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Review Article

Association of rs11614913 (C > T) in miR-196a2 with breast cancer and gastric cancer: a meta-analysis

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Abstract: Previous studies have suggested that single nucleotide polymorphism (SNP) rs11614913 (C > T) in miR-196a2 is associated with a reduced risk of breast cancer (BC) and gastric cancer (GC), but the evidence has been conflicting. To obtain a better assessment of the association between rs11614913 in miR-196a2 and cancer risk, the present meta-analysis was conducted using systematic reviews of PubMed, Embase, Wanfang, and China's National Knowledge Infrastructure. Moreover, 95% confidence intervals and pooled odds ratios were used to assess the association with breast cancer and gastric cancer. A total of 6 case-control studies of BC and 6 case-control studies of GC were included. The present meta-analysis revealed that rs11614913 in miR-196a2 was significant related with decreased risk of GC (TT vs CC: OR = 0.644, 95% CI = 0.475-0.874, P = 0.005). However, rs11614913 in miR-196a2 was not related to a reduced risk of breast cancer in any of the models. Meta-analysis results demonstrate that rs11614913 in miR-196a2 is related to a significantly decreased risk of gastric cancer. However, there was no significant association between miR-196a2 rs11614913 and susceptibility to BC.

Keywords: Breast cancer, gastric cancer, miR-196a2, genetic polymorphism, meta-analysis

Introduction

MicroRNAs are a type of non-coding RNA. The 39 non-translated regions of mRNA are targeted by mature miRNAs, resulting in mRNA translation or degradation inhibition [1, 2]. According to reports, a single miRNA could bind to mRNAs of about 200 genes. Thus, miRNAs play an important role in gene regulation [3, 4] and participate in pathophysiological processes [1], including tumorigenesis [5] and proliferation [6].

Furthermore, rs11614913 polymorphism in miR-196a2 may influence the expression of mature miRNA [7, 8]. It has been shown to be associated with cancer risk [9]. Thus far, several groups have confirmed that rs11614913 in miR-196a2 is closely correlated with a decreased risk of human GC and BC [10-21]. However, the relationship between rs11614913 polymorphism in pre-miRNA and human BC and GC remains inconclusive in the literature, due to limited sample sizes and racial differences of the patients. Linhares et al. [12] found that individuals with TT genotype of miR-196a2 rs11614913 had a higher prevalence of breast cancer than normal, but Gao et al. [22] found that individuals carrying the TT genotype of miR-196a2 rs11614913 were related with decreased BC risk. In addition, some studies have shown that miR-196a2 rs11614913 and GC have a close association [16-21]. However, the association of miR-196a2 rs11614913 with human GC remains inconclusive. To better assess the association of miR-196a2 rs11614913 with susceptibility to BC and GC, the present meta-analysis of all published case-control studies was conducted to assess the impact of miR-196a2 rs11614913 on BC and GC risk.

Methods

Identification of eligible studies

Eligible case-control studies were extracted by electronic database searches and manual retrieval of references to relevant articles and reviews. Embase, China National Knowledge Infras-

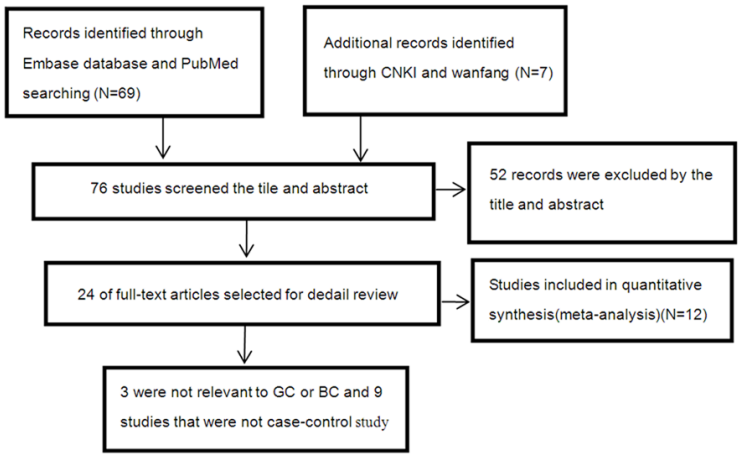

Figure 1. Flow chart of study selection.

tructure (CNKI), Wanfang, and PubMed were searched, using the following terms in combination: miR-196a2, rs11614913, breast cancer, gastric cancer, gene, genotype, mutation, and polymorphism. The last search was updated on September 18, 2017. To obtain additional eligible studies, relevant reviews and meta-analyses were examined.

Criteria for inclusion and exclusion

Studies to be included met the following requirements: (a) Investigated the association between rs11614913 polymorphisms in pre-miRNAs and BC or GC risks; (b) Independent case-control studies for humans; (c) Cancers diagnosed by histopathology; (d) Specific genotype frequencies were provided. Studies that did not provide specific genotype frequencies were excluded; and (e) Sufficient published data for calculating odds ratios (ORs) with their 95% confidence intervals (95% CIs).

Data extraction

Two reviewers (He and Zhu) collected studies strictly in accordance with inclusion criteria. They collected data on eligible studies. The following data was collected: authors of the study, year of publication, the number of control and case groups, nation where the study was conducted, ethnicity, and cancer type. Different races were divided into Asian, Caucasian, and non-Caucasian. Cancer types were classified as breast cancer (BC) and gastric cancer (GC). Two commentators checked each item carefully to ensure reliability.

Statistical analysis

Association between rs11614913 polymorphism and risk of GC and BC was measured by odds ratios (OR) and 95% confidence intervals (95% CI). Total ORs value was determined by calculating a weighted average of ORs for each study. Statistical significance testing used 95% CI, when OR was less than 1, indicating that there was a downside risk. Otherwise, the risk was increased. Z test was used to determine the statistical significance of pooled OR, with $P < 0.05$ considered statistically significant. Subgroup analyses were also conducted by cancer type (GC and BC). Sensitivity analysis was conducted to determine the impact of individual studies on the combined results and to test the reliability of results. Heterogeneity assessment across studies was measured by Q-measures based on Chi-squared test [23]. There was significant heterogeneity among the studies when $P < 0.10$. In addition, an additional method of $I^2 = 100\% \times (Q\text{-}df)/Q$ was used to measure the effects of heterogeneity [24]. Two models were used to process data from different studies. Random effects models were used when there was significant heterogeneity. Otherwise, fixed effects models were used. Publication bias was assessed by funnel plot and Begg's test was used to quantitatively detect publication bias ($P < 0.05$ is considered significant). STATA software (version 11.0) was used for statistical analysis.

Results

Characteristics of eligible studies

Using different combinations of key items, a total of 76 reports were obtained after a preliminary search of PubