Systematic evaluation of cancer risk associated with rs2292832 in miR-149 and rs895819 in miR-27a: a comprehensive and updated meta-analysis

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Keywords: miR-149, miR-27a, cancer, susceptibility, systematic evaluation

Received: November 05, 2015 Accepted: February 24, 2016 Published: March 14, 2016

ABSTRACT

The aim of this study is to provide a precise quantification for the association between miR-149 T > C (rs2292832) and miR-27a A > G (rs895819) and the risk of cancer. We conducted a systematic literature review and evaluated the quality of included studies based on Newcastle-Ottawa Scale (NOS). Pooled odds ratios (ORs) and corresponding 95% confidence intervals (95% CIs) were calculated to assess the strengths of the associations. We identified 40 studies for pooled analyses. Overall, the results demonstrated that the rs2292832 polymorphism was subtly decrease the risk of breast cancer (CT + CC vs TT: OR = 0.83, 95% CI: 0.70–0.98, P = 0.03; CC vs CT + TT: OR = 0.80, 95% CI: 0.68–0.93, P = 0.00), and the rs895819 polymorphism was associated with significantly increased cancer risk in the Asian population (AG + GG vs AA: OR = 1.24, 95% CI: 1.03–1.50, P = 0.02) and in colorectal cancer subgroup (GG vs AA: OR = 1.45, 95% CI: 1.10–1.92, P = 0.00; AG + GG vs AA: OR = 1.35, 95% CI: 1.15–1.58, P = 0.00; GG vs AG + AA: OR = 1.36, 95% CI: 1.04–1.77, P = 0.02). In addition, a subtly decreased risk was observed in the Caucasian population and in breast cancer subgroup. In conclusion, the rs2292832 polymorphism was significantly associated with increased breast cancer risk, and the rs895819 polymorphism contributes to the susceptibility of colorectal and breast cancer.

INTRODUCTION

MicroRNAs (miRNAs) are a group of short noncoding RNAs of about 22 nucleotides which are involved in diverse physiological and developmental processes by controlling the gene expression of target mRNAs [1, 2]. Accumulating evidence has shown that miRNAs regulate the expression of roughly 10–30% of the all human genes through post-transcriptional mechanisms [3], contributing to excessive physiologic and pathologic conditions, including cell differentiation, apoptosis, development, and deregulation of these processes play critical roles in carcinogenesis [4].
studied in diverse cancers. Research results about two sites were inconsistent [9, 10], this discrepancy maybe partially attributed to the heterogeneity of the cancer subtype, small sample size, and ethnicity of the patients.

To further determine whether there is an association of the rs2292832 and rs895819 in the miRNA genes with the risk for developing cancer, a comprehensive review and analysis of published data from different studies is needed. In this study, we performed a meta-analysis on all eligible case-control studies to drive a more powerful estimation of the association of rs2292832 and rs895819 SNP with cancer risks.

RESULTS

Study characteristics

The search process and the final selection of relevant studies are shown in Figure 1. A comprehensive literature search yielded 348 potentially relevant published articles. After further identification and screening individual study, 43 articles (49 studies) [11–53] underwent full-text assessment, and 6 articles (10 studies, not including one site according to HWE) [14, 17, 19, 20, 35, 42] were excluded due to inconsistently with HWE. Finally, 37 articles (40 studies) [11–13, 15, 16, 18, 21–34, 36–41, 43–53] were conducted in quantitative synthesis.

Characteristics of included studies are presented in Table 1. A total of 39 eligible studies met the prespecified inclusion criteria, in which two articles [24, 52] included two tumor types respectively, and one article included [23] rs2292832 and rs895819. As for rs2292832, involving 9,994 cases and 10,757 controls were ultimately analyzed from 21 studies (20 articles) [11–13, 15, 16, 18, 21–34], and 19 studies (17 articles) [23, 36–41, 43–53] involving 7,800 cases and 9,060 controls for rs895819.

All studies were case-control studies, including 40 studies on 10 breast cancer, 7 gastric cancer, 7 colorectal cancer, 4 lung cancer, and 12 on other cancer types. There were 28 studies of Asian descendant, 11 of Caucasian descendant. A classic PCR-RFLP assay was used in 17 out of 40 studies, the other molecular genotyping methods, such as Taqman, MassARRAY, and HRM, were used in other studies. 32 studies were randomly repeated a portion of samples as quality control while genotyping.

Quality assessment

According to the NOS for quality of case-control, the study-specific quality scores are summarized in Table 2. A star system of the NOS (range, 0–9 scores) has been developed for the evaluation, and the quality scores ranged from 4 to 8. The average scores of case-control studies were 6.49.

Quantitative data synthesis

For all of control subjects included in this study, the frequencies of risk C allele in rs2292832 for Caucasians and Asians were 33.66% (Mean ± SEM, 33.66% ± 2.18%) and 50.20% (Mean ± SEM, 50.20% ± 12.34%) (Figure 2A). The frequencies of risk G allele in rs895819 for Caucasians and Asians were 30.78% (Mean ± SEM, 30.78% ± 2.04%) and 29.63% (Mean ± SEM, 29.63% ± 1.45%) (Figure 2B). The frequencies of risk C allele in rs2292832 varied greatly among different control populations (P = 0.00).

