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ORIGINAL ARTICLE

Association between the receptor for advanced glycation end products gene polymorphisms and cancer risk: a systematic review and meta-analysis

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Summary

Purpose: *Polymorphisms in the receptor for advanced glycation end products (RAGE) gene may influence the risk of cancer, but the results are inconsistent. Therefore, we performed a systematic review to identify statistical evidence of the association between the 3 polymorphisms rs2070600 G/S (82G>S), rs1800624 T/A (-374 T>A) and rs1800625C/T (-429 C>T) and the risk of cancer.*

Methods: *We searched PubMed database (http://www.ncbi.nlm.nih.gov/pubmed/), EMBASE database (http://www.elsevier.com/online-tools/embase) and China National Knowledge Infrastructure (CNKI) database (http://www.cnki.net/) until Aug 30, 2014 to identify eligible studies.*

Results: *The pooled analysis revealed positive association between RAGE rs2070600 polymorphism and cancer risk in all genetic models (homozygous: OR=1.831, 95%CI: 1.548-2.166, p<0.001, allele: OR=1.321, 95%CI: 1.164-1.499, p<0.001, heterozygous: OR=1.42, 95%CI:1.126-1.792, p=0.003, dominant: OR=1.499, 95%CI: 1.200-1.874 ; p<0.001, recessive: OR=1.376, 95%CI: 1.197-1.583, p<0.001). We failed to get an effective conclusion about the association between the rs1800624 and rs1800625 polymorphisms and cancer risk in overall comparison. But in subgroup analysis, the rs1800624 polymorphism significantly increased lung cancer susceptibility in the homozygous model (OR=1.486, 95%CI:1.147-1.924, p=0.003) and the allele model (OR=1.15, 95%CI:1.029-1.285, p=0.014), but most likely contributed to decreased susceptibility to breast cancer in the allele model (OR=0.791 95%CI: 0.648-0.965, p=0.021), the heterozygous model (OR=0.733, 95%CI:0.577-0.931, p=0.011) and the dominant model (OR=0.741, 95%CI:0.588-0.934, p=0.011). No significant association was found between RAGE rs1088625 polymorphism and cancer risk in Caucasians, but these results should be interpreted with caution.*

Conclusion: *The polymorphism of rs2070600 in the RAGE gene may increase the susceptibility to several human cancers, especially to lung cancer and to Asians. The rs1800264 most likely contributes to decreased susceptibility to breast cancer but increased susceptibility to lung cancer. However, large-scale studies involving various cancer types and different populations are needed for a precise conclusion.*

Key words: *cancer risk, gene polymorphism, meta-analysis, receptor for advanced glycation end-products*

Introduction

RAGE, a member of the immunoglobulin super-family of cell surface molecules, is a multi-ligand receptor, first described as receptor for advanced glycation end products [1]. RAGE takes part in the pathogenesis of many diseases, among them diabetes mellitus, coronary heart disease and cancer by interaction with advanced glycation end products and other molecules like proinflam-

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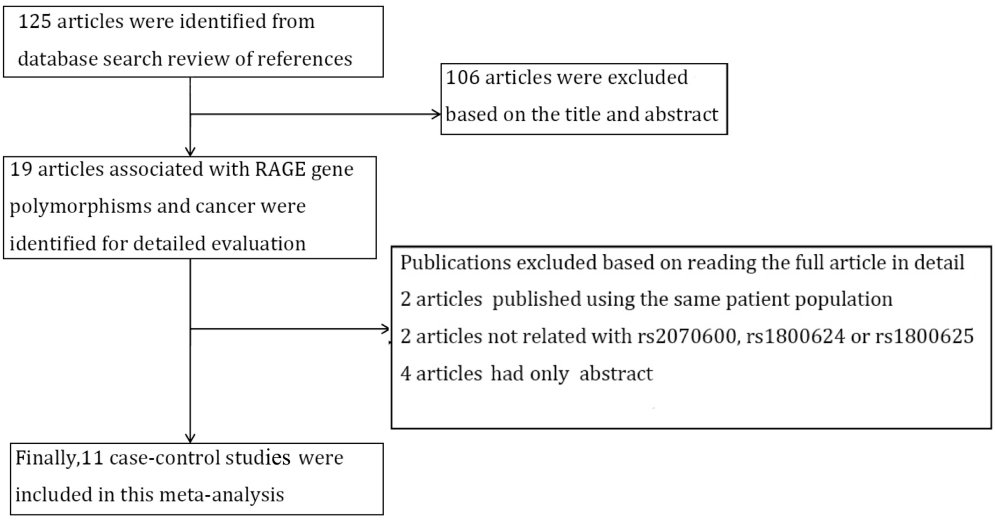

Figure 1. Flow chart of the study selection based on the inclusion and exclusion criteria.

matory S100 proteins/calgranulins (EN-RAGE), High Mobility Group proteins including HMGB1/amphoterin and amyloid β peptide [2-4]. Recent studies indicated that RAGE plays a key role in tumor growth, progression and metastasis in various types of cancers. Clinical studies showed that the expression of RAGE correlated with tumor growth, progression, invasion and metastasis in breast, lung, esophageal, hepatocellular and colorectal cancers. In a recent meta-analysis, soluble form of RAGE (sRAGE), which consisted of the extracellular ligand-binding domain of RAGE and acted as a decoy to neutralize the impact of circulating RAGE ligands, had a protective role in the development of cancer [5].

