Associations between ADIPOQ rs2241766 SNP and breast cancer risk: a systematic review and a meta-analysis

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Abstract

Purpose: We aimed to conduct a meta-analysis to accurately evaluate the potential association between ADIPOQ rs2241766 gene SNP and breast cancer risk.

Methods: A systematic literature search on Cochrane Library, PubMed, Embase, Web of Science and China National Knowledge Infrastructure (CNKI) identified 8 articles with 1692 cases and 1890 controls. Strength of association was evaluated by pooled odds ratio (OR), 95 % confidence interval (CI) and p value. Funnel plots and Begger’s regression test were applied for testing the publication bias. Statistical analysis of all data was performed by Stata 12.0.

Results: The meta-analysis results indicated that the ADIPOQ rs2241766 gene polymorphism did not significantly associated with the risk of breast cancer for these genetic models (TT vs. TG + GG: OR = 1.20, 95 % CI = 0.77–1.89, p=0.417; TT + TG vs. GG: OR = 1.05, 95 % CI = 0.71–1.56, p=0.805; T vs. G: OR =1.17, 95 % CI = 0.79–1.74, p=0.437).

Conclusions: This study indicated that no significant relationship between the ADIPOQ rs2241766 SNP and breast cancer. Further large-scale and well-designed studies will be indispensable to confirm our result.

Keywords: Breast, Cancer, Genetics, Meta-analysis, Polymorphism

Introduction

Breast cancer was the most common malignant tumor in women, which was the second most common malignant tumor worldwide [1]. According to data from the World Health Organization and the International Agency for Research on Cancer in 2012, a total of 1.67 million breast cancer patients were confirmed worldwide. This number accounted for 11.8 % of all tumors [2]. So far, the pathogenesis of breast cancer remains unclear.

Recent studies had shown that adiponectin (ADIPOQ) was inversely related to breast cancer and other tumors [3–6]. ADIPOQ gene was found on the 3q27 chromosomal expressed by adipose tissue and had more than 620 variants [7, 8]. ADIPOQ gene polymorphism was closely related to cancer risk by influencing plasma level of ADIPOQ [9]. To date, previous studies on the relationship between the polymorphism of ADIPOQ rs2241766 gene and breast cancer susceptibility were limited and rather contradictory [10–17]. For lack of powerful evidence to provide a reliable conclusion in a single study, we conducted a comprehensive meta-analysis to assess the strength relationship between ADIPOQ rs2241766 SNP and breast cancer risk, which would have much greater possibility to reach reasonably reliable conclusions.
Materials and methods

Publication search
We systematically searched on database of Cochrane Library, Pubmed, Embase, Web of Science and China National Knowledge Infrastructure, up to October 31, 2019, using the following terms: (“ADIPOQ” OR “adiponectin receptor” OR “rs2241766”) AND (“variant” OR “polymorphism” OR “mutation”) AND (“breast cancer” OR “breast tumor”). Two investigators manually checked the reference of retrieved articles and extracted the publications independently. In addition, only English and Chinese articles were included.

Selection criteria
All selected studies complied with the inclusion criteria: (1) full text can be found; (2) case-control studies focused on relationship between the ADIPOQ rs2241766 polymorphism and risk of breast cancer; (3) ADIPOQ rs2241766 genotype was obtained. Main exclusion criteria as followed: (1) repeat of other articles; (2) not case–control studies; (3) unpublished studies, conference articles, meta-analysis and systematic evaluations; (4) pedigree studies. Consulting the Preferred Reporting Project (PRISMA) Guide for Systematic Evaluation and Meta-Analysis[18], by screening all retrieved literatures, we constructed an information flow diagram about the final eligible data.

Data extraction
Two investigators extracted data independently according to the selection criteria. The following items were collected: first author, country, publication year, amount of cases and controls, Hardy-Weinberg equilibrium, control group source and the availability of ADIPOQ rs2241766 genotype. Only the article with maximum sample size was selected while same data appearing in multiple publications. To insure the data accuracy, a third investigator reviewed the final results. Discussions were executed to solve disagreements.

Study quality assessment
Two researchers performed independent quality assessment for each eligible article according to 9-point Newcastle-Ottawa Scale (NOS) applied to quality evaluation of observational studies [19]. Different results from two evaluators were solved by the third assessor. Assessment score principally included these aspects: (1) case and control selection (4 point); (2) Confounding factor quality corrected in cases and controls (2 point); (3) exposure ascertainment (3 point). The total scores ranged from 0 to 9, and scores above 6 indicate high quality.