For the rs2292832 polymorphism, no significant risk association was observed in the overall pooled analysis (Table 3, Figure 3). When grouped by the cancer types, significant associations were found in breast cancer (CT + CC vs TT: OR = 0.83, 95% CI: 0.70–0.98, P = 0.03; CC vs CT + TT: OR = 0.80, 95% CI: 0.68–0.93, P = 0.00) (Table 4).

For the rs895819 polymorphism, we failed to find any associations between rs895819 polymorphism and cancer risk (Table 3, Figure 4). In the subgroup analysis by ethnicity, statistically significantly reduced cancer risks were found among Asian for dominant contrast (AG + GG vs AA: OR = 1.24, 95% CI: 1.03–1.50, P = 0.02) (Table 5). In contrast, a subtly decreased risk was observed in the Caucasian population (G vs A: OR = 0.92, 95% CI: 0.85–0.99, P = 0.03; AG vs AA: OR = 0.92, 95% CI: 0.85–0.99, P = 0.00) (Table 4). Subgroup analysis by cancer types revealed a decreased risk in breast cancer (G vs A: OR = 0.92, 95% CI: 0.86–0.99, P = 0.03; AG vs AA: OR = 0.83, 95% CI: 0.75–0.92, P < 0.01; AG + GG vs AA: OR = 0.88, 95% CI: 0.80–0.97, P = 0.01), whereas a significantly increased risk was observed in colorectal cancer (GG vs AA: OR = 1.45, 95% CI: 1.10–1.92, P < 0.01; AG + GG vs AA: OR = 1.35, 95% CI: 1.15–1.58, P < 0.01; GG vs AG + AA: OR = 1.36, 95% CI: 1.04–1.77, P = 0.02) (Table 5).

Test of heterogeneity

In the overall pooled analysis, the results showed that both rs2292832 and rs895819 had heterogeneity in part of genotype with P value less than 0.05. Therefore, we analyzed the summary ORs with random-effect models if the heterogeneity existed. Fixed-effect models were used to analyze the summary odds ratios for the rest. Subsequently, meta regression in Stata12.0 was used to assess the source of heterogeneity for rs2292832 and rs895819, including publication year, ethnicity (Asians, Caucasians), cancer type, matched controls (yes or not), language (English or Chinese), source of control (hospital or population), assay, sample size (300 as the boundary) and quality control (with or without). It was detected that the systemic results were not altered by these characteristics (Table 6).
Evaluation of publication bias

Begg’s funnel plot and Egger’s test (Table 7) were performed to assess the publication bias of the currently available literature. The shape of the funnel plots did not reveal any evidence of obvious asymmetry in all comparison models (Figure 5 and Figure 6).

Sensitivity analysis

A single study included in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially changed (data not shown).

DISCUSSION

In the present study, an association between the two common SNPs in microRNAs (rs2292832 and rs895819) and cancer risk was evaluated by the pooled results from 40 published studies. The results demonstrated that the rs2292832 was associated with a significantly reduced risk for developing cancer in the breast cancer (dominant and recessive model), and for the rs895819 G allele, AG genotype and dominant model were associated with a decreased risk for Caucasian population and breast cancer, in contrast, a subtly increased risk was observed in a Asian population (dominant model) and colorectal cancer (GG genotype, dominant model and recessive model).

Figure 1: Flow chart of literature search and study selection.
Table 1: Main characteristics of included studies