The RAGE gene, located on chromosome 6p21.3 in the major histocompatability locus (MHC) locus class II/III junction, is composed of a 1.7-kb 5' flanking region and 11 exons. Experimental studies had demonstrated that RAGE (–/–) mice were protected against tumorigenesis [6]. Further studies focused on the background of RAGE gene demonstrated that RAGE gene polymorphisms were associated with amplification of the inflammatory response and the level of circulating RAGE [7-9]. To date, several genetic variants have been identified in RAGE gene, and 3 well-studied common single nucleotide polymorphisms (SNPs), which are rs2070600 G/S (82G>S), rs1800624 T/A (-374 T>A) and rs1800625C/T (-429 C>T),are being investigated extensively in relation to the susceptibility of cancer. However, the observed associations of these studies were inconsistent or even contradictory. In this study, we conducted a meta-analysis of all eligible studies to identify statistical evidence of the association between the 3 polymorphisms and the risk of cancer.

Methods

Literature search

A literature search was performed in PubMed, Embase electronic databases and Chinese National Knowledge Infrastructure (CNKI) databases, using the keywords :"RAGE" or "AGER" or "receptor for advanced glycation end products" or "advanced glycosylation end product-specific receptor", "polymorphism" or "polymorphisms" or "variant" or "variants" or "mutation" or "mutations", "cancer" or "cancers" or "carcinoma" or "carcinomas" or "tumor" or "tumors" or "neoplasm" or "neoplasms" or "malignancy" or "malignant". All eligible studies were published up to August 30, 2014. Search results were restricted to papers written in English and Chinese. The references of related articles were searched manually to find other relevant publications. Our meta-analysis included only published studies with full text articles. If more than one article was published using the same patient population, we selected the most complete study.

Inclusion criteria

All of the selected studies should meet the following inclusion criteria:1) the study should have evaluated the association between the RAGE polymorphisms and cancer risk; 2) human case–control study; 3) sufficient data should have been provided in order to calculate odds ratios (OR) and 95% confidence interval (CI). Studies were excluded if any of the following conditions applied:1) only abstracts or reviews were available without sufficient data; 2) animal studies; 3) studies

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

No.	*Author*	*Year*	*Design*	*Country*	*Ethnicity*	*Genotyping method*	*Control sources*	*Sample size (case/control)*	*Cancer type*	*HWE*
1	Qian	2014	Retrospective	China	Asian	PCR-RFLP	HB	90/78	CRC	Y
2	Pan	2014	Retrospective	China	Asian	PCR-LDR	HB	509/504	BC	Y
3	Pan	2013	Retrospective	China	Asian	PCR-LDR	HB	819/803	LC	Y
4	Zhang	2013	Retrospective	China	Asian	PCR-RFLP	HB	190/210.	EOC	Y
5	Wang	2012	Retrospective	China	Asian	PCR-RFLP	HB	562/764	LC	Y
6	Xu	2012	Retrospective	China	Asian	TaqMan	HB	488/715	CC	Y
7	Hashemi	201;	Retrospective	Iran	Caucasians	H-ARMS-PCR	HB	71/93	BC	Y
8	Krechler	2010	Retrospective	Czech	Caucasians	PCR-RFLP	HB	99/154	PC	Y
9	Gu	2008	Retrospective	China	Asian	PCR-RFLP	HB	283/283	GC	Y
10	Tesarova	2007	Retrospective	Czech	Caucasians	PCR-RFLP	HB	120/92	BC	Y
11	Toth	2007	Retrospective	Hungarian	Caucasians	PCR-RFLP	HB	183/141	CRC	Y

HB: Hospital-based, HWE: Hardy Weinberg equilibrium in control population, PCR-RFLP: Polymerase chain reaction restriction fragment length polymorphism, LDR: ligase detection reaction, H-ARM: hexaprimer amplification refractory mutation system, CRC: Colorectal cancer, BC: Breast cancer, LC: Lung cancer, EOC: Epithelial Ovarian cancer, CC: Cervical cancer, PC: Pancreatic cancer, GC: Gastric cancer

were repeated or publications overlapped; 4) studies deviated from the Hardy-Weinberg equilibrium (HWE).

Data extraction

Data was extracted from all eligible articles by two investigators (Dachuan Zhao and Hongwei Lu) according to the inclusion criteria. The following data were recorded from each included study : first author's last name, year of publication, ethnicity, country, type of cancer, number of cases and controls, number of different genotypes in cases and controls, HWE, genotyping methods, and matching criteria. Ethnicity was categorized as Asian and Caucasian. Any discrepancies between these two authors were resolved by discussion and consensus.

