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Receptor for advanced glycation end-product rs1800624 polymorphism contributes to increase breast cancer risk

Evidence from a meta-analysis

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Abstract

Background: Although several studies have identified an association between the receptor for advanced glycation end-product (RAGE) rs1800624 polymorphism and breast cancer, the results have been conflicting. Therefore, we conducted a meta-analysis to assess the relationship between the RAGE rs1800624 polymorphism and breast cancer risk.

Methods: Studies were searched in the PubMed, Web of Science, Embase, Wanfang Med Online, and China National Knowledge Infrastructure databases until September 20, 2019 to identify all potential literature on this association. Fixed-effect or random-effect models were used to calculate odds ratios (ORs) and their corresponding 95% confidence intervals (95% CIs). Subgroup and sensitivity analyses and tests for publication bias were also performed.

Results: Five eligible studies involving 2823 subjects (1410 patients and 1413 healthy controls) were included in the current meta-analysis. The pooled analysis indicated a positive correlation between the RAGE rs1800624 polymorphism and the risk of breast cancer in a homozygous genetic model (OR = 1.423, 95% CI = 1.043–1.941, $P = .026$). Ethnicity-based subgroup analysis demonstrated that RAGE rs1800624 polymorphism may increase the risk of breast cancer in the Asian population in homozygous model (OR = 1.661, 95% CI = 1.178–2.342, $P = .004$).

Conclusion: The RAGE rs1800624 polymorphism may increase the risk of breast cancer in the homozygous genetic model, especially in Asian populations. Large-scale and well-designed studies are needed in different populations to further evaluate the role of the RAGE polymorphism in breast cancer.

Abbreviations: CIs = confidence intervals, HWE = Hardy–Weinberg equilibrium, ORs = odds ratios, RAGE = receptor for advanced glycation end-product.

Keywords: breast cancer, meta-analysis, polymorphism, receptor for advanced glycation end-product gene

Highlights

- Several studies tried to investigate the associations between RAGE rs1800624 polymorphism and breast cancer. However, the results were inconsistent.
- The Purpose of the meta-analysis was to analyze the effects of RAGE rs1800624 polymorphism on susceptibility to breast cancer. As far as we know, this is so far the first meta-analysis about RAGE rs800624 polymorphism and breast cancer.
- The pooled analysis showed that the RAGE rs1800624 polymorphism increased the risk of breast cancer, especially among Asians.

1. Introduction

Breast cancer is the most malignant neoplasm among females worldwide and the commonest cause of death among women.[1,2] According to the GLOBOCAN estimates, approximately 2.09

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The datasets generated during and/or analyzed during the current study are publicly available.

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million newly diagnosed breast cancer patients and 0.63 million deaths occurred globally in 2018.[3] Breast cancer is the top cancer in women worldwide and it ranks as the first leading cause of cancer death in women. The early diagnosis of breast cancer could result in a good prognosis and a high survival rate. Because of the timely diagnosis of breast cancer, the 5-year relative survival rate of breast cancer patients is above 80% in North America.[4] Environmental and genetic factors are among the many risk factors that contribute to the development of breast cancer.[5] Genetic susceptibility plays a key role in the development of cancer. Most inherited cases of breast cancer are associated with gene mutations.

Receptor for advanced glycation end-product (RAGE), a receptor for advanced glycation end-product, is a member of the immunoglobulin superfamily, a cell surface transmembrane multiligand receptor.[6] Numerous studies have confirmed an association between RAGE expression and the malignant potential of cancer, such as pancreatic cancer,[7] prostate cancer,[8] colorectal cancer,[9] and breast cancer.[10] The RAGE rs1800624 polymorphism is located in the promoter region of the gene. RAGE–ligand interaction and their interaction with other molecules play an important role in the pathogenesis of cancer progression and metastasis.[6,11]

Recent studies have focused on the relationship between the RAGE rs1800624 polymorphism and the risk of breast cancer. Both Hashemi et al[12] and Pan et al[13] failed to detect association between the rs1800624 polymorphism and the risk of breast cancer. However, the study conducted by Feng et al[14] indicated that the correlation between rs1800624 polymorphism and breast cancer risk reduction. Accordingly, this association has not reached the same conclusion, there are still contradictions in the relevant literature. Therefore, we conducted this meta-analysis to clarify the possible association between the RAGE rs1800624 polymorphism and the risk of breast cancer.