| First author | Year | Ethnicity | Cancer type | Source of control | Genotyping | Match* | Sample size | $P_{\text{HWE}}$ | $Y/N$ | Case/Control | Source of control |
|--------------|------|-----------|-------------|-------------------|------------|--------|-------------|-----------------|-------|--------------|------------------|
| He BS [11]   | 2015 | Asian     | Breast cancer | Population       | MassARRAY  | Y      | 450/450     | 0.13            |       |              |                   |
| Du ML [12]   | 2014 | Asian     | Renal cell cancer | Population     | TaqMan     | Y      | 355/362     | 0.46            |       |              |                   |
| Dikeakos P [13] | 2014 | Caucasian | Gastric cancer | Hospital      | PCR-RFLP   | Y      | 163/480     | 0.45            |       |              |                   |
| Pu JY [14]   | 2014 | Asian     | Gastric cancer | Hospital      | PCR-RFLP   | N      | 220/530     | < 0.01          |       |              |                   |
| Wei WJ [15]  | 2014 | Asian     | PTC          | Population     | MassARRAY  | Y      | 838/1006    | 0.73            |       |              |                   |
| Wang R [16]  | 2014 | Asian     | HCC          | Population     | MassARRAY  | N      | 944/984     | 0.86            |       |              |                   |
| Wu RR [17]   | 2014 | Asian     | Colorectal cancer | Hospital    | ASA       | N      | 175/300     | < 0.01          | 0.02  | Y            |                   |
| Huang GL [18] | 2013 | Asian     | NPC          | Population     | PCR-RFLP   | N      | 158/242     | 0.72            |       |              |                   |
| Chu YH [19]  | 2013 | Asian     | HCC          | Population     | PCR-RFLP   | N      | 188/337     | < 0.01          |       |              |                   |
| Lv M [20]    | 2013 | Asian     | Colorectal cancer | Population  | PCR-RFLP  | N      | 353/540     | < 0.01          |       |              |                   |
| Song XC [21] | 2013 | Caucasian | OSCC        | Population     | PCR-RFLP  | Y      | 325/335     | 0.99            |       |              |                   |
| Tu HF [22]   | 2012 | Asian     | HNSCC        | Hospital      | PCR-RFLP   | N      | 122/273     | 0.27            |       |              |                   |
| Zhang M [23] | 2012 | Asian     | Breast Cancer | Population    | PCR-RFLP  | Y      | 252/248     | 0.21            | 0.12  | Y            |                   |
| Zhang MW(C) [24] | 2012 | Asian     | Colorectal Cancer | Population | PCR-RFLP  | Y      | 443/435     | 0.43            |       |              |                   |
| Zhang MW(G) [24] | 2012 | Asian     | Gastric Cancer | Population   | PCR-RFLP  | Y      | 274/269     | 0.70            |       |              |                   |
| Min KT [25]  | 2012 | Asian     | Colorectal Cancer | Population   | PCR-RFLP  | N      | 446/502     | 0.62            |       |              |                   |
| Ahn DH [26]  | 2012 | Asian     | Gastric Cancer | Population     | PCR-RFLP  | N      | 461/447     | 0.98            |       |              |                   |
| Kim WH [27]  | 2012 | Asian     | HCC          | Population     | PCR-RFLP  | N      | 159/201     | 0.34            |       |              |                   |
| Vinci S [28] | 2013 | Caucasian | Colorectal Cancer | Population  | HRM       | Y      | 160/178     | 0.91            |       |              |                   |
| Vinci S [29] | 2011 | Caucasian | Lung Cancer  | Population     | HRM       | Y      | 101/129     | 0.97            |       |              |                   |
| Li PY [30]   | 2011 | Asian     | NPC          | Hospital      | TaqMan     | Y      | 791/1016    | 0.49            |       |              |                   |
| Zhang MW [31] | 2011 | Asian     | Lung Cancer  | Population     | PCR-RFLP  | Y      | 232/231     | 0.12            |       |              |                   |
| Liu ZS [32]  | 2010 | Caucasian | HNSCC       | Population     | PCR-RFLP  | Y      | 1109/1130   | 0.72            |       |              |                   |
| Tian T [33]  | 2009 | Asian     | Lung Cancer  | Population     | PCR-RFLP  | Y      | 1058/1035   | 0.86            |       |              |                   |
| Wang ZW [34] | 2009 | Asian     | Breast Cancer | Population   | PCR-RFLP  | Y      | 1009/1093   | 0.16            |       |              |                   |
| Ma JY [35]   | 2015 | Asian     | NSCC         | Population     | TaqMan     | Y      | 542/557     | 0.02            |       |              |                   |
| Qi P [36]    | 2015 | Asian     | Breast cancer | Population     | TaqMan     | Y      | 321/290     | 0.69            |       |              |                   |
| Yin ZH [37]  | 2015 | Asian     | Lung Cancer  | Hospital       | TaqMan     | Y      | 258/310     | 0.70            |       |              |                   |
Thus far, for the rs2292832, no significant association was observed in overall pooled results [54, 55]. In contrast to the published results, this study revealed the different association between rs2292832 polymorphism and breast cancer risk. This suggests that the molecular mechanisms underlying the genetic associations of miRNA-SPNs with cancer are complex and vary by cancer site. Considering the influence of the T allele in rs2292832 might be masked by the presence of other as-yet unidentified causal genes involved in cancer development on this polymorphism [56], our results should be interpreted with caution, and more studies will need to be analyzed to confirm the results.

The rs895819 is well recognized to be involved in the pathogenesis, metastasis, and invasion of multiple cancer types, by functioning as an oncogene via complex mechanisms [57–59]. The rs895819, as an oncomiR, exhibited its oncogenic activity through regulating target genes [60, 61]. It means that down-regulation of miR-27a may contribute to decreased cancer risk through up-regulating the targets. Although the binding of the mature miRNA to target mRNAs was not influenced by the rs895819 [62], some published studies had demonstrated that polymorphisms in premiRNAs could influence the expression of their mature forms, as well as were involved in the binding of some nuclear factors in miRNA processing [63]. Therefore, we presumed that rs895819 affected the processing or/and expression of miR-27a, which resulted in down-regulation of miR-27a. The presumption was supported by our findings in breast cancer subgroup.

This comprehensive and updated meta-analysis further support the rs895819 G allele was associated with a decreased risk for breast cancer, whereas a subtly
Table 2: Quality assessment of included studies based on the Newcastle-Ottawa scale

