recessive model (AA vs. GA+GG) and the allele model (A vs. G). In Asian populations, both Gly82Ser and -374T/A polymorphisms were associated with increased cancer risk in the co-dominant models (AA vs. GG; AA vs. TT). Subgroup analysis indicated that the *RAGE* Gly82Ser polymorphism was associated with lung cancer susceptibility in the co-dominant models (AA vs. GG).

Our conclusion is biologically plausible. The polymorphisms of the *RAGE* gene may affect the expression or function of *RAGE*, which increases the incidence of a variety of diseases, including cancer [33-36]. Stimulation of *RAGE* probably potentiates the process of growth, infiltration and metastases of tumor via activating nuclear factor κB. The *RAGE*-ligand interaction is followed by generation of oxidative stress and triggering of inflammatory and proliferative process which critically contributes to tissue injury [7]. With previous results and present meta-analysis results, we can put forward a simplest hypothesis that *RAGE* Gly82Ser and -374T/A polymorphisms may have an important regulatory function of upregulation the production of *RAGE*, which leads to a high level serum concentration of *RAGE* and contributes to an increasing risk on cancer susceptibility.

Our study showed that *RAGE* -374T/A contributes to increased cancer susceptibility but not decreased risk of any cancer, which was different from other two former meta-analyses [19, 20]. There may be two reasons which may contribute to this difference. First, the two former meta-analyses were carried out in the last year. However, there were four new studies evaluating the relationship between the three *RAGE* polymorphisms and cancer risk published this year. So we got more comprehensive and up-to-date data. Second, the two former meta-analyses did not apply any criteria to evaluate the credibility of genetic association, such as Venice criteria, false positive report probability (FPRP) or Baysian false discovery probability (BFDP). In our study, we calculated the FPRPs for the statistically significant association to avoid false positive outcomes. Therefore, we think our conclusion is more credible.

Heterogeneity is the most common problem when explaining the results of a meta-analysis. A significant heterogeneity among studies was found in the current meta-analysis. So we performed subgroup analyses by ethnicity and cancer type. The decrease of heterogeneity in some subgroups could partly suggest that cancer type and ethnicity were the sources of heterogeneity. However, we still found significant heterogeneity in some genetic models of the -374T/A polymorphism in breast cancer, and some genetic models of the three polymorphisms in lung cancer and Asian population. For breast cancer, we found Feng LJ's [31] study was the source of heterogeneity due to significant higher A allele frequencies compared with other three studies. For lung cancer, Wang X's [16] study was considered as the source of heterogeneity because it only focused on non-small cell lung cancer, while other two studies focused on all kinds of lung cancer. For Asian population, the heterogeneity may have resulted from the follows factors: 1) different genotyping methods of each study; 2) different types of cancer may be caused by different mechanisms; 3) different age distribution of the studied people of each study.

Some limitations of this meta-analysis should be considered. Firstly, insufficient studies and small sample sizes were the problem when we made subgroup analysis by cancer types. The lack of association in other cancers may be a result of insufficient studies. Secondly, only published studies in a few databases were identified and some relevant published studies or unpublished studies with null results were missed, which may bias the results. Thirdly, only Asian- and Caucasian-based case-control studies were included while analyses concerning other ethnic groups such as African were not applicable. Fourthly, the gene-gene and gene-environment interactions were not discussed due to lack of original information. Despite of these limitations, we minimized the bias through the whole process based on means in study identification, data selection, statistical analysis, and control of publication bias. These methods resulted in a guaranteed reliability of the results.

In conclusion, the present study suggested that the *RAGE* Gly82Ser and the *RAGE* -374T/A polymorphisms were associated with increased cancer risk, especially in Asians. Besides, the *RAGE* Gly82Ser polymorphism was associated with lung cancer susceptibility. More well designed original studies with larger sample size

focusing on more ethnicities or cancer types are needed to confirm the results.

Disclosure of conflict of interest

None.

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