2. Methods

2.1. Search strategy

We used the following terms to search for relevant literature in the PubMed, Web of Science, Embase, Wanfang Med Online, and China National Knowledge Infrastructure databases up to September 20, 2019: "RAGE," "receptor for advanced glycation end-product," "rs1800624," "-374T/A," "polymorphism," "single nucleotide polymorphism," "mutation," "variant," "breast cancer," "breast carcinoma," "breast malignant tumor," and "human mammary carcinoma." Two investigators (Zhang and Deng) conducted an extensive independent literature search, limited to human studies. References in articles retrieved were checked by manual retrieval to determine studies that may not be included in these databases.

2.2. Inclusion and exclusion criteria

All studies included in the meta-analysis must have met the following inclusion criteria:

(1) case–control study
(2) an investigation of the association between the RAGE rs1800624 polymorphism and breast cancer risk
(3) sufficient genotype information to calculate the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs)

The exclusion criteria were:

(1) duplicate publication
(2) review articles, letters, comments, meta-analyses, irrelevant studies

2.3. Data extraction

Information and data were extracted carefully from all the qualified independent articles by 2 authors (Zhang and Deng), based on the inclusion and exclusion criteria above. The data included the first author's name, publication year, ethnicity, country, source of controls, genotyping method, numbers of cases and controls with the RAGE genotypes, and the estimated Hardy–Weinberg equilibrium (HWE) in the controls. In order to reduce bias and improve the credibility, we have discussed and re-examined the data to reach consensus. If an agreement is not reached, then the dispute will be settled by a third reviewer (Wang).

2.4. Quality assessment

A quality assessment was conducted for all the included articles by 2 authors (Zhang and Tang) using the Newcastle–Ottawa scale.[15] The Newcastle–Ottawa scale checklist comprises 3 parameters of quality: selection, comparability, and exposure. Each article was evaluated using a score of 0 to 9. Studies with scores of 6 to 9 points were considered to be high–quality articles.

2.5. Statistical analysis

Based on the genetic model of homozygous (AA vs TT), heterozygous (AT vs TT), dominant (AA+AT vs TT), recessive (AA vs AT+TT), and allelic (A vs T), the association between the RAGE rs1800624 polymorphism and breast cancer risk was assessed using ORs and 95% CIs. As in previous studies,[16,17] a Z-test was used to assess the significance of the pooled ORs. A P value of $<.05$ indicated that the results were statistically significant. Heterogeneity was assessed using a chi-squared Q test and I^2 statistics. If $P<.10$ or $I^2>50\%$, the heterogeneity was considered significant. The random effects model (the DerSimonian and Laird method) was used to determine the outcomes in the presence of heterogeneity; otherwise, the fixed effects model (the Mantel–Haenszel method) was calculated. Sensitivity analysis was performed to determine whether the results were stable after omitting any single study. Begg funnel plot and Egger test were applied to explore publication bias.[18,19] All the tests in this meta-analysis were performed using STATA software version 12.0 (Stata Corporation, College Town, TX). All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

3. Results

3.1. Literature selection and study characteristics

Based on the search terms, 5 articles involving 2823 subjects (1410 patients and 1413 healthy controls) were identified for this meta-analysis.[12–14,20,21] The detailed process of the literature selection was shown in Figure 1, and the primary characteristics of the 5 studies were summarized in Table 1, with 3 papers focusing on Asians and 2 on Caucasians. All of these studies were

