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META-ANALYSIS

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Association of *RAGE* rs1800625 Polymorphism and Cancer Risk: A Meta-Analysis of 18 Case-Control Studies

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Data Interpretation D
Manuscript Preparation E
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Background: Accumulating evidence suggests that the rs1800625 polymorphism in *RAGE* promoter region might be associated with cancer risk; however, data from different studies show conflicting results. Here, a meta-analysis was conducted to evaluate the associations between *RAGE* rs1800625 polymorphism and cancer risk.

Material/Methods: We searched Embase (Excerpt Medica Database), PubMed, and CNKI (Chinese National Knowledge Infrastructure) databases until March 15, 2019 to identify potential studies for the meta-analysis.

Results: Eighteen eligible studies were included in the current meta-analysis, representing 6246 cases and 6819 controls. Pooled analysis showed positive correlation between the *RAGE* rs1800625 polymorphism and susceptibility of cancer in recessive genetic model [CC versus TC+TT: odds ratio (OR)=1.397, 95% confidence interval (CI): 1.031–1.894, *P*=0.031]. Subgroup analysis revealed this association in the Asian, but not Caucasian population, and this correlation was not detected in either breast or lung cancer. Sensitivity analysis indicated unstable results, which should be interpreted with caution. No publication bias was observed.

Conclusions: In conclusion, the *RAGE* rs1800625 polymorphism was associated with increased overall cancer risk in Asians in recessive genetic model. However, large-scale and well-designed studies in different populations and diverse cancer types are needed for a precise conclusion.

MeSH Keywords: **Disease Susceptibility • Meta-Analysis • Polymorphism, Genetic**

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Background

Receptor for advanced glycation end product (RAGE), also called as advanced glycation end product receptor (AGER), is a transmembrane receptor expressed in a number of cells, belonging to the immunoglobulin superfamily of receptors. Advanced glycation end product (AGE) is a ligand that binds RAGE to amplify immune and inflammatory responses. A number of other ligands of RAGE were reported recently, including amyloid-β, amphoterin, collagen IV, S100 proteins, and integrin Mac-1 [1]. RAGE-ligand interactions are known to elicit oxidative stress, evoked inflammatory, proliferative, angiogenic reactions, and essential processes in the pathogenesis of various types of cancers [2]. Moreover, RAGE was reported to be increased in several solid tumors [3,4].

The *RAGE* gene is located on chromosome 6p21.3, containing 1.7 kb in the 5' flanking region and 11 exons ranging 3.27 kb in length. *RAGE* gene polymorphisms are correlated with the level of circulating RAGE [5]. To date, several *RAGE* polymorphisms have been identified including rs2070600 (82G>S), rs1800624 (–374 T>A), and rs1800625 (–429 C>T), and were found to be correlated with susceptibility to cancers [6]. The *RAGE* rs1800625 polymorphism has been widely reported to be correlated with cancer risk, including breast, lung, gastric, cervical, and hepatocellular carcinoma. However, these studies showed controversial results in different types of cancer, or even within the same type of cancer. Some meta-analysis studies summarized this correlation with limited studies and cancer types [7,8]. Yin et al. [7] reported positive correlation between the *RAGE* rs1800625 polymorphism and lung cancer risk; however, only 2 studies were included. In another meta-analysis by Zhao et al. [8], no remarkable correlation was found in either breast or lung cancer.

The current meta-analysis study pooled 18 eligible case-control studies to evaluate the association between *RAGE* rs1800625 polymorphism and cancer risk in different ethnic populations and different cancer types.

Material and Methods

Literature search

Embase (Excerpt Medica Database, a biomedical and pharmacological bibliographic database), PubMed, and CNKI (Chinese National Knowledge Infrastructure) databases were searched until March 15, 2019 to explore eligible studies with the keywords "RAGE OR AGER OR receptor for advanced glycation end products" and "polymorphism OR rs1800625 OR –429T>C OR –429A>G OR –429T/C OR –429A/G" and "cancer OR tumor OR carcinoma OR metastasis". Reference lists were manually examined to explore relevant publications.