Statistics

Deviation from HWE in controls was tested by the chi-square test. The association between the RAGE gene polymorphisms and cancer risk was estimated for each study by calculating OR with 95 % CI. Five overall ORs were calculated under different genetic models: homozygous model, allele model, heterozygous model, dominant model and recessive model. The significance of the overall ORs was determined by Z test. Heterogeneity across individual studies were performed based on the Q-test and I^2 test. A p value >0.05 for the Q-test and I^2 <50% for the I^2 test indicated lack of heterogeneity, and a fixed effects model was used. Otherwise, the overall OR estimate of each study was calculated by the random effects model. Furthermore, stratified analysis was performed by ethnicity and cancer type to explore the potential effect modification. One-way sensitivity analysis were performed by removing a single study each time, in order to assess the stability of the results. Potential publication bias was examined by Begg's funnel plot and Egger's test. All statistical analyses were performed with the STATA software, version 12.0 (Stata Corporation, College station, TX, USA). A p value <0.05 was considered statistically significant.

Results

Characteristics of studies

The process of the study search and selection is presented in Figure 1. A total of 19 publications on RAGE gene polymorphisms and cancer risk were identified. Eight articles were excluded after full view. Finally, 11 studies [10-20] were included in the meta-analysis, 9 studies with 3160 cases and 3603 controls for rs2070600 polymorphism,7 eligible studies with 2666 cases and 3121 controls for rs1800624 polymorphism and 8 studies with 2851 cases and 3266 controls for rs1800625 polymorphism. The characteristics of the 11 articles are shown in Table 1. All studies were hospital-based (HB) case-control trials, conducted among Asians (7 studies) and Caucasians (4 studies) and focused on colorectal cancer (2 studies), breast cancer (3 studies), lung cancer (2 studies), and 1 study for each of the following cancers: epithelial ovarian cancer, cervical cancer, pancreatic cancer and gastric cancer.

Association of rs2070600 G/A polymorphism with cancer risk

In Table 2 and Figure 2, a positive association between RAGE rs2070600 G/A polymorphism and susceptibility to cancer is shown in

Table 2. Meta-analysis results of the association between the rs2070600 polymorphism and cancer risk

Comparisons	*Study*	*Gene model*	*Association*			*Heterogeneity*	
			OR	*95% CI*	P_{OR}	*I-square*	P_H
Total	9						
		AA vs GG	1.831	1.548-2.166	0	0.00%	0.507
		A vs G	1.321	1.164-1.499	0	0.536	0.028
		AG vs GG	1.42	1.126-1.792	0.003	0.682	0.001
		AG+AA vs GG	1.499	1.200-1.874	0	0.685	0.001
		AA vs AG+GG	1.376	1.197-1.583	0	0.408	0.107
Ethnicity							
Caucasians	2						
		AA vs GG	0.521	0.021-12.919	0	-	0.69
		A vs G	0.83	0.390-1.766	0.629	0	0.568
		AG vs GG	0.922	0.421-2.017	0.838	0	0.409
		AG+AA vs GG	0.873	0.402-1.894	0.73	0	0.483
		AA vs AG+GG	0.514	0.021-12.749	0.685	-	0.107
Asians	7						
		AA vs GG	1.839	1.554-2.176	0	0	0.459
		A vs G	1.339	1.176-1.526	0	0.615	0.016
		AG vs GG	1.472	1.151-1.883	0.002	0.745	0.001
		AG+AA vs GG	1.562	1.237-1.973	0	0.743	0.001
		AA vs AG+GG	1.379	1.199-1.586	0	0.476	0.075
Disease							
Lung	2						
		AA vs GG	1.719	1.353-2.183	0	0	1
		A vs G	1.237	1.113-1.375	0	0	0.965
		AG vs GG	1.507	0.815-2.785	0.191	0.915	0.001
		AG+AA vs GG	1.531	0.947-2.474	0.082	0.871	0.005
		AA vs AG+GG	1.264	0.782-2.043	0.34	0.819	0.019
Digestive	4						
		AA vs GG	2.4	1.184-4.865	0.015	0	0.521
		A vs G	1.438	0.905-2.285	0.124	0.525	0.097
		AG vs GG	1.506	1.133-2.003	0.005	0.394	0.176
		AG+AA vs GG	1.516	0.911-2.524	0.109	0.506	0.108
		AA vs AG+GG	1.994	0.990-4.018	0.053	0	0.63