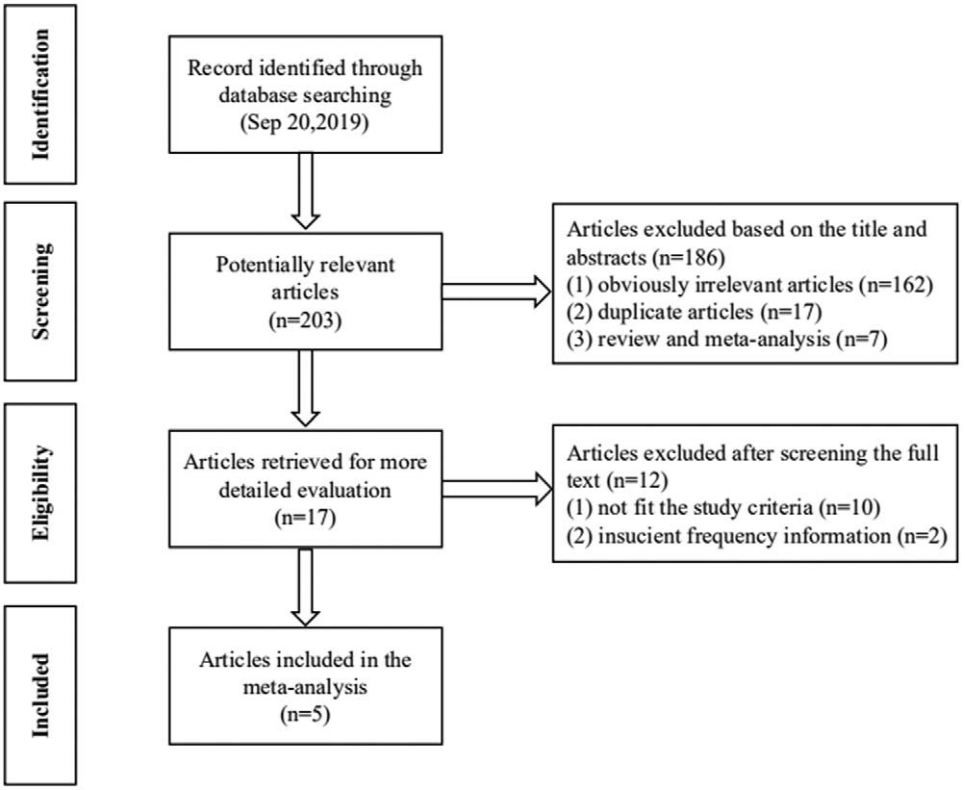

Figure 1. Flow diagram of literature search and articles selection.

hospital-based sources of control. The genotyping methods included polymerase chain reaction ligase detection reaction (PCR-LDR), polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and amplification refractory mutation system PCR (ARMS-PCR). The HWE of the controls was calculated according to the genotypes. Except for 1 article, the control group was consistent based on the HWE.[14] In terms of quality score, all articles were of high-quality.

3.2. Meta-analysis results

The results of the meta-analysis of the RAGE rs1800624 polymorphism and the risk of breast cancer were listed in Table 2. In the overall analysis, the risk of breast cancer was significantly increased in homozygous genetic model (OR = 1.423, 95% CI = 1.043–1.941, $P = .026$)(Table 2 and Fig. 2), not in the other models (heterozygous: OR = 1.022, 95% CI = 0.655–1.594, $P = 0.924$; dominant: OR = 1.034, 95% CI = 0.664–1.610, $P = .884$; recessive: OR = 1.252, 95% CI = 0.937–1.673, $P = .129$; and allelic: OR = 1.029, 95% CI = 0.736–1.439, $P = .867$). Subgroup analysis based on ethnicity showed that the RAGE rs1800624 polymorphism significantly increased the risk of breast cancer in Asians in homozygous model (OR = 1.661, 95% CI = 1.178–2.342, $P = .004$), while the breast cancer risk in Caucasians was reduced in the dominant model (OR = 0.649, 95% CI = 0.426–0.991, $P = .045$).