Inclusion and exclusion criteria

Inclusion criteria included: 1) case-control study, 2) association between *RAGE* rs1800625 polymorphism and cancer risk, 3) sufficient genotype information. Exclusion criteria included: 1) reviews, 2) insufficient genotype information, 3) duplicated study, 4) study deviated from Hardy-Weinberg equilibrium (HWE).

Data extraction

To independently carry out meta-analyses, the following data were extracted from all eligible articles: year, first author name, region, sample size, ethnicity, male ratio, age, cancer type, genotyping method, genotype, minor allele frequency (MAF), and *P* value for HWE.

Statistical analysis

All data were analyzed using STATA 12.0 (STATA Corporation, College Station, TX, USA). The odds ratio (OR) and 95% confidence intervals (CIs) were calculated to determine the correlation between *RAGE* rs1800625 polymorphism and cancer risk determined with Z test. Four genetic models were applied: allelic (C versus T), dominant (CC+TC versus TT), recessive (CC versus TC+TT), and additive (CC versus TT) genetic models. HWE of the control group was evaluated by χ^2 test. I^2 statistic and Cochran Q test were applied to examine the heterogeneity, and random effect model was applied in this meta-analysis. Meta regression analysis was used to estimate the risk factors of heterogeneity. Sensitivity analysis was conducted through sequential deletion of a single study. Funnel plot, Begg's test, and Egger's test were applied to determine publication bias.

Results

Characteristics of the included 18 case-control studies

The study selection was carried out as shown in Figure 1. A total of 62 studies were screened from the databases. Studies not related to polymorphism (N=8), not related to cancer (N=21), not relevant to rs1800625 polymorphism (N=8), without control (N=1), with insufficient frequency information (N=2), and reviews (N=4) were excluded. Finally, 18 studies with 6246 cases and 6819 controls were included in this meta-analysis [9–26]. The characteristics of the included 18 studies are listed in Tables 1 and 2.

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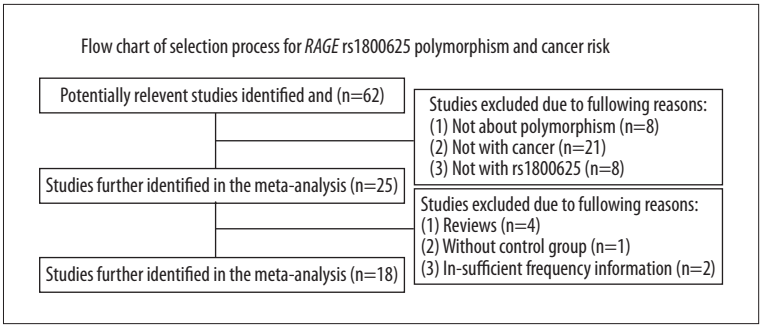

Figure 1. Flow diagram of literature search and selection of studies.

Table 1. Characteristics of 18 studies included in this meta-analysis.

Author	Year	Region	Ethnicity	Cancer	Method	Sample size		Age	
						Case	Control	Case	Control
Hu D et al.	2019	Mainland China	Asian	Gastric cancer	PCR-LDR	369	493	–	–
Lee CY et al.	2018	Taiwan	Asian	Cervical cancer	TaqMan	201	320	48.8±13.5	44.0±10.2
Yamaguchi K et al.	2017	Japan	Asian	Lung cancer	TaqMan	189	303	64.3±11.0	55.5±7.8
Li T et al.	2017	Mainland China	Asian	Gastric cancer	PCR-RFLP	200	207	54.43±11.77	53.23±4.34
Wang D et al.	2017	Mainland China	Asian	Hepatocellular carcinoma	PCR-LDR	540	540	51.5±6.7	50.4±6.8
Yue L et al.	2016	Mainland China	Asian	Breast cancer	PCR-LDR	524	518	53.76±12.62	56.49±10.04
Wang H et al.	2015	Mainland China	Asian	Lung cancer	PCR-RFLP	275	126	59.8±10.4	57.1±11.2
Su SC et al.	2015	Taiwan	Asian	Hepatocellular carcinoma	TaqMan	265	300	62.99±11.97	62.75±10.33
Su S	2015	Taiwan	Asian	Oral squamous cell carcinoma	TaqMan	618	592	–	–
Chocholatý M et al.	2015	Czech Republic	Caucasian	Renal cell carcinoma	PCR-RFLP	214	154	63±11	57±10
Pan H et al.	2014	Mainland China	Asian	Breast cancer	PCR-LDR	509	504	55.63±10.14	56.27±9.29
Pan H et al.	2013	Mainland China	Asian	Lung cancer	PCR-LDR	819	803	57.35±10.51	57.04±9.72
Wang X et al.	2012	Mainland China	Asian	Lung cancer	PCR-RFLP	562	764	–	–
Xu Q et al.	2012	Mainland China	Asian	Cervical cancer	TaqMan	488	715	54.6±5.7	54.5±2.61
Hashemi M et al.	2012	Iran	Caucasian	Breast cancer	ARMS-PCR	71	93	45.25±11.75	43.25±12.97
Krechler T et al.	2010	Czech Republic	Caucasian	Pancreas cancer	PCR-RFLP	99	154	64±11	57±10
Tesarová P et al.	2007	Czech Republic	Caucasian	Breast cancer	PCR-RFLP	120	92	61.2±11.9	56.2±9.2
Tóth EK et al.	2007	Hungary	Caucasian	Colorectal cancer	PCR-RFLP	183	141	65.7±10.5	68.4±6.6

PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; PCR-LDR – polymerase chain reaction-ligase detection reaction; ARMS-PCR – amplification refractory mutation system-polymerase chain reaction.

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Table 2. Genotype frequencies of *RAGE* rs1800625 in 18 studies included in this meta-analysis.

Author	Year	Ethnicity	Cancer	Sample size		Genotype (case)			Genotype (control)			MAF		HWE
				Case	Control	TT	TC	CC	TT	TC	CC	Case	Control	
Hu D et al.	2019	Asian	Gastric cancer	369	493	324	44	1	410	77	6	6.23%	9.03%	0.277
Lee CY et al.	2018	Asian	Cervical Cancer	201	320	181	19	1	270	48	2	5.22%	8.13%	0.932
Yamaguchi K et al.	2017	Asian	Lung cancer	189	303	160	24	5	254	44	5	8.99%	8.91%	0.066
Li T et al.	2017	Asian	Gastric cancer	200	207	184	13	3	184	22	1	4.75%	5.80%	0.698
Wang D et al.	2017	Asian	Hepatocellular carcinoma	540	540	403	107	30	417	113	10	15.46%	12.31%	0.471
Yue L et al.	2016	Asian	Breast cancer	524	518	330	174	20	360	143	15	20.42%	16.70%	0.861
Wang H et al.	2015	Asian	Lung cancer	275	126	195	76	4	100	26	0	15.27%	10.32%	0.197
Su SC et al.	2015	Asian	Hepatocellular carcinoma	265	300	216	44	5	277	22	1	10.19%	4.00%	0.434
Su S et al.	2015	Asian	Oral squamous cell carcinoma	618	592	509	102	7	532	57	3	9.39%	5.32%	0.280
Chocholatý M et al.	2015	Caucasian	Renal cell carcinoma	214	154	142	57	15	109	39	6	20.33%	16.56%	0.300
Pan H et al.	2014	Asian	Breast cancer	509	504	379	124	6	365	130	9	13.36%	14.68%	0.507
Pan H et al.	2013	Asian	Lung cancer	819	803	447	303	69	485	289	29	26.92%	21.61%	0.077
Wang X et al.	2012	Asian	Lung cancer	562	764	201	274	87	229	387	148	39.86%	44.70%	0.496
Xu Q et al.	2012	Asian	Cervical cancer	488	715	129	188	171	182	344	189	54.30%	50.49%	0.314
Hashemi M et al.	2012	Caucasian	Breast cancer	71	93	59	11	1	85	8	0	9.15%	4.30%	0.665
Krechler T et al.	2010	Caucasian	Pancreas cancer	99	154	71	26	2	109	39	6	15.15%	16.56%	0.300
Tesarová P et al.	2007	Caucasian	Breast cancer	120	92	85	32	3	63	26	3	15.83%	17.39%	0.875
Tóth EK et al.	2007	Caucasian	Colorectal cancer	183	141	4	44	135	5	35	101	85.79%	84.04%	0.376

Association of the *RAGE* rs1800625 polymorphism and cancer risk

In the overall analysis, the *RAGE* rs1800625 polymorphism was correlated with increased cancer risk in the recessive genetic model (CC versus TC+TT: OR=1.397, 95% CI: 1.031–1.894, *P*=0.031), but not in the allelic (C versus T), dominant (CC+TC versus TT), or additive (CC versus TT) genetic models (Figure 2, Table 3).