OR: odds ratio, CI: confidence interval, p: p value

5 genetic models: homozygous model (OR=1.831, 95%CI: 1.548-2.166, p<0.001), allele model (OR=1.321, 95%CI: 1.164-1.499, p<0.001), heterozygous model (OR=1.42, 95%CI: 1.126-1.792, p=0.003), dominant model (OR=1.499, 95%CI: 1.200-1.874, p<0.001) and recessive model (OR=1.376, 95%CI: 1.197-1.583, p<0.001). Due to the existence of significant heterogeneities with overall analyses, subgroup analyses were performed by ethnicity and cancer type. In the subgroup analysis based on ethnicity, a increased risk of cancer susceptibility was observed under all genetic models in Asians: homozygous models (OR= 1.839, 95%CI: 1.554-2.176 , p<0.001), allele model (OR=1.339 , 95%CI: 1.176-1.526, p<0.001), heterozygous model (OR=1.472, 95%CI: 1.151-1.883, p=0.002), dominant model (OR=1.562, 95%CI: 1.237-1.973, p<0.001) and recessive model (OR=1.379, 95%CI: 1.199-1.586, p<0.001). In the subgroup analyses by cancer type, increased cancer risk was found in lung cancer in the homozygous model (OR=1.719, 95%CI: 1.353-2.183, p<0.001) and the allele model (OR=1.237, 95%CI: 1.113-1.375, p<0.001) and digestive cancer in the homozygous model (OR=2.40, 95%CI: 1.184-4.865, p=0.015) and the heterozygous model (OR=1.506, 95%CI: 1.133-2.003, p=0.005).

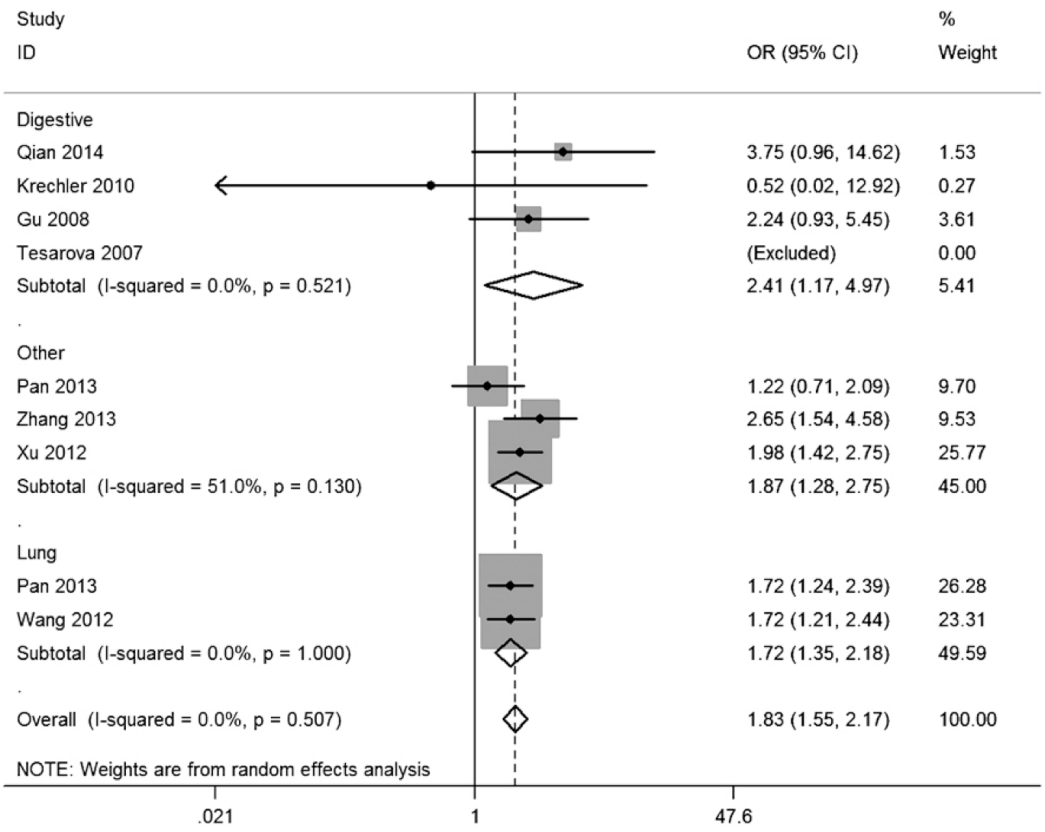

Figure 2. Meta-analysis shows positive association between RAGE rs2070600 polymorphism and cancer risk under the homozygous model.

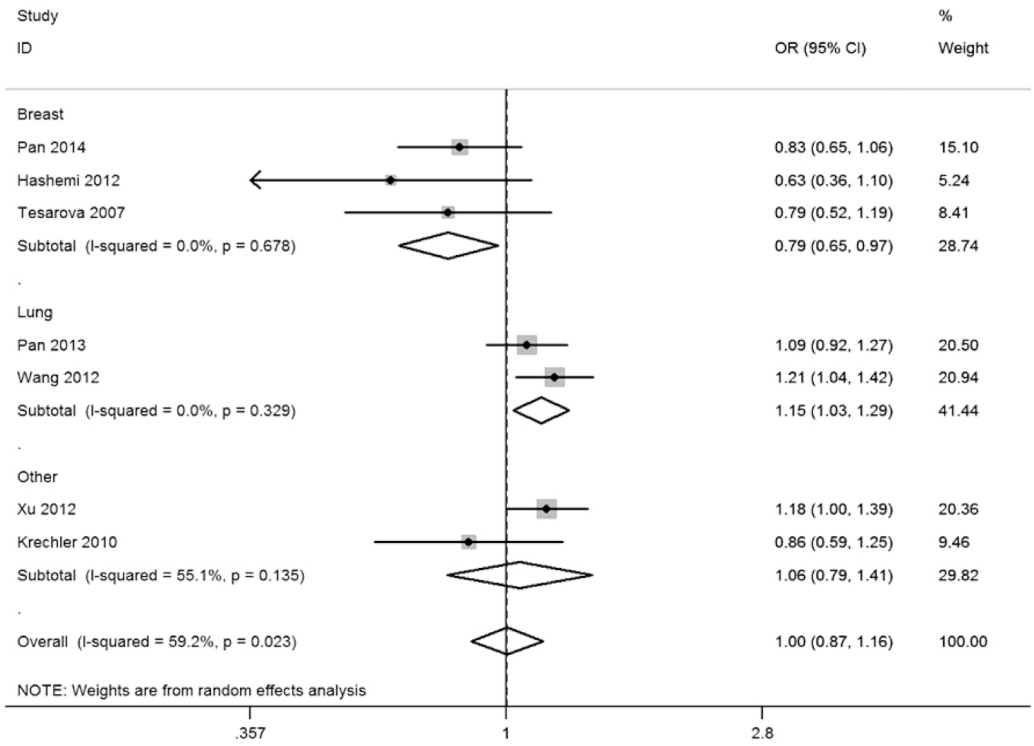

Figure 3. Meta-analysis of the association between RAGE rs1800624 polymorphism and cancer risk under the allele model. The Figure shows that rs1800624 polymorphism significantly increased lung cancer susceptibility but it decreased susceptibility to breast cancer in the allele model

Table 3. Meta-analysis results of the association between the rs1800624 polymorphism and cancer risk

Comparisons	*Study*	*Gene model*	*Association*			*Heterogeneity*	
			OR	*95% CI*	P_{OR}	*I-square*	P_H
Total	7						
		AA vs TT	1.3	1.079-1.566	0.006	0.166	0.303
		A vs T	1.004	0.869-1.158	0.962	0.592	0.023
		AT vs TT	0.967	0.759-1.233	0.786	0.694	0.003
		AT+AA vs TT	0.982	0.778-1.241	0.881	0.701	0.003
		AA vs AT+TT	1.186	1.015-1.386	0.033	0	0.439
Ethnicity							
Caucasians	3						
		AA vs TT	0.672	0.388-1.163	0.155	0	0.989
		A vs T	0.783	0.610-1.005	0.055	0	0.662
		AT vs TT	0.786	0.557-1.108	0.169	0.122	0.32
		AT+AA vs TT	0.753	0.545-1.041	0.086	0	0.452
		AA vs AT+TT	0.719	0.426-1.213	0.216	0	0.922
Asians	4						
		AA vs TT	1.421	1.164-1.734	0.001	0	0.831
		A vs T	1.091	0.952-1.250	0.213	0.579	0.068
		AT vs TT	1.058	0.787-1.424	0.708	0.8	0.002
		AT+AA vs TT	1.103	0.838-1.452	0.485	0.786	0.003
		AA vs AT+TT	1.244	1.057-1.464	0.009	0	0.591
Disease							
Breast	3						
		AA vs TT	0.797	0.435-1.461	0.463	0	0.789
		A vs T	0.791	0.648-0.965	0.021	0	0.678
		AT vs TT	0.733	0.577-0.931	0.011	0	0.644
		AT+AA vs TT	0.741	0.588-0.934	0.011	0	0.621
		AA vs AT+TT	0.898	0.498-1.621	0.722	0	0.858
Lung	2						
		AA vs TT	1.486	1.147-1.924	0.003	0	0.537
		A vs T	1.15	1.029-1.285	0.014	0	0.329
		AT vs TT	1.286	0.784-2.108	0.319	0.871	0.005
		AT+AA vs TT	1.303	0.842-2.016	0.236	0.849	0.01
		AA vs AT+TT	1.156	0.933-1.434	0.185	0	0.397

For abbreviations see footnote of Table 2

Association of rs1800624 T/A polymorphisms with cancer risk

As shown in Table 3, we observed a positive association between RAGE rs1800624 T/A polymorphisms and susceptibility to cancer in the homozygous models (OR=1.3, 95%CI: 1.079-1.566, p=0.006) and the recessive model (OR=1.186 , 95%CI: 1.015-1.386, p=0.033). Stratified analyses based on ethnicity implied that rs1800624 T/A polymorphism in the RAGE gene may be the main risk factor for cancers in Asian populations under the homozygous model (OR=1.421, 95%CI 1.164-1.734, p=0.001) and the recessive model (OR=1.244, 95%CI:1.057-1.464, p=0.009) but not in Caucasian populations under the 2 genetic models (homozygous: OR= 0.672, 95%CI:I 0.388-1.163, p=0.155; recessive: OR=0.719, 95%CI: 0.426-1.213, p=0.216).

We also performed stratified analyses by cancer type (Figure 3). Significantly increased lung cancer susceptibility in the homozygous models (OR=1.486, 95%CI:1.147-1.924, p=0.003) and the allele model (OR=1.15, 95%CI:1.029-1.285, p=0.014) was found; interestingly, rs1800624 most likely contributed to decreased susceptibility to breast cancer in the allele model (OR=0.791,

Table 4. Meta-analysis results of the association between the rs1800625 polymorphism and cancer risk

Comparisons	*Study*	*Gene model*	*Association*			*Heterogeneity*	
			OR	*95% CI*	P_{OR}	*I-square*	P_H
Total	8						
		CC vs TT	1.123	0.682-1.850	0.647	0.737	0
		C vs T	1.052	0.876-1.264	0.587	0.719	0.001
		CT vs TT	0.947	0.842-1.065	0.363	0.265	0.217
		CT+CC vs TT	0.995	0.824-1.201	0.957	0.515	0.044
		CC vs CT+TT	1.164	0.778-1.742	0.461	0.727	0.001
Ethnicity							
Caucasians	4						
		CC vs TT	1.042	0.465-2.334	0.921	0	0.547
		C vs T	1.062	0.818-1.380	0.652	0.163	0.31
		CT vs TT	1.116	0.771-1.616	0.561	0	0.555
		CT+CC vs TT	1.091	0.764-1.560	0.631	0	0.394
		CC vs CT+TT	1.042	0.669-1.624	0.855	0	0.652
Asians	4						
		CC vs TT	1.144	0.614-2.129	0.672	0.877	0
		C vs T	1.039	0.820-1.317	0.749	0.859	0
		CT vs TT	0.91	0.754-1.098	0.327	0.546	0.085
		CT+CC vs TT	0.963	0.763-1.214	0.749	0.732	0.011
		CC vs CT+TT	1.24	0.714-2.152	0.445	0.872	0
Disease							
Breast	3						
		CC vs TT	0.785	0.343-1.796	0.566	0	0.542
		C vs T	0.947	0.761-1.178	0.623	0.457	0.158
		CT vs TT	0.966	0.735-1.240	0.788	0.116	0.323
		CT+CC vs TT	0.954	0.748-1.217	0.705	0.34	0.22
		CC vs CT+TT	0.795	0.348-1.815	0.586	0	0.578
Lung	2						
		CC vs TT	1.302	0.347-4.892	0.695	0.956	0
		C vs T	1.046	0.648-1.689	0.853	0.945	0
		CT vs TT	0.964	0.689-1.350	0.832	0.775	0.035
		CT+CC vs TT	0.992	0.607-1.621	0.973	0.904	0.001
		CC vs CT+TT	1.351	0.429-4.253	0.607	0.946	0

For abbreviations see footnote of Table 2

95%CI: 0.648-0.965, p=0.021) ,the heterozygous model (OR=0.733, 95%CI:0.577-0.931, p=0.011) and the dominant model (OR=0.741, 95% CI:0.588-0.934, p=0.011).

Association of rs1800625 T/C polymorphisms with cancer risk

No significant association of the rs1800625 T/C in RAGE with cancer risk in all genetic models was found (Table 4). As shown in the stratified analysis of ethnicity, no significant associations with cancer risk were found in Asians (heterozygous: OR=0.91, 95%CI:0.754-1.098, p=0.327) and Caucasians (heterozygous: OR=1.116 95%CI:0.771-1.616, p=0.561). The subgroup analysis among different types of cancer also showed no significant association in breast cancer (heterozygous : OR=0.966, 95%CI:0.735-1.240, p=0.788) and in lung cancer (heterozygous : OR=0.964, 95%CI:0.689-1.350, p=0.832).

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of literature (Table 5). The sharpness of the funnel plot seemed a little asymmetric in the allele model of

Table 5. Beggs and Eggers test results for publication bias risk

	Begg's test		*Egger's test*	
	z	*p value*	*t*	*p value*
rs2070600				
AA vs GG Homozygous	0.12	0.902	-0.05	0.962
A vs G Allele	0.1	0.917	-0.23	0.826
AG vs GG Heterozygous	0.52	0.602	0.6	0.565
AG+AA vs G Dominant	1.15	0.251	0.7	0.506
AA vs AG+GG Recessive	0.12	0.902	0.12	0.911
rs1800624				
AA vs TT Homozygous	0.9	0.368	0.39	0.714
A vs T Allele	2.1	0.035	2.91	0.033
AT vs TT Heterozygous	0.9	0.368	1.68	0.153
AT+AA vs TT Dominant	1.2	0.23	2.18	0.081
AA vs AT+TT Recessive	0	1	-0.36	0.731
rs1800625				
CC vs TT Homozygous	0.87	0.386	0.2	0.848
C vs T Allele	0.62	0.536	0.44	0.673
CT vs TT Heterozygous	0.12	0.902	-0.14	0.896
CT+CC vs TT Dominant	0.12	0.902	0.07	0.947
CC vs CT+TT Recessive	0.12	0.902	0.16	0.881

For abbreviations see footnote of Table 2

rs1800624 (Figure 4) and the Egger's test also indicated the existence of publication bias (t=2.91, p=0.033). No publication bias was detected for rs2070600, rs1800625 and the other 4 genetic models of rs1800264.

Sensitivity analysis

A single study involved in the meta-analysis was deleted each time to assess whether the present meta-analysis is stable. The corresponding pooled ORs were not substantially altered for rs2070600 in 5 genetic models (Figure 4). For rs1800624, the significance of the pooled ORs in overall analysis was influenced in the homozygous model by studies conducted by Wang et al. [14] and the recessive model by studies conducted by Pan et al. [12] and Xu et al. [15]. No significant association was found after removal of the studies mentioned above (homozygous model OR=1.186, 95%CI:0.947-1.485; recessive model OR=1.158, 95%CI: 0.978-1.370; OR=1.080, 95%CI: 0.889-1.312). Therefore, the association of overall analysis about the homozygous and the recessive model with cancer risk should be interpreted with caution. For rs1800625, the association of overall analysis about the heterozygous model with cancer risk was changed by exclusion of the study conducted by Pan et al. [12] (OR=0.866, 95%CI: 0.750-1.000).

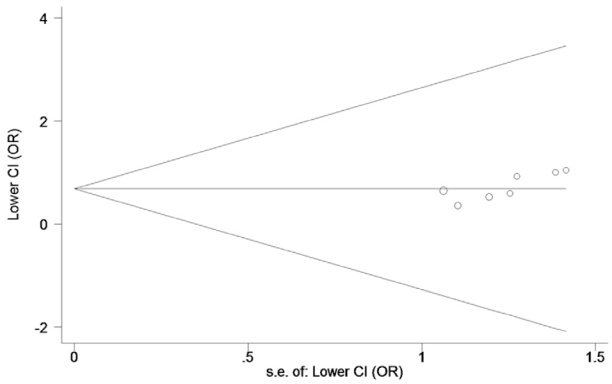

Figure 4. Begg's funnel plot with pseudo 95% confidence limits analysis to detect publication bias for contrast allele model of RAGE rs1800624 polymorphism in overall analysis. The Figure shows asymmetric Begg's funnel plot in the allele model of rs1800624.

Discussion

The objective of this meta-analysis was to investigate any possible relationship of rs2070600 G/A (82G>S), rs1800624 T/A (-374 T>A) and rs1800625C/T (-429 C>T) polymorphism in the RAGE gene with cancer susceptibility. We found that RAGE rs2070600 G/S (82G>S) polymorphism might be closely related to the pathogenesis of human cancer in Asians, indicating that rs2070600 polymorphism might be a major risk factor in hu-

man cancer development. We failed to reach an effective conclusion about the association between the rs1800624 and rs1800625 polymorphisms and cancer risk in the overall comparison. Further analysis demonstrated that rs1800264 polymorphism most likely contributed to decreased susceptibility to breast cancer but increased susceptibility to lung cancer. No significant association between rs1800625 and cancer risk was found in Caucasians.

RAGE is a member of the immunoglobulin superfamily of cell surface receptors, and its interaction with advanced glycation end products and other molecules plays a role in the pathogenesis of cancer progression and metastasis [19]. In patients with colorectal cancer and in most cell lines of gastric cancer, gallbladder cancer, prostate cancer and pancreatic cancer, the expression of RAGE increased with tumor progression, depth of tumor invasion and the presence of metastasis in lymph nodes [21-25]. On the other hand, in the cells of human non-small cell lung cancer, the expression of RAGE was decreased [26], and the induced expression of RAGE decreased the rate of growth of tumor cells [27] and limited the proliferation of lung fibroblasts [28].

Experimental studies have demonstrated that blocking RAGE signaling in mice can reduce the migration and invasiveness of tumor cells. Further studies that examined the genetic backgrounds of RAGE gene found that circulating RAGE level was largely determined by its genetic defects [7-9]. To date, more than 20 single nucleotide polymorphisms in the RAGE gene have been identified, and it is of interest to determine which genetic defects have a functional potential to affect the final bioavailability of RAGE.

For rs2070600 G/S, the results of this meta-analysis showed a positive association with the risk of cancer in Asians. We failed to detect a significant association in Caucasians, which could be partially due to the fact that only 2 studies were conducted in Caucasian populations with 465 subjects and the Tesarova's study [19] was excluded in 3 genetic models. Therefore, whether there is a relationship between rs2070600 polymorphism and cancer risk in Caucasians should be further elucidated in the future with large sample size. In the subgroup analysis by cancer type, significant association was found in lung cancer and digestive system cancers.