| Study          | Selection (score) | Comparability (score) | Exposure (score) | Same method of ascertainment for participants | Non-response rate | Total score |
|----------------|-------------------|-----------------------|------------------|-----------------------------------------------|------------------|------------|
| Adequate definition of patient case | Representativeness of patients cases | Definition of control | Control for important factor or additional factor | Ascertainment of exposure (blinding) |                        |            |
| He BS [11]    | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Du ML [12]    | 1                 | 1                     | 1                | 1                                             | 1                | 2          | 0           | 1           | 7           |
| Dikeakos P [13]| 1                 | 1                     | 0                | 1                                             | 2                | 0          | 1           | 1           | 7           |
| Wei WJ [15]   | 1                 | 1                     | 1                | 1                                             | 1                | 2          | 0           | 1           | 7           |
| Wang R [16]   | 1                 | 1                     | 0                | 1                                             | 0                | 1          | 1           | 0           | 5           |
| Huang GL [18] | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Song XC [21]  | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 1           | 8           |
| Tu HF [22]    | 1                 | 1                     | 0                | 1                                             | 2                | 0          | 1           | 0           | 6           |
| Zhang M [23]  | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Zhang MW [24] | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Min KT [25]   | 1                 | 1                     | 1                | 1                                             | 1                | 0          | 1           | 0           | 7           |
| Aho DH [26]   | 1                 | 1                     | 1                | 2                                             | 0                | 0          | 1           | 0           | 7           |
| Kim WH [27]   | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Vinci S [28]  | 1                 | 1                     | 1                | 1                                             | 1                | 0          | 1           | 0           | 6           |
| Vinci S [29]  | 1                 | 1                     | 0                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Li PY [30]    | 1                 | 1                     | 0                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Zhang MW [31] | 1                 | 1                     | 1                | 1                                             | 1                | 2          | 0           | 1           | 0           | 7           |
| Liu ZS [32]   | 1                 | 1                     | 1                | 2                                             | 0                | 0          | 1           | 1           | 8           |
| Tian T [33]   | 1                 | 1                     | 1                | 2                                             | 0                | 0          | 1           | 0           | 7           |
| Wang ZW [34]  | 1                 | 1                     | 1                | 1                                             | 1                | 0          | 1           | 0           | 6           |
| Qi P [36]     | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Yin ZH [37]   | 1                 | 1                     | 0                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Cao Y [38]    | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Kupcinskas J (C) [39] | 1       | 1                     | 0                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Kupcinskas J (G) [40] | 1       | 1                     | 0                | 1                                             | 2                | 0          | 1           | 0           | 6           |
| Song B [41]   | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Zhang JJ [42] | 1                 | 1                     | 1                | 1                                             | 2                | 0          | 1           | 0           | 7           |
| Zhang N [43]  | 1                 | 1                     | 1                | 1                                             | 1                | 2          | 0           | 1           | 0           | 7           |
| Catsu I [44]  | 1                 | 1                     | 0                | 1                                             | 1                | 0          | 1           | 0           | 5           |
| Hezova R [45] | 1                 | 1                     | 1                | 1                                             | 1                | 0          | 1           | 0           | 6           |
| Shi DN [46]   | 1                 | 1                     | 1                | 2                                             | 0                | 0          | 1           | 0           | 7           |
| Zhang MW [47] | 1                 | 1                     | 1                | 1                                             | 1                | 0          | 1           | 0           | 5           |
A comprehensive literature search was conducted using the PubMed, Springer, Elsevier, CNKI (Chinese), and Wanfang (Chinese) Digital Dissertations Databases for relevant articles published in English or Chinese up to July 2015 with key words ‘microRNA/miR-149/miR-27a’, ‘rs2292832/rs895819’, ‘polymorphism’, and ‘cancer’. The full text of the candidate articles were examined carefully to determine whether they accorded with the inclusion criteria for the meta-analysis. The present study was conducted in accordance with PRISMA guidelines [66].

The inclusion criteria were as follows: 1) about the rs2292832/rs895819 polymorphisms and cancer risk, 2) based on case-control studies (including cohort studies), 3)
Table 3: Main results of pooled ORs of the rs2292832 and rs895819 polymorphisms on cancer risk in the meta-analysis

| comparisons     | Cases n/N | Controls n/N | Heterogeneity test | Summary OR (95% CI) | Hypothesis test | Studies |
|-----------------|-----------|--------------|--------------------|---------------------|-----------------|---------|
| rs2292832       |           |              |                    |                     |                 |         |
| C vs T          | 7995/19596 | 8591/20464  | 20.34              | 0.93 (0.84,1.06)    | 0.52            | 20      |
| CT vs TT        | 4129/7759 | 4611/8511   | 23.96              | 0.95 (0.89,1.01)    | 1.58            | 20      |
| CC vs TT        | 1910/5536 | 2020/5820   | 21.82              | 0.97 (0.82,1.14)    | 0.40            | 20      |
| CT + CC vs TT   | 6039/9669 | 6650/10550 | 32.71              | 0.93 (0.85,1.01)    | 0.68            | 20      |
| CC vs CT + TT   | 2068/9994 | 2182/10757 | 47.55              | 1.00 (0.88,1.14)    | 0.08            | 21      |
| rs895819        |           |              |                    |                     |                 |         |
| G vs A          | 4725/15804 | 5412/17610  | 43.16              | 0.99 (0.91,1.17)    | 0.09            | 19      |
| AG vs AA        | 3179/7062 | 3692/7976   | 30.95              | 0.99 (0.88,1.12)    | 0.19            | 19      |
| GG vs AA        | 798/4681 | 873/5217    | 27.45              | 1.07 (0.91,1.26)    | 0.80            | 19      |
| AG + GG vs AA   | 3987800 | 4464/9060  | 42.79              | 1.13 (0.97,1.31)    | 1.55            | 19      |
| GG vs AG + AA   | 798/7770 | 873/8911    | 37.20              | 1.06 (0.90,1.25)    | 0.69            | 19      |