Statistical analysis
Odds ratio (OR) and 95% confidence interval (CI) were calculated to estimate the relationship between ADIPOQ rs2241766 gene SNP and the risk of breast cancer. The Chi-square based Q-test and I-squared test was used to analyze the heterogeneity (P<0.10 suggested Heterogeneity) [20, 21]. The pooled OR was estimated by fixed effect model (Mantel–Haenszel) when no heterogeneity existed. Otherwise, the pooled OR was estimated by random effect model (DerSimonian and Laird) [22, 23]. In controls, Chi-square test was used to examine Hardy–Weinberg equilibrium (HWE). In order to estimate the influence of the pooled ORs caused by individual data set, we performed sensitivity analysis for each comparison models respectively. The publication bias was tested by Funnel plot and Begg linear regression [24, 25]. Stata 12.0 was used to perform all analysis (Stata Corp, College Station, United States).

Results

Characteristic of studies
Flow diagram for the retrieve strategy was demonstrated in Fig. 1. 311 publications were identified initially. 68 duplicate publications were excluded by verified and deleted, while 243 publications entered our study. 54 publications were reviewed for full-text review by reading title and abstract. Ultimately, 8 studies with 1692 breast cancer patients and 1890 controls were screened out for the final meta-analysis which published between 2008 and 2019. The gene distributions in control groups were all consistent with HWE. In addition, all studies were high quality because of the NOS scores ranging from 7 to 8. The relevant feature information was presented in Table 1.

Meta-analysis results
Chi-square was used to determine the heterogeneity of the three genetic models. The heterogeneity was significant in these models according to Table 2 (TT vs. TG + GG (recessive model): p<0.001, I² = 84.2%); T vs. G (allele model): p<0.001, I² = 84.3%). However, the heterogeneity was not considered significant in these models (TT + TG vs. GG (dominant model): p=0.308, I² = 16.0%) Fig. 2. So the recessive model and allele models were analyzed by random effect model. The fixed was applied to analyze the dominant model. There was no significant association between ADIPOQ rs2241766 polymorphism and breast cancer risk under the model of TT vs. TG + GG (OR = 1.20, 95% CI = 0.77–1.89, p = 0.417), TT + TG vs. GG (OR = 1.05, 95% CI = 0.71–1.56, p = 0.805), C vs. T (OR = 1.17, 95% CI = 0.79–1.74, p = 0.437). We also performed a subgroup analysis according to ethnicity, source of control, case size and
control size. We find the statistically significant association for the dominant model which observed in Asian population (OR=1.48, 95%CI=1.08-2.05), control from population (OR=1.49, 95%CI=1.01-2.18) and studies with less or more than 100 controls (OR=1.67, 95%CI=1.01-2.77), and less or more than 100 cases. The pooled OR and 95% CI of the relationship between ADIPOQ rs2241766 polymorphism and breast cancer were in Table 1. A sensitivity analysis was conducted to reflect the effect of each independent study on the whole studies. As shown in Fig. 3, none of the study affected the overall results of Begg’s funnel plot was used to assess the publication bias. The results showed that there was no publication bias reflected in three genetic models (TT vs. TG + GG: \( p=0.458 \); TT + TG vs. GG: \( p=0.881 \); T vs. G: \( p=0.322 \)) (Fig. 4).

**Discussion**
In recent years, several case–control studies have shown an association between the importance of ADIPOQ rs2241766 gene SNP and breast cancer risk, however, to date, it is still inconclusion. The first study had been reported ADIPOQ rs2241766 gene polymorphisms in relation to breast cancer risk in 2008 [10], in this study, the

| Author                      | Year | Country | Ethnicity | Source of control | Sample size | NOS score | HWE  |
|-----------------------------|------|---------|-----------|-------------------|-------------|-----------|------|
| Macias-Gomez NM et al.      | 2019 | Mexico  | Non-Asian | HB                | 64          | 0.603     |      |
| Pasha HF et al.             | 2019 | Egypt   | Non-Asian | HB                | 120         | 0.053     |      |
| Kaklamani VG et al.         | 2013 | America | Non-Asian | HB                | 366         | 0.944     |      |
| Kaklamani VG et al.         | 2008 | America | Non-Asian | HB                | 712         | 0.822     |      |
| Erbay B et al.              | 2016 | Turkey  | Non-Asian | PB                | 97          | 0.473     |      |
| Al Khaldi RM et al.         | 2011 | Kuwait  | Asian     | PB                | 60          | 0.208     |      |
| Cui HK et al.               | 2009 | China   | Asian     | PB                | 68          | 0.829     |      |
| Khandouzi M et al.          | 2016 | India   | Asian     | HB                | 205         | 0.090     |      |