Stratification based on ethnicity revealed similar results in Asian but not in the Caucasian population. Moreover, stratification by cancer type did not find any significant correlation in either breast or lung cancer (Table 3).

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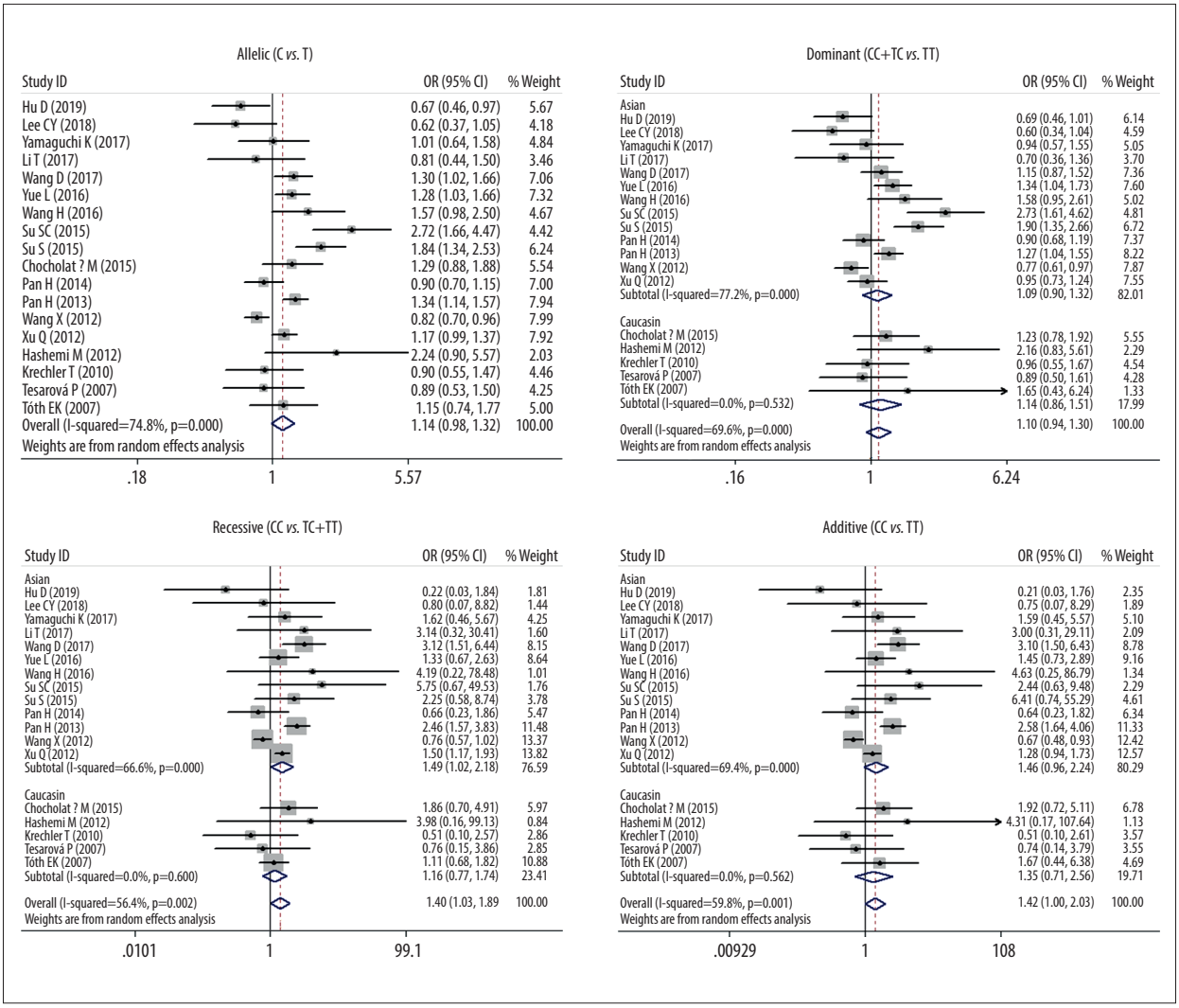

Figure 2. Forest plots for meta-analysis of the *RAGE* rs1800625 polymorphism and cancer risk.

