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

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Source of support: Departmental sources

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 (Excerpta 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

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/916260
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 χ² test. I² 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.
Flow chart of selection process for RAGE rs1800625 polymorphism and cancer risk

Potentially relevant studies identified and (n=62)

Studies excluded due to following reasons:
1. Not about polymorphism (n=8)
2. Not with cancer (n=21)
3. Not with rs1800625 (n=8)

Studies excluded due to following reasons:
1. Reviews (n=4)
2. Without control group (n=1)
3. In-sufficient frequency information (n=2)

Studies further identified in the meta-analysis (n=25)

Studies further identified in the meta-analysis (n=18)

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

| Author          | Year | Region         | Ethnicity | Cancer              | Method           | Sample size | Age Case | Age 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  |
| Yamaguchi K et al. | 2017 | Japan          | Asian     | Lung cancer         | TaqMan           | 189         | 303      | 64.3±11.0  |
| Li T et al.     | 2017 | Mainland China | Asian     | Gastric cancer      | PCR-RFLP         | 200         | 207      | 54.43±11.77 |
| Wang D et al.   | 2017 | Mainland China | Asian     | Hepatocellular carcinoma | PCR-LDR   | 540         | 540      | 51.5±6.7   |
| Yue L et al.    | 2016 | Mainland China | Asian     | Breast cancer       | PCR-LDR          | 524         | 518      | 53.76±12.62 |
| Wang H et al.   | 2015 | Mainland China | Asian     | Lung cancer         | PCR-RFLP         | 275         | 126      | 59.8±10.4  |
| Su SC et al.    | 2015 | Taiwan         | Asian     | Hepatocellular carcinoma | TaqMan   | 265         | 300      | 62.99±11.97 |
| 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      |
| Pan H et al.    | 2014 | Mainland China | Asian     | Breast cancer       | PCR-LDR          | 509         | 504      | 55.63±10.14 |
| Pan H et al.    | 2013 | Mainland China | Asian     | Lung cancer         | PCR-LDR          | 819         | 803      | 57.35±10.51 |
| 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   |
| Hashemi M et al.| 2012 | Iran           | Caucasian | Breast cancer       | ARMS-PCR         | 71          | 93       | 45.25±11.75 |
| Krechler T et al.| 2010 | Czech Republic | Caucasian | Pancreas cancer     | PCR-RFLP         | 99          | 154      | 64±11      |
| Tesarová P et al.| 2007 | Czech Republic | Caucasian | Breast cancer       | PCR-RFLP         | 120         | 92       | 61.2±11.9  |
| Tóth EK et al.  | 2007 | Hungary        | Caucasian | Colorectal cancer   | PCR-RFLP         | 183         | 141      | 65.7±10.5  |

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.
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).

### Association of the RAGE rs1800625 polymorphism and cancer risk

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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.
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

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

| Genetic model | $P_c$ | $I^2$ | 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  | 0.002| 69.6% | 1.105| 0.976, 1.252  | 0.240|
| CC vs. TT+TT  | 0.002| 56.4% | 1.397| 1.031, 1.894  | 0.031|

**Ethnicity**

| 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. TT+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. TT+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**

| Disease |       |       |      |               |      |
|---------|-------|-------|------|---------------|------|
| **Lung cancer** | 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. TT+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. TT+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.

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Figure 3. Sensitivity analysis for meta-analysis of the 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 with cancer risk.

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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.

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

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

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

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.
Conflict of interest
None.

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