Figure 3: Forest plot of cancer risk associated with rs2292832 for the recessive model (CT vs TT). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study specific weight. The diamond represents the pooled OR and 95% CI.
Table 4: Stratified analyses of rs2292832 polymorphism on cancer risk

| Comparisons          | Heterogeneity test | Summary OR (95% CI) | Hypothesis test | Studies |
|----------------------|--------------------|---------------------|-----------------|---------|
|                      | Q   | P  | F(%) | OR          | Z  | P  |         |         |
| **Ethnic**           |      |    |      |             |    |    |         |         |
| **Asian**            |      |    |      |             |    |    |         |         |
| C vs T               | 51.04 | < 0.01 | 49 | 0.90 (0.81,1.01) | 1.86 | 0.06 | 16 |
| CT vs TT             | 18.78 | 0.22 | 20 | 0.94 (0.88,1.01) | 1.70 | 0.09 | 16 |
| CC vs TT             | 33.84 | 0.01 | 41 | 0.93 (0.78,1.11) | 0.79 | 0.43 | 16 |
| CT + CC vs TT        | 3.93  | 0.02 | 44 | 0.94 (0.87,1.03) | 1.31 | 0.19 | 16 |
| CC vs CT + TT        | 32.41 | 0.02 | 38 | 1.00 (0.88,1.14) | 0.08 | 0.94 | 16 |
| **Caucasian**        |      |    |      |             |    |    |         |         |
| C vs T               | 2.55  | 0.28 | 22 | 1.06 (0.84,1.33) | 0.47 | 0.63 | 4  |
| CT vs TT             | 4.73  | 0.19 | 37 | 1.02 (0.82,1.25) | 0.14 | 0.89 | 4  |
| CC vs TT             | 10.45 | 0.02 | 61 | 1.16 (0.67,2.01) | 0.54 | 0.59 | 4  |
| CT + CC vs TT        | 6.09  | 0.11 | 11 | 1.08 (0.88,1.31) | 0.72 | 0.47 | 4  |
| CC vs CT + TT        | 8.12  | 0.09 | 51 | 1.10 (0.86,1.41) | 0.79 | 0.43 | 5  |
| **Cancer types**     |      |    |      |             |    |    |         |         |
| **Colorectal Cancer**|      |    |      |             |    |    |         |         |
| C vs T               | 0.79  | 0.67 | 0   | 0.97 (0.85,1.10) | 0.48 | 0.63 | 3  |
| CT vs TT             | 0.02  | 0.99 | 0   | 0.85 (0.71,1.02) | 1.72 | 0.09 | 3  |
| CC vs TT             | 1.02  | 0.60 | 0   | 0.94 (0.71,1.25) | 0.42 | 0.68 | 3  |
| CT + CC vs TT        | 1.12  | 0.57 | 0   | 0.87 (0.67,1.15) | 0.97 | 0.33 | 3  |
| CC vs CT + TT        | 0.32  | 0.96 | 0   | 1.13 (0.97,1.33) | 1.56 | 0.12 | 3  |
| **Lung Cancer**      |      |    |      |             |    |    |         |         |
| C vs T               | 3.65  | 0.16 | 45 | 0.97 (0.86,1.08) | 0.63 | 0.53 | 3  |
| CT vs TT             | 1.99  | 0.37 | 0   | 0.86 (0.67,1.11) | 1.14 | 0.25 | 3  |
| CC vs TT             | 4.43  | 0.11 | 55 | 0.93 (0.73,1.20) | 0.53 | 0.60 | 3  |
| CT + CC vs TT        | 1.62  | 0.44 | 0   | 1.03 (0.83,1.28) | 0.25 | 0.80 | 3  |
| CC vs CT + TT        | 3.28  | 0.19 | 39 | 0.96 (0.83,1.12) | 0.48 | 0.63 | 3  |
| **Breast Cancer**    |      |    |      |             |    |    |         |         |
| C vs T               | 13.72 | < 0.01 | 55 | 0.82 (0.61,1.10) | 1.31 | 0.19 | 3  |
| CT vs TT             | 2.19  | 0.33 | 9   | 0.86 (0.72,1.03) | 1.64 | 0.10 | 3  |
| CC vs TT             | 5.81  | 0.55 | 46 | 0.82 (0.65,1.03) | 1.73 | 0.08 | 3  |
| CT + CC vs TT        | 2.72  | 0.26 | 26 | 0.83 (0.70,0.98) | 2.18 | 0.03 | 3  |
| CC vs CT + TT        | 2.82  | 0.24 | 29 | 0.80 (0.68,0.93) | 2.81 | 0.00 | 3  |
| **Other cancers**    |      |    |      |             |    |    |         |         |
| C vs T               | 13.42 | 0.06 | 45 | 0.91 (0.78,1.05) | 1.29 | 0.20 | 11 |
| CT vs TT             | 19.35 | 0.04 | 48 | 0.96 (0.85,1.08) | 0.75 | 0.45 | 11 |
| CC vs TT             | 16.28 | 0.02 | 57 | 1.06 (0.83,1.35) | 0.47 | 0.64 | 11 |
| CT + CC vs TT        | 13.67 | 0.09 | 41 | 1.06 (0.96,1.16) | 1.17 | 0.24 | 11 |
| CC vs CT + TT        | 5.98  | 0.54 | 0   | 1.18 (1.06,1.31) | 3.14 | 0.00 | 12 |
| **Source of control**|      |    |      |             |    |    |         |         |
| C vs T               | 78.91 | < 0.01 | 60 | 0.92 (0.83,1.02) | 1.53 | 0.13 | 17 |
| CT vs TT             | 20.50 | 0.20 | 22 | 0.95 (0.88,1.01) | 1.59 | 0.11 | 17 |
| CC vs TT     | 29.47 | 0.02 | 46  | 1.00 (0.86,1.16) | 0.04 | 0.97 | 17 |
| CT + CC vs TT| 26.00 | 0.05 | 38  | 0.96 (0.90,1.03) | 1.06 | 0.29 | 17 |
| CC vs CT + TT| 27.06 | 0.06 | 38  | 1.01 (0.94,1.10) | 0.32 | 0.75 | 18 |

Hospital

| C vs T       | 13.71 | 0.01 | 65  | 0.97 (0.68,1.38) | 0.17 | 0.86 | 3  |
| CT vs TT     | 3.34  | 0.19 | 40  | 0.98 (0.83,1.15) | 0.30 | 0.77 | 3  |
| CC vs TT     | 17.29 | < 0.01 | 68  | 0.83 (0.64,2.03) | 0.40 | 0.69 | 3  |
| CT + CC vs TT| 7.75  | 0.02 | 64  | 0.99 (0.69,1.43) | 0.05 | 0.96 | 3  |
| CC vs CT + TT| 15.24 | < 0.01 | 67  | 0.82 (0.57,1.80) | 0.49 | 0.62 | 3  |

Sample size

| ≥ 300 |
|-------|
| C vs T     | 76.76 | < 0.01 | 66  | 0.99 (0.87,1.12) | 0.19 | 0.85 | 12 |
| CT vs TT    | 12.83 | 0.30 | 14  | 0.99 (0.92,1.06) | 0.34 | 0.74 | 12 |
| CC vs TT    | 35.77 | < 0.01 | 59  | 1.04 (0.86,1.26) | 0.42 | 0.68 | 12 |
| CT + CC vs TT| 21.90 | 0.03 | 50  | 1.00 (0.91,1.10) | 0.04 | 0.97 | 12 |
| CC vs CT + TT| 30.33 | < 0.01 | 64  | 1.03 (0.90,1.19) | 0.47 | 0.64 | 13 |

| < 300 |
|-------|
| C vs T     | 7.50  | 0.38 | 7   | 0.92 (0.94,1.11) | 1.88 | 0.06 | 8  |
| CT vs TT    | 4.34  | 0.74 | 0   | 0.89 (0.78,1.02) | 1.74 | 0.08 | 8  |
| CC vs TT    | 12.99 | 0.07 | 46  | 0.82 (0.65,1.04) | 1.66 | 0.10 | 8  |
| CT + CC vs TT| 5.03  | 0.66 | 0   | 0.90 (0.80,1.03) | 1.70 | 0.09 | 8  |
| CC vs CT + TT| 13.13 | 0.07 | 47  | 0.93 (0.75,1.14) | 0.73 | 0.47 | 8  |