3.3. Sensitivity analysis and Publication bias

The control group in Feng et al study[14] inconsistent with HWE based control population (Table 1). The results of the sensitivity analysis remain unchanged whether this article is included or not. Sensitivity analysis was conducted to detect the influence of each individual study on the pooled ORs by sequentially removing 1

Table 1

Characteristics and quality assessment of the included studies.

Author (Refs.)	Year	Country	Ethnicity	Source of controls	Genotyping methods	Cases AA/AT/TT	Controls AA/AT/TT	P^*	Quality score†
Yue et al[21]	2016	China	Asian	HB	PCR-LDR	29/199/296	25/152/341	.137	8
Feng et al[14]	2015	China	Asian	HB	PCR-RFLP	71/66/51	59/59/92	<.05	7
Pan et al[13]	2014	China	Asian	HB	PCR-LDR	8/119/382	7/143/354	.077	8
Hashemi et al[12]	2012	Iran	Caucasian	HB	ARMS-PCR	3/17/49	5/33/51	.911	6
Tesarova et al[20]	2007	Czech	Caucasian	HB	PCR-RFLP	13/44/63	12/39/41/	.574	7

ARMS-PCR = amplification refractory mutation system-PCR, HB = hospital-based, PCR-LDR = PCR-ligase detection reaction, PCR-RELP = PCR-restriction fragment length polymorphism.

* HWE in the control group.

† assessed by the NOS for case-control studies.

Table 2

Meta-analysis results of overall and subgroup analysis.

Genetic model	Pooled OR (95% CI)	Heterogeneity test I^2 (%) P for Q test		Analysis model	*Z* test	*P*
Homozygous						
Overall	**1.423 (1.043–1.941)**	**42.1**	**0.141**		**2.23**	.026
Asian	**1.661 (1.178–2.342)**	**19.7**	**0.288**	FEM	**2.89**	.004
Caucasian	0.683 (0.321–1.452)	0.0	0.890		0.99	.321
Heterozygous						
Overall	1.022 (0.655–1.594)	82.9	0.000		0.09	.924
Asian	1.299 (0.752–2.246)	88.0	0.000	REM	0.94	.348
Caucasian	0.646 (0.412–1.013)	0.0	0.501		1.91	.057
Dominant						
Overall	1.034 (0.664–1.610)	84.9	0.000		0.15	.884
Asian	1.325 (0.774–2.269)	89.1	0.000	REM	1.03	.305
Caucasian	**0.649 (0.426–0.991)**	**0.0**	**0.519**		**2.00**	**.045**
Recessive						
Overall	1.252 (0.937–1.673)	0.0	0.627		1.52	.129
Asian	1.365 (0.994–1.875)	0.0	0.659	FEM	1.92	.055
Caucasian	0.798 (0.386–1.650)	0.0	0.945		0.61	.543
Allelic						
Overall	1.029 (0.736–1.439)	83.2	0.000		0.17	.867
Asian	1.233 (0.833–1.826)	87.1	0.000	REM	1.05	.296
Caucasian	0.730 (0.523–1.018)	0.0	0.518		1.85	.064

CI = confidence interval, FEM = fixed-effects model, OR = odds ratio, REM = random-effects model.

single study each time. The results indicated that the pooled ORs were stable with the removal of any study in any of the genetic models (Fig. 3).

Begg funnel plot and Egger test were conducted to estimate the publication bias in the meta-analysis. No publication bias was detected for the polymorphism in all genetic models (homozygous: $t = 2.54$, $P = .085$; heterozygous: $t = 0.48$, $P = .661$; dominant: $t = 0.58$, $P = .603$; recessive: t = 2.37, $P = .098$; allelic: t = 1,09, $P = .357$)(Fig. 4), indicating that the meta-analysis was reliable.

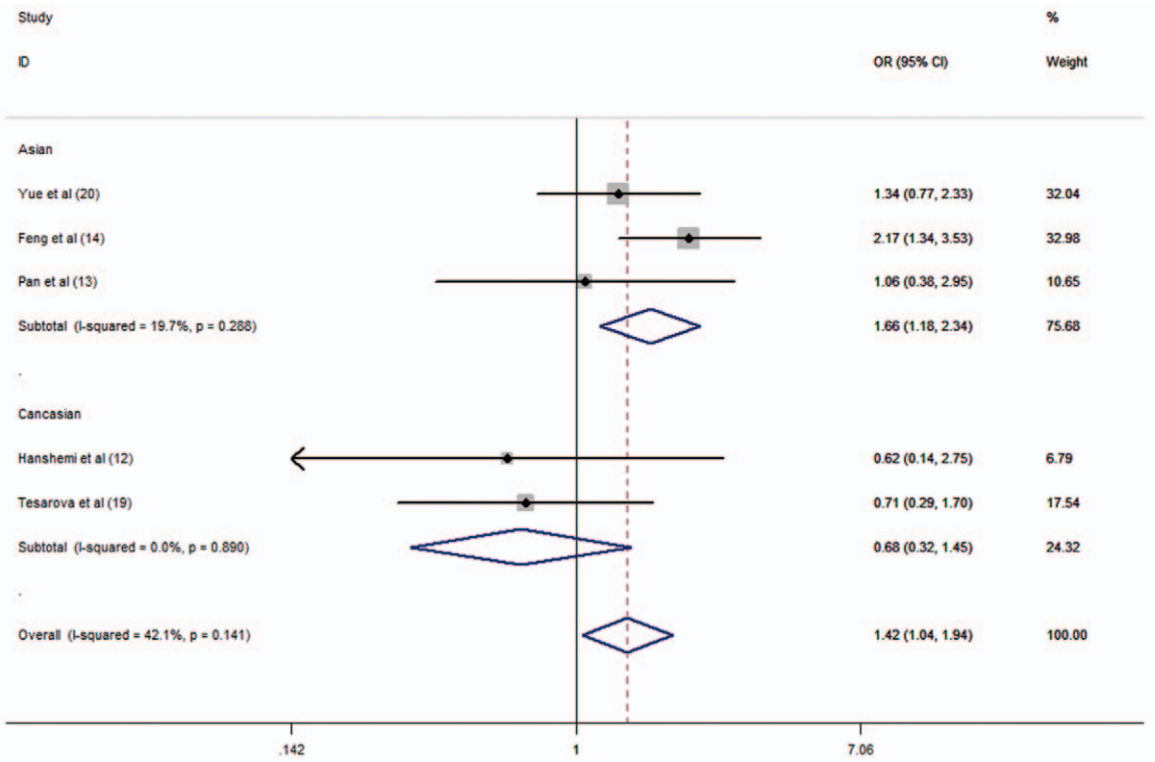

Figure 2. Forest plot of analysis for the association between rs1800624 polymorphism and breast cancer in a fixed effects model (homozygous model).

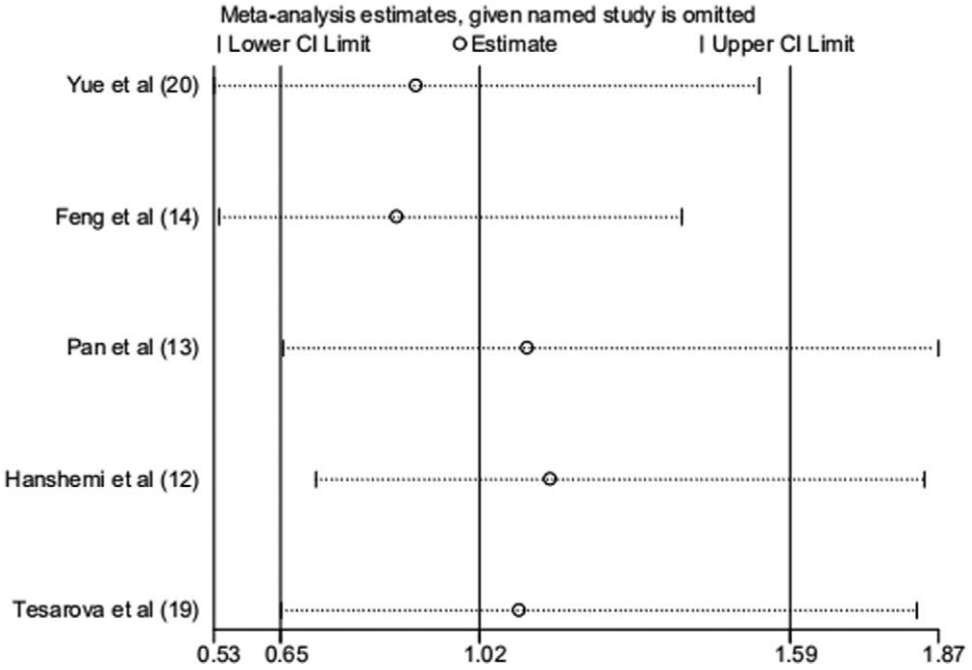

Figure 3. Sensitivity analysis for the association between rs1800624 polymorphism and breast cancer (heterozygous model).

4. Discussion

The objective of this meta-analysis was to explore any possible association between the RAGE rs1800624 polymorphism and breast cancer risk. The results indicated that the RAGE rs1800624 polymorphism may increase the risk of breast cancer in homozygous genetic model, especially in the Asian population. Unexpectedly, a weak association of Caucasians was found in the dominant genetic model through the ethnic-based subgroup analysis. The data suggested that the rs1800624 polymorphism may decrease the risk of breast cancer in the Caucasian population.

As a multiligand cell receptor, RAGE is a key component in the pathogenesis of many diseases. Genetic polymorphisms of RAGE should be considered as responsible for the development of diseases.[22,23] The genetic background of RAGE suggests that certain gene polymorphisms are associated with various pathological states. For example, in diabetes complications, the amplification of the inflammatory responses, non-small cell lung cancer, gastric cancer, and breast cancer.[6] Zhao et al[24] pointed out that the RAGE rs1800624 polymorphism stratified analysis by cancer type is most likely to lead a decrease in the susceptibility of heterozygous model, allele model, and dominant model to breast cancer. As well as Zhao et al, Xia et al[25] came to a similar conclusion after their research. As more articles and research on a larger sample size included in our study, we have obtained different results. Our data indicated that the risk of breast cancer is significantly increased in the homozygous model. After further analysis based on ethnicity, we found that the RAGE rs1800624 polymorphism may play a more important role in breast cancer risk in Asians than other populations. A number of factors may have contributed to this unique finding. First, breast cancer is a complex disease with multiple determinants, such as gender, aging, family history, reproductive factors, estrogen, and lifestyle, which are independent risk factors in breast cancer.[26–29] Second, linkage disequilibrium patterns in different ethnicities could be the possible cause for this phenomenon. Third, it is hard to draw accurate and reliable conclusions due to the various genotyping methods, different sample sizes used in these studies, and the different ethnicities. In addition, a small number of articles included in this study may also be the reason.

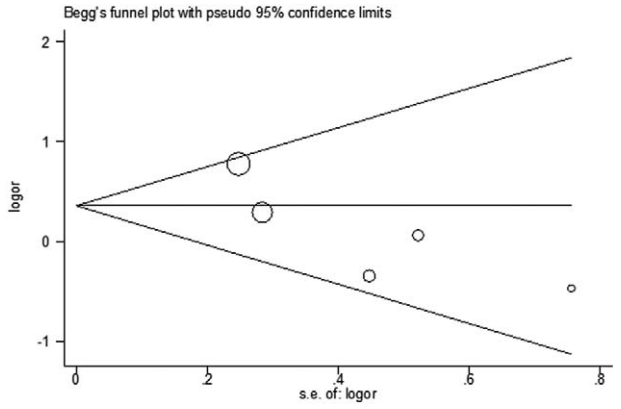

Figure 4. Funnel plot for the association between rs1800624 polymorphism and breast cancer (homozygous model).