Meta-regression analysis was carried out to screen risk factors of the heterogeneity considering publication year, ethnicity (Asian versus Caucasian), and genotyping method [polymerase chain reaction (PCR)-restriction fragment length polymorphism (RFLP), PCR-ligase detection reaction (LDR), and amplification refractory mutation system (ARMS)-PCR, versus TaqMan] as possible covariates. However, none of these mentioned covariates remarkably contributed to the heterogeneity (data not shown).

Sensitivity analysis

Sensitivity analysis indicated that the positive correlation found in recessive genetic model in pooled analysis and in Asian subgroup was unstable (Figure 3). After omitting the studies by Wang et al. (2017), Pan et al. (2013), or Xu et al. (2012), the *RAGE* rs1800625 polymorphism was not correlated with cancer risk in recessive genetic model.

Publication bias

Egger's and Begg's tests were applied to determine publication bias, and no publication bias existed (Figure 4, Table 4), indicating that this meta-analysis was reliable.

Discussion

The objective of this meta-analysis was to investigate any possible relationship of the *RAGE* rs1800625 polymorphism with cancer susceptibility. We found that the *RAGE* rs1800625 polymorphism might be closely associated with increased risk of human cancer in the Asian population. However, subgroup analysis did not support this positive correlation in either lung or breast cancer in Asians. Sensitivity analysis revealed unstable results, and therefore, these conclusions should be interpreted with caution.

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Table 3. Meta-analysis of *RAGE* rs1800625 polymorphism and cancer susceptibility.

Genetic model	P_Q	I^2	OR	95% CI	P_z
Overall					
C *vs.* T	0.000	74.8%	1.139	0.982, 1.321	0.085
CC+TC *vs.* TT	0.000	69.6%	1.105	0.936, 1.305	0.240
CC *vs.* TC+TT	0.002	56.4%	1.397	1.031, 1.894	0.031
CC *vs.* TT	0.001	59.8%	1.423	0.996, 2.033	0.053
Ethnicity					
Asian					
C *vs.* T	0.000	81.0%	1.139	0.956, 1.357	0.146
CC+TC *vs.* TT	0.000	77.2%	1.090	0.898, 1.324	0.384
CC *vs.* TC+TT	0.000	66.6%	1.491	1.018, 2.183	0.040
CC *vs.* TT	0.000	69.4%	1.465	0.960, 2.236	0.077
Caucasian					
C *vs.* T	0.373	5.8%	1.128	0.901, 1.412	0.294
CC+TC *vs.* TT	0.532	0.0%	1.141	0.862, 1.511	0.355
CC *vs.* TC+TT	0.600	0.0%	1.156	0.770, 1.736	0.485
CC *vs.* TT	0.562	0.0%	1.354	0.715, 2.565	0.353
Disease					
Lung cancer					
C *vs.* T	0.000	85.7%	1.125	0.807, 1.567	0.487
CC+TC *vs.* TT	0.004	77.3%	1.075	0.771, 1.498	0.671
CC *vs.* TC+TT	0.000	84.9%	1.523	0.631, 3.679	0.350
CC *vs.* TT	0.000	87.4%	1.521	0.561, 4.128	0.410
Breast					
C *vs.* T	0.062	59.1%	1.105	0.827, 1.477	0.500
CC+TC *vs.* TT	0.087	54.4%	1.127	0.828, 1.533	0.448
CC *vs.* TC+TT	0.561	0.0%	1.075	0.633, 1.826	0.789
CC *vs.* TT	0.463	0.0%	1.126	0.661, 1.920	0.662

Cochran Q test and I^2 statistical test were applied to examine the heterogeneity, and random effect model was applied in this meta-analysis. The correlation between *RAGE* rs1800625 polymorphism and cancer risk was determined using Z test.