Heterogeneity is always a major problem in meta-analyses. In this meta-analysis, heterogeneity existed in some genetic models, so we performed a subgroup analysis 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. Other reasons for heterogeneity may be the following: (A) 4 different kinds of genotyping methods were used; (B) the control group population involved the selection of both healthy people from medical centers, and non-cancer population suffering from other diseases. More important, in the lung cancer group, Pan et al. [12] focused on all kinds of lung cancer, including small cell lung cancer, but Wang et al. [14] only focused on non-small cell lung cancer; this may be one reason for the existence of heterogeneity. Although we found some reasons for the existence of the heterogeneity, we failed to confirm our hypothesis with statistical evidence for insufficient available data. However, the corresponding pooled ORs in sensitivity analysis were not substantially altered for rs2070600 in 5 genetic models and no publication bias was found. So, we think our conclusion about rs2070600 was stable based on the existing results. Precise association needs further investigation by more individual studies with high quality.

In addition, functional studies of the rs2070600 polymorphism found that this polymorphism promoted N-linked glycosylation of Asn81, which had implications for the structure of the ligand binding region of RAGE to influence its interaction with the S108B ligand, and explains the enhanced functions associated with the rs2070600 polymorphisms [29,30]. Therefore, it is reasonable to conclude that RAGE rs2070600G/A polymorphism may play a crucial role in cancer development and progression, especially in Asians.

For rs1800624 T/A and rs1088625 T/C, we found that the corresponding pooled ORs in statistical analysis were substantially altered in some genetic models, and in stratified analysis of rs1800624 T/A polymorphism, contradictory findings about the association between rs1800624 and cancer risk have shown that rs1800624 most likely contributes to decreased susceptibility to breast cancer but increased susceptibility to lung cancer. Considering the existence of heterogeneity and publication bias, we were not able to make a sound conclusion about the association between the 2 polymorphisms and cancer risk in the overall comparison. However, in subgroup analysis by ethnicity, we found no significant association between RAGE rs1088625 polymorphisms and cancer risk in Caucasians, but these results need to be

interpreted with caution.

Interestingly, limited by its small sample size, no relationship between RAGE rs1800624 polymorphism and breast cancer risk was observed in the study by Pan et al. [11], Hashemi et al. [16], and Tesarova et al. [19]. However, our results showed that rs1800624 most likely contributes to decreased susceptibility to breast cancer. Three studies with 700 cases and 689 controls were included in the stratified analysis by cancer type. The variant genotypes of RAGE rs1800624 were related to decreased risk of breast cancer in 3 models : allele (OR=0.791, 95%CI: 0.648-0.965, p=0.021) ,heterozygous (OR=0.733, 95%CI:0.577-0.931, p=0.011) and dominant (OR=0.741, 95%CI:0.588-0.934, p=0.011). Nonetheless, the overall sample size was still limited. So more individual studies with high quality are warranted to precisely estimate the role of RAGE rs1800624 polymorphism in breast cancer considering the influence of diverse ethnicities, source of controls, and histological types.

Indeed, some advantages could be highlighted in this meta-analysis. One of the major superiority could be that the present research shed light on the relationship of genetic polymorphisms in the RAGE gene, especially the rs2070600 variant, and the increased susceptibility to human cancers. Additionally, we found that a correlation exists between rs1800624 polymorphism and breast cancer. On the other hand, some limitations of this meta-analysis should also be acknowledged when interpreting the results. Firstly, our meta-analysis was based on unadjusted estimates. If we wanted to get a precise analysis, we should get more information, such as patients'age, environmental factors, living conditions, risk factors for each cancer, genetic factors and so on, as they might influence tumorigenesis and susceptibility. Secondly, we also failed to detect a correlation between different kinds of SNPs, due to lack of information. Lack of information for the data analysis may result in confounding bias. Another major concern may be the bias due to selective publication (no publications were included other than those written in English and Chinese). What's more, all of the studies were performed in Asians and Caucasians with a small sample number. In order to capture the full range of possible ethnic differences in RAGE polymorphisms, further large sample number of studies are needed in other ethnic groups, such as among Africans. Thus, deeper investigation from different populations is needed to clarify the present results.

In summary, this meta-analysis indicated that the polymorphism of rs2070600 in the RAGE gene may increase the susceptibility to several human cancers, especially to lung cancer and in Asians. No effective conclusion has been reached about the association between the rs1800624 and rs1800625 polymorphisms and cancer risk in overall comparison. The polymorphism of rs1800264 most likely contributes to decreased susceptibility to breast cancer but to increased susceptibility to lung cancer. Rs2070600 and rs1800624 in RAGE gene may considerably function as a potential candidate of biomarker for cancer screening, diagnosis, and future target for treatments. To precisely estimate the role of RAGE polymorphisms, more individual studies with high quality are needed with larger sample size in diverse ethnic populations in the near future.

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