*HB* Hospital-based, *PB* population-based
Fig. 2 Forest plots of the ADIPOQ rs2241766 polymorphism under different genetic models. A is the model of TT vs. TG + GG; B is the model of TT + TG vs. GG; C is the model of T vs. G.
The association between the high expression of rs2241766 G allele (GT and GG genotype) and low risk of breast cancer was detected. In 2019, Macias-Gomez et al. [16] found that the G allele of ADIPOQ rs2241766 polymorphisms and the TG+GG genotype had protective effects on the occurrence of breast cancer. Series of studies supported the conclusion while others objected. Pasha et al. [17] detected that the ADIPOQ rs2241766 SNP might cause breast cancer (OR=6.2, 95 %CI=1.3–29.6). Al Khaldi et al. [12] found that individuals with GG genotypes showed an increased risk of breast cancer (OR = 2.1, 95 %CI=1.1–4.1). Others studies suggested that there was no association between ADIPOQ rs2241766 gene SNP and increased risk of breast cancer [11, 13–15].

In the recessive model (OR = 1.20, 95 %CI = 0.77–1.89), dominant model (OR = 1.05, 95 %CI = 0.71–1.56) and allele model (OR = 1.17, 95 %CI = 0.79–1.74), the ADIPOQ rs2241766 polymorphism was not significantly associated with breast cancer risk. Considerable heterogeneity was discovered among these studies. We also conducted a subgroup analysis according to racial classification, case size, control size and source of control. In dominant genetic model, the significant correlation was not found in stratification analysis by racial classification, case size, control size and source of control. But in Asians, the statistically significant association for the dominant model was observed (OR=1.48, 95 %CI=1.08–2.05), control from population (OR=1.49, 95 %CI=1.01–2.18) and studies with less than 100 controls (OR=1.67, 95 %CI=1.01–2.77). Moreover, the significant associations were observed in allele genetic model in stratified analysis among Asians (OR=1.36, 95 %CI=1.04–1.78) and studies with less than 100 controls (OR=1.52, 95 %CI=1.00–2.30). Because of the limited samples and finite studies [11, 12], it would be immature to conclude that the ADIPOQ rs2241766 SNP has no relationship with breast cancer. New further discoveries will appear and the information will be constantly renovated. There should be plenty of research data to support more objective results.

The detailed mechanism of the association between ADIPOQ rs2241766 and breast cancer is unclear. Previous epidemiological studies [26, 27] have confirmed a significant association between obesity and some adipokines and breast cancer risk. Logically, adiponectin may play a role in the development of breast cancer. Uncontrolled cellular proliferation is a hallmark of tumorigenesis. Adiponectin is an important regulator of cell proliferation and apoptosis. Adiponectin has been shown to significantly suppress the proliferation of MDAMB-231 cells by arresting the cells at G0/G1 phase and inducing apoptosis [28]. Furthermore, adiponectin also significantly inhibits cell proliferation induced by leptin, oxidized, low-density lipoprotein, platelet-derived growth factor BB, basic fibroblast growth factor (bFGF), and heparinbinding epidermal growth factor-like growth factor [28].