Heterogeneity represents a major problem in meta-analyses. Herein, we performed stratified analysis by cancer type and ethnicity. Decreased heterogeneity was observed in Caucasian population in all 4 genetic models, and in breast cancer in some genetic models. These results suggest that ethnicity and cancer type may partially explain the source of heterogeneity, although we failed to confirm our hypothesis with statistical evidence in the meta-regression analysis considering ethnicity, publication year, and genotyping method as possible covariates. Moreover, even in the same subgroup of lung cancer, Wang et al. [16] and Pan et al. [19] both recruited squamous cell cancer, small cell cancer, and adenocarcinoma. Wang et al. [21] only studied non-small cell lung cancer (NSCLC) and Yamaguchi et al. [11] only focused on adenocarcinoma. These studies might contribute to the existence of heterogeneity.

Different cancer types might affect the overall result. In the current meta-analysis, gastric, cervical, lung, breast, hepatocellular carcinoma, pancreas, and colorectal cancers were included. However, only breast and lung cancers were included in 4 different studies, and gastric cancer, cervical cancer, and hepatocellular carcinoma were included in 2 studies. Stratified analysis

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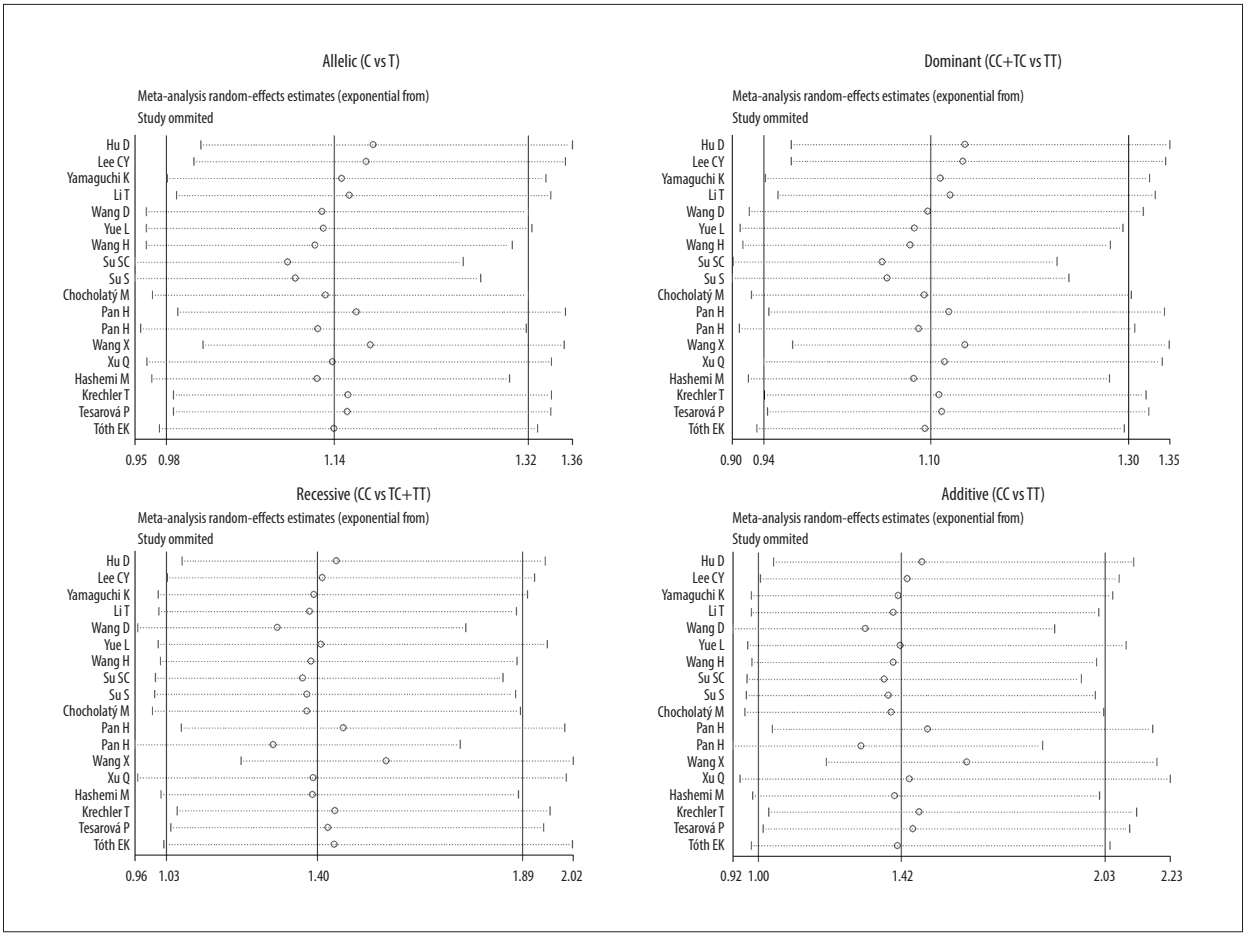