It is important to note that the control group in the study by Feng et al[14] was inconsistent with HWE. There was no statistically significant change in the corresponding pooled ORs after omitting the article. The sensitivity analysis have shown that the pooled ORs were stable, regardless of deleting any studies in any genetic models. In addition, Begg funnel plot and Egger test showed that there was no obvious publication bias in the current

meta-analysis. Although there were some confounding factors in the included studies, our results were reliable.

The present meta-analysis has some possible limitations in interpreting the results. First, our meta-analysis consists of only 5 articles. In addition, the relatively small sample-size and different genotyping methods used in these studies may affect the accuracy of the results. Second, due to the limited number of articles, we only conducted the stratified analysis by ethnicity. Lack of genetic association in other models may be due to insufficient literature. Third, breast cancer is a complex disease with multiple determinants. As the limited original data contained in the study, we did not perform more hierarchical analysis, which could lead to a loss of significant evaluation subgroup. Finally, the number of studies incorporating the meta-analysis was less than ten, so Begg funnel plot and Egger test were not sufficient to determine the source of heterogeneity.[16] Accordingly, better-designed large-sample studies should be undertaken to deepen the investigations of different ethnic groups and thus strengthen the findings.

5. Conclusion

The findings of the meta-analysis indicated clearly that the RAGE rs1800624 polymorphism increased the risk of breast cancer, especially among Asians. Well-designed, large-scale studies of different ethnic groups are needed to accurately estimate the role of the RAGE polymorphism in breast cancer.

Author contributions

Wei Zhang drafted the manuscript. Hong Wang and Ruijun Tang performed quality assessment and data classification. Wei Zhang and Xiaowei Deng conducted statistical analysis. All authors have read and approved the final manuscript.

References

[1] Torre LA, Siegel RL, Ward EM, et al. Global cancer incidence and mortality rates and trends–an update. Cancer Epidemiol Biomarkers Prev 2016;25:16–27.

[2] Winters S, Martin C, Murphy D, et al. Breast cancer epidemiology, prevention, and screening. Prog Mol Biol Transl Sci 2017;151: 1–32.

[3] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68:394–424.

[4] Ahmad A. Breast cancer statistics: recent trends. Adv Exp Med Biol 2019;1152:1–7.

[5] Barnard ME, Boeke CE, Tamimi RM. Established breast cancer risk factors and risk of intrinsic tumor subtypes. Biochim Biophys Acta 2015;1856:73–85.

[6] Serveaux-Dancer M, Jabaudon M, Creveaux I, et al. Pathological implications of receptor for advanced glycation end-product (AGER) gene polymorphism. Dis Markers 2019;2019:2067353.

[7] Duan Z, Chen G, Chen L, et al. Determinants of concentrations of N (epsilon)-carboxymethyl-lysine and soluble receptor for advanced glycation end products and their associations with risk of pancreatic cancer. IJMEG 2014;5:152–63.

[8] Kolonin MG, Sergeeva A, Staquicini DI, et al. Interaction between tumor cell surface receptor RAGE and proteinase 3 mediates prostate cancer metastasis to bone. Cancer Res 2017;77:3144–50.

[9] Qian F, Xiao J, Gai L, et al. HMGB1-RAGE signaling facilitates Ras-dependent Yap1 expression to drive colorectal cancer stemness and development. Mol Carcinog 2019;58:500–10.