Figure 4: Forest plot of cancer risk associated with rs895819 for the GG vs AA compared with the AA genotype.
| Ethnic          | Comparisons      | Q     | P     | F(%) | Summary OR (95% CI) | Hypothesis test | Studies |
|-----------------|------------------|-------|-------|------|----------------------|-----------------|---------|
|                 |                  |       |       |      |                      |                 |         |
| Asian           | G vs A           | 34.11 | < 0.01 | 68   | 1.02 (0.91,1.14)     | 0.27            | 0.79    | 12      |
|                 | AG vs AA         | 27.19 | 0.01  | 60   | 1.09 (0.95,1.26)     | 1.25            | 0.21    | 12      |
|                 | GG vs AA         | 24.68 | 0.01  | 55   | 1.09 (0.87,1.37)     | 0.73            | 0.47    | 12      |
|                 | AG + GG vs AA    | 53.69 | < 0.01 | 80   | 1.24 (1.03,1.50)     | 2.28            | 0.02    | 12      |
|                 | GG vs AG + AA    | 30.73 | < 0.01 | 64   | 1.03 (0.81,1.31)     | 0.25            | 0.80    | 12      |
| Caucasian       | G vs A           | 6.91  | 0.33  | 13   | 0.92 (0.86,0.99)     | 2.27            | 0.02    | 7       |
|                 | AG vs AA         | 7.70  | 0.26  | 22   | 0.81 (0.73,0.89)     | 3.82            | 0.00    | 7       |
|                 | GG vs AA         | 6.74  | 0.35  | 11   | 0.95 (0.80,1.12)     | 0.65            | 0.51    | 7       |
|                 | AG + GG vs AA    | 4.17  | 0.65  | 0    | 0.87 (0.79,0.95)     | 2.69            | 0.00    | 7       |
|                 | GG vs AG + AA    | 6.47  | 0.37  | 7    | 1.03 (0.88,1.02)     | 0.34            | 0.74    | 7       |
| Breast cancer   | G vs A           | 8.76  | 0.12  | 43   | 0.92 (0.86,0.99)     | 2.15            | 0.03    | 6       |
|                 | AG vs AA         | 11.41 | 0.04  | 56   | 0.83 (0.75,0.92)     | 3.51            | 0.00    | 6       |
|                 | GG vs AA         | 1.17  | 0.95  | 0    | 0.90 (0.76,1.07)     | 1.21            | 0.23    | 6       |
|                 | AG + GG vs AA    | 5.80  | 0.33  | 14   | 0.88 (0.80,0.97)     | 2.58            | 0.01    | 6       |
|                 | GG vs AG + AA    | 2.40  | 0.79  | 0    | 0.98 (0.84,1.15)     | 0.24            | 0.81    | 6       |
| Gastric cancer  | G vs A           | 16.96 | 0.00  | 62   | 1.11 (0.84,1.46)     | 0.70            | 0.48    | 4       |
|                 | AG vs AA         | 10.15 | 0.02  | 50   | 1.08 (0.80,1.47)     | 0.50            | 0.42    | 4       |
|                 | GG vs AA         | 15.44 | 0.00  | 60   | 1.05 (0.55,1.99)     | 0.15            | 0.88    | 4       |
|                 | AG + GG vs AA    | 13.52 | 0.00  | 58   | 1.10 (0.79,1.53)     | 0.55            | 0.58    | 4       |
|                 | GG vs AG + AA    | 12.52 | 0.01  | 56   | 1.02 (0.59,1.76)     | 0.07            | 0.94    | 4       |
| Colorectal Cancer | G vs A       | 1.78  | 0.62  | 0    | 1.07 (0.94,1.21)     | 1.06            | 0.29    | 4       |
|                  | AG vs AA         | 3.42  | 0.33  | 12   | 1.14 (0.96,1.35)     | 1.47            | 0.14    | 4       |
|                  | GG vs AA         | 3.40  | 0.33  | 12   | 1.45 (1.10,1.92)     | 2.66            | 0.00    | 4       |
|                  | AG + GG vs AA    | 7.81  | 0.05  | 62   | 1.35 (1.15,1.58)     | 3.65            | 0.00    | 4       |
|                  | GG vs AG + AA    | 2.52  | 0.47  | 0    | 1.36 (1.04,1.77)     | 2.27            | 0.02    | 4       |
| Other cancers   | G vs A           | 2.12  | 0.55  | 0    | 0.87 (0.79,0.96)     | 2.87            | 0.00    | 4       |
|                  | AG vs AA         | 7.08  | 0.07  | 58   | 0.92 (0.81,1.04)     | 1.30            | 0.19    | 4       |
|                  | GG vs AA         | 2.49  | 0.48  | 0    | 0.96 (0.76,1.22)     | 0.30            | 0.77    | 4       |
|                  | AG + GG vs AA    | 22.87 | 0.00  | 70   | 1.26 (0.77,2.07)     | 0.92            | 0.36    | 4       |
|                  | GG vs AG + AA    | 1.70  | 0.64  | 0    | 1.05 (0.84,1.33)     | 0.45            | 0.65    | 4       |
| Source of control | Population   |       |       |      |                      |                 |         |
| G vs A           | 28.89           | 0.01  | 58   | 0.99 (0.90,1.10)     | 0.18            | 0.86    | 13      |
| AG vs AA         | 43.20           | 0.00  | 72   | 1.02 (0.86,1.21)     | 0.22            | 0.83    | 13      |
| GG vs AA         | 14.44           | 0.27  | 17   | 1.06 (0.93,1.21)     | 0.83            | 0.41    | 13      |
| AG + GG vs AA    | 61.57           | 0.00  | 81   | 1.14 (0.94,1.38)     | 1.36            | 0.17    | 13      |
| GG vs AG + AA    | 20.53           | 0.06  | 42   | 1.03 (0.91,1.17)     | 0.46            | 0.65    | 13      |
| Hospital         | G vs A           | 14.18 | 0.01  | 65   | 0.99 (0.86,1.15)     | 0.08            | 0.94    | 6       |
| AG vs AA         | 7.78            | 0.17  | 36   | 0.94 (0.84,1.05)     | 1.11            | 0.27    | 6       |
| GG vs AA         | 18.75           | 0.00  | 73   | 0.98 (0.65,1.49)     | 0.08            | 0.94    | 6       |
| AG + GG vs AA    | 27.21           | 0.00  | 82   | 1.10 (0.84,1.43)     | 0.68            | 0.50    | 6       |
GG vs AG + AA 16.68  0.01  70  1.06 (0.73,1.55)  0.32  0.75  6

Sample size

≥ 300

G vs A  22.21  0.02  59  0.95 (0.87,1.04)  1.16  0.25  10
AG vs AA  27.95  0.01  68  0.92 (0.80,1.05)  1.23  0.22  10
GG vs AA  21.34  0.01  58  0.99 (0.80,1.23)  0.05  0.96  10
AG + GG vs AA  76.99  0.00  88  1.09 (0.88,1.35)  0.77  0.44  10
GG vs AG + AA  17.22  0.05  48  1.03 (0.91,1.16)  0.42  0.67  10

< 300

G vs A  13.95  0.08  43  1.08 (0.98,1.18)  1.45  0.15  9
AG vs AA  12.81  0.12  38  1.15 (1.00,1.33)  2.02  0.04  9
GG vs AA  8.96  0.35  11  1.22 (0.99,1.50)  1.85  0.06  9
AG + GG vs AA  9.82  0.28  19  1.19 (0.98,1.32)  1.74  0.07  9
GG vs AG + AA  19.99  0.01  60  1.08 (0.77,1.35)  0.44  0.66  9