Figure 3. Sensitivity analysis for meta-analysis of the *RAGE* rs1800625 polymorphism and cancer risk.

based on cancer type was only performed for lung and breast cancer. Male ratio in different cancers might also influence the results. Among the included 18 studies, 6 studies focused on breast or cervical cancer [10,14,20,22,24,26], which did not include male patients. In the studies by Yamaguchi et al. [11], Li et al. [13], Chocholatý et al. [18], Krechler et al. [23], and Tóth et al. [25] involving lung, gastric, renal, pancreas, and colorectal cancers respectively, the male ratios were not consistent between cases and controls. Moreover, the sample size among these included studies varied from less than 100 to more than 800. In the stratified analysis of breast cancer, studies by Hashemi et al. [22] and Tesarová et al. [24] involved less than 100 controls, and both studies showed no significant association, which might affect the overall OR of the subgroup. The mean age between cases and controls were not well matched in some studies. In the study by Yamaguchi et al. [11], the mean age of cases was 64.3±11.0, while the mean age of controls was 55.5±7.8, and similar results were found in the studies by Krechler et al. [23] and Tesarová et al. [24]. The MAF varied significantly among studies, even in the same ethnic populations. In Asian population, the MAF varied from 4.00% to 50.49% [15,20], while in the Caucasian population, it varied from 4.30% to 84.04% [22,25]. Finally, the genotyping methods might also contribute to the overall result. PCR-LDR, TaqMan, PCR-RFLP, and ARMS-PCR were used by different studies. These factors together might make the overall heterogeneity complicated and influence the pooled result. Rigorously designed studies with larger sample size might help clarify this association between *RAGE* rs1800625 polymorphism and cancer risk.

Several potential limitations existed in the current meta-analysis. First, selection bias might exist, as eligible articles in English language were screened. In this meta-analysis, only 5 articles were included for the Caucasian population, and this bias might influence the null result for Caucasian population. Second, we only performed stratified analysis for lung and breast cancers but not all types of cancer, due to limited number of studies. Third, not all published studies on the correlation between the *RAGE* rs1800625 polymorphism and susceptibility of cancer were included. Studies by Zhang et al. [27] and Kádár et al. [28] were ruled out due to insufficient genotype information for the calculation of OR. Fourth, this meta-analysis was not adjusted by gender, age, and environment factors like circulating soluble RAGE. Breast cancer was gender specific and was not suitable