[10] Nankali M, Karimi J, Goodarzi MT, et al. Increased expression of the receptor for advanced glycation end-products (RAGE) is associated with advanced breast cancer stage. Oncol Res Treat 2016;39:622–8.

[11] Torres MC, Beltrame MH, Santos IC, et al. Polymorphisms of the promoter and exon 3 of the receptor for advanced glycation end products (RAGE) in Euro- and Afro-Brazilians. Int J Immunogenet 2012;39:155–60.

[12] Hashemi M, Moazeni-Roodi A, Arbabi F, et al. Genotyping of -374A/T, -429A/G, and 63 bp Ins/del polymorphisms of RAGE by rapid one-step hexaprimer amplification refractory mutation system polymerase chain reaction in breast cancer patients. Nucleos Nucleot Nucl 2012;31:401–10.

[13] Pan H, He L, Wang B, et al. The relationship between RAGE gene four common polymorphisms and breast cancer risk in northeastern Han Chinese. Sci Rep 2014;4:4355.

[14] Feng LJ, Liu HL, Tan Q, et al. -374T/A polymorphism of the receptor for advanced glycation end products is associated with decreased risk of breast cancer in a Chinese population. Int J Clin Exp Med 2015;8:10109–13.

[15] Zhang Y, Guo Q, Yin X, et al. Association of XPA polymorphism with breast cancer risk: A meta-analysis. Medicine 2018;97:e11276.

[16] Higgins JP, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ (Clinical research ed) 2003;327:557–60.

[17] Melsen WG, Bootsma MC, Rovers MM, et al. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect 2014;20:123–9.

[18] Yang Y, Wang W, Liu G, et al. Association of single nucleotide polymorphism rs3803662 with the risk of breast cancer. Sci Rep 2016;6:29008.

[19] Minelli C, Thompson JR, Abrams KR, et al. The choice of a genetic model in the meta-analysis of molecular association studies. Int J Epidemiol 2005;34:1319–28.

[20] Tesarova P, Kalousova M, Jachymova M, et al. Receptor for advanced glycation end products (RAGE)–soluble form (sRAGE) and gene polymorphisms in patients with breast cancer. Cancer Invest 2007;25:720–5.

[21] Yue L, Zhang Q, He L, et al. Genetic predisposition of six well-defined polymorphisms in HMGB1/RAGE pathway to breast cancer in a large Han Chinese population. J Cell Mol Med 2016;20:1966–73.

[22] Salonen KM, Ryhanen SJ, Forbes JM, et al. Circulating concentrations of soluble receptor for AGE are associated with age and AGER gene polymorphisms in children with newly diagnosed type 1 diabetes. Diabetes Care 2014;37:1975–81.

[23] Sun W, Kechris K, Jacobson S, et al. Common genetic polymorphisms influence blood biomarker measurements in COPD. PLoS Genet 2016;12:e1006011.

[24] Zhao DC, Lu HW, Huang ZH. Association between the receptor for advanced glycation end products gene polymorphisms and cancer risk: a systematic review and meta-analysis. J BUON 2015;20:614–24.

[25] Xia W, Xu Y, Mao Q, et al. Association of RAGE polymorphisms and cancer risk: a meta-analysis of 27 studies. Medical oncol 2015;32:442.

[26] Sun YS, Zhao Z, Yang ZN, et al. Risk factors and preventions of breast cancer. Int J Biol Sci 2017;13:1387–97.

[27] Jung S, Wang M, Anderson K, et al. Alcohol consumption and breast cancer risk by estrogen receptor status: in a pooled analysis of 20 studies. Int J Epidemiol 2016;45:916–28.

[28] Horn J, Vatten LJ. Reproductive and hormonal risk factors of breast cancer: a historical perspective. Int J Womens Health 2017;9:265–72.

[29] Brewer HR, Jones ME, Schoemaker MJ, et al. Family history and risk of breast cancer: an analysis accounting for family structure. Breast Cancer Res Treat 2017;165:193–200.