### Table 2 Pooled ORs and 95 % CIs of the association between ADIPOQ rs2241766 polymorphism and breast cancer

| Total and subgroups | Studies | TT vs. TG + GG OR (95 %CI) | P values for OR $I^2$ | TT + TG vs. GG OR (95 %CI) | P values for OR $I^2$ | T vs. G OR (95 %CI) | P values for OR $I^2$ |
|---------------------|---------|---------------------------|------------------------|---------------------------|------------------------|---------------------|------------------------|
| Total               | 8       | 1.2 (0.77-1.89)            | 0.417                  | 84.20 %                  | 1.05 (0.71-1.56)       | 0.805                | 16.00 %                | 1.17 (0.79-1.74)       | 0.437                  | 84.30 %                |
| Ethnicity           |         |                           |                        |                          |                        |                      |                        |                        |                        |                      |
| Asian               | 3       | 1.48 (1.08-2.05)           | 0.016                  | 0.00 %                   | 1.26 (0.61-2.59)       | 0.551                | 0.00 %                 | 1.36 (1.04-1.78)       | 0.024                  | 0.00 %                 |
| Non-Asian           | 5       | 0.83 (0.70-0.99)           | 0.040                  | 88.00 %                  | 0.97 (0.61-1.56)       | 0.913                | 36.10 %                | 1.04 (0.57-1.87)       | 0.907                  | 88.70 %                |
| Source of control   |         |                           |                        |                          |                        |                      |                        |                        |                        |                      |
| HB                  | 5       | 1.06 (0.58-1.95)           | 0.085                  | 89.10 %                  | 1.00 (0.65-1.54)       | 0.997                | 33.30 %                | 1.06 (0.60-1.84)       | 0.849                  | 89.50 %                |
| PB                  | 3       | 1.49 (1.01-2.18)           | 0.041                  | 0.00 %                   | 1.37 (0.50-3.77)       | 0.539                | 0.00 %                 | 1.36 (0.99-1.88)       | 0.056                  | 0.00 %                 |
| Case size           |         |                           |                        |                          |                        |                      |                        |                        |                        |                      |
| <100                | 4       | 1.08 (0.78-1.50)           | 0.655                  | 74.00 %                  | 0.95 (0.39-2.31)       | 0.912                | 19.10 %                | 1.04 (0.57-1.88)       | 0.907                  | 74.70 %                |
| >100                | 4       | 0.92 (0.77-1.09)           | 0.329                  | 90.50 %                  | 1.08 (0.69-1.68)       | 0.740                | 37.30 %                | 1.31 (0.72-2.37)       | 0.378                  | 90.60 %                |
| Control size        |         |                           |                        |                          |                        |                      |                        |                        |                        |                      |
| <100                | 3       | 1.67 (1.01-2.77)           | 0.046                  | 0.00 %                   | 0.98 (0.64-1.49)       | 0.347                | 20.10 %                | 1.52 (1.00-2.30)       | 0.047                  | 0.00 %                 |
| >100                | 5       | 0.90 (0.77-1.05)           | 0.183                  | 86.90 %                  | 1.74 (0.55-5.50)       | 0.922                | 0.00 %                 | 1.07 (0.67-1.72)       | 0.770                  | 87.20 %                |

*HB* Hospital-based, *PB* population-based, ORs odds ratios, CI confidence interval; *p* values for $I^2$ less than 0.05.
Fig. 3  Sensitivity analysis examining the association between the ADIPOQ rs2241766 polymorphism and risk of breast cancer under these models (TT vs. TG + GG, TT +TG vs. GG, T vs. G)
Fig. 4 Begg’s funnel plot for publication bias analysis. A is the model of TT vs. TG + GG; B is the model of TT + TG vs. GG; C is the model of T vs. G.
Several limitations in the study should be considered. First, only 8 studies were selected into our meta-analysis. The sample size and amount of studies were comparatively small, which affected the reliability of the results. Second, the case size and control size of some studies were relatively small to confirm the risk of ADIPOQ rs2241766 SNP. Finally, in all genetic models, the heterogeneity of the recessive model and allele model may have a significant impact on the result of meta-analysis.

Conclusions
In conclusion, we find the significant associations in the recessive model and allele genetic model in stratification analysis. The risk of ADIPOQ rs2241766 SNP could not be confirmed due to the relatively limited sample and small amount of study. Scholars had conducted extensive research on the susceptibility factors of breast cancer, which believed that the breast cancer occurrence was influenced by multiple factors [29–33], especially genetic factors and lifestyle. Therefore, the influence of confounding risk factors will be eliminated by further studies, such as age, BMI and environmental factors.

Abbreviations
CNKI: China National Knowledge Infrastructure; ADIPOQ: adiponectin; IARC: International Agency for Research on Cancer; WHO: World Health Organization; NOS: Newcastle-Ottawa Scale; OR: odds ratio; CI: confidence interval

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Authors’ contributions
Manuscript writing, articles search, editing and review were conducted by Xue Hu and Wan Wang, Chunguo Cui and Tong Sun performed data analysis and evaluation the quality of the selected studies. The author(s) read and approved the final manuscript.

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Competing interests
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