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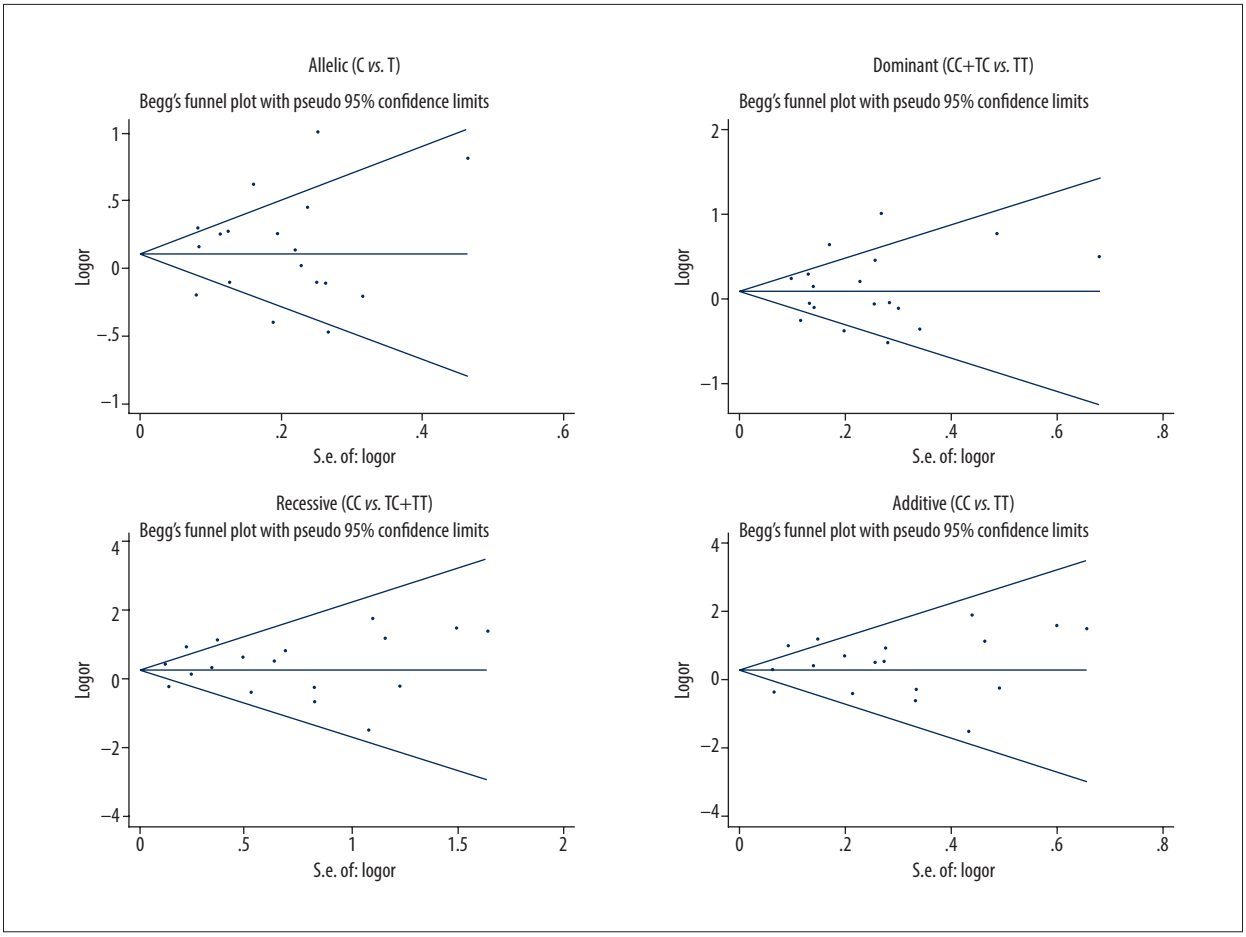

Figure 4. Funnel plots of the associations between the *RAGE* rs1800625 polymorphism and cancer risk.

Table 4. Publication bias analysis of this meta-analysis.

Genetic model	Test	t	95% CI	*P*
C *vs.* T	Begg's test			0.880
	Egger's test	0.37	–1.858, 2.634	0.719
CC+TC *vs.* TT	Begg's test			0.880
	Egger's test	0.32	–1.916, 2.588	0.756
CC *vs.* TC+TT	Begg's test			0.940
	Egger's test	0.54	–0.879, 1.483	0.595
CC *vs.* TT	Begg's test			0.940
	Egger's test	0.86	–0.749, 1.765	0.404

for comparison with other types of cancer. Fifth, only about 28% of the studies included Caucasian population; therefore, it is not surprising that stratification analysis showed similar results in Asian, but not Caucasian population. The Caucasian population is not representative and therefore it is hard to extrapolate the result to the general population. Sixth, there were significant age differences between case and control groups in some studies and no adjustment was made in our analysis to account for this.

Conclusions

The *RAGE* rs1800625 polymorphism was associated with increased overall cancer risk in Asians in a recessive genetic model. However, this polymorphism might not be correlated with lung or breast cancer risk in Asians. Nonetheless, large-scale and well-designed studies in different populations and diverse cancer types are needed for a precise conclusion.

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Conflict of interest

None.

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