Table 6: The results of heterogeneity test for rs2292832 and rs895819

| Comparisons   | Publication year | Ethnicity | Cancer type | Match | Language | Source of control | Assay | Sample size | Quality control |
|---------------|------------------|-----------|-------------|-------|----------|-------------------|-------|-------------|----------------|
| rs2292832     |                  |           |             |       |          |                   |       |             |                |
| C vs T        | 0.737            | 0.339     | 0.256       | 0.812 | 0.653    | 0.547             | 0.417 | 0.291       | 0.781          |
| CT vs TT      | 0.392            | 0.440     | 0.331       | 0.329 | 0.220    | 0.514             | 0.519 | 0.765       | 0.529          |
| CC vs TT      | 0.388            | 0.838     | 0.463       | 0.784 | 0.463    | 0.875             | 0.772 | 0.573       | 0.514          |
| CT + CC vs TT | 0.737            | 0.440     | 0.547       | 0.956 | 0.853    | 0.443             | 0.949 | 0.552       | 0.554          |
| CC vs CT + TT | 0.519            | 0.519     | 0.440       | 0.331 | 0.389    | 0.396             | 0.838 | 0.336       | 0.815          |
| rs895819      |                  |           |             |       |          |                   |       |             |                |
| G vs A        | 0.418            | 0.426     | 0.275       | 0.581 | 0.593    | 0.581             | 0.336 | 0.581       | 0.225          |
| AG vs AA      | 0.440            | 0.841     | 0.415       | 0.797 | 0.596    | 0.797             | 0.554 | 0.797       | 0.442          |
| GG vs AA      | 0.838            | 0.721     | 0.487       | 0.998 | 0.827    | 0.498             | 0.423 | 0.998       | 0.366          |
| AG + GG vs AA | 0.418            | 0.426     | 0.159       | 0.989 | 0.656    | 0.989             | 0.359 | 0.989       | 0.396          |
| GG vs AG + AA | 0.327            | 0.841     | 0.881       | 0.077 | 0.914    | 0.077             | 0.073 | 0.077       | 0.990          |

Table 7: Publication bias of rs2292832 and rs895819 for Egger’s test

| Comparisons | T     | p      | 95% CI    |
|-------------|-------|--------|-----------|
| rs2292832   |       |        |           |
| T vs C      | 0.96  | 0.358  | –1.657~4.245 |
| CT vs CC    | –0.45 | 0.661  | –1.748~1.151 |
| TT vs CC    | 0.96  | 0.358  | –1.171~3.001 |
| CT + TT vs CC | 0.37 | 0.715  | –1.256~1.777 |
| TT vs CT + CC | 1.60 | 0.083  | –0.572~3.100 |
| rs895819    |       |        |           |
| G vs A      | 0.44  | 0.673  | –2.337~3.452 |
| AG vs AA    | 1.18  | 0.270  | –1.122~3.555 |
| GG vs AA    | 0.28  | 0.789  | –1.792~2.291 |
| AG + GG vs AA | 1.12 | 0.292  | –1.219~3.612 |
| GG vs AG + AA | –0.07 | 0.943  | –1.923~1.803 |
Figure 5: Funnel plot of rs2292832 polymorphism and cancer risk for dominant models (TT + CT vs CC). The horizontal line in the funnel plot indicates the fixed-effects summary estimate, whereas the sloping lines indicate the expected 95% CI for a given SE.

Figure 6: Funnel plot of rs895819 polymorphism and cancer risk for dominant models (TT + CT vs CC).
sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI), and 4) genotype distribution of control groups must be in accordance with the assumptions of Hardy-Weinberg equilibrium (HWE).

In case of redundant publications, only the studies with the largest sample size and/or latest published date were included.

Data extraction

Data were extracted independently by two investigators (YJF and FJD). Data for analyses, including first author, publication year, cancer type, country of origin, ethnicity, study design, genotype detection methods and quality control or not. If discrepancies existed, consensus would be finally reached on discussion.

Quality assessment

Quality assessment criteria were utilized to evaluate methodological quality of included studies based on Newcastle-Ottawa Scale (NOS) [67] for quality of case-control. A nine-point scale of the NOS (range, 0–9 points) has been developed for the evaluation, a high-quality study was defined as one with a score of ≥ 7.

Statistical analysis

The analyses were conducted in Review Manager 5.0 (Version 5 for Windows, Cochrane Collaboration, Oxford, UK). The overall strength of an association between rs2292832 and rs895819 polymorphisms and cancer risk assessed by crude ORs together with their corresponding 95% CIs. The stratified analysis was conducted by ethnicity (Asians, Caucasians), cancer type, source of control and sample size (300 as the boundary).

Heterogeneity in meta-analysis refers to the variation in study outcomes between different studies. Between-study heterogeneity was evaluated with a χ² based Q-test among the studies [68]. Heterogeneity was considered significant when \( P < 0.05 \). In case of no significant heterogeneity, point estimates and 95% CI was estimated using the fixed effect model (Mantel-Haenszel), otherwise, random effects model (DerSimonian Laird) was employed [69, 70]. The significance of overall OR was determined by the Z-test.

If there were significant heterogeneity among included studies, the sources of heterogeneity would be explored using meta-regression in Stata 12.0 (StataCorp, College Station, TX, USA). To assess the stability of the results, one-way sensitivity analyses were performed to assess the stability of the results, in which a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled OR. The publication bias was diagnosed by using inverted funnel plots, Begg’s test and the Egger’s test by Stata 12.0. Statistical tests performed in the present analysis were considered significant whenever the corresponding null-hypothesis probability was \( P < 0.05 \).

ACKNOWLEDGMENTS AND FUNDING

This research was supported by National Natural Science Foundation of China (No.81202278), and Program for Science and Technology Key Projects of Henan Province (201303005).

CONFLICTS OF INTEREST

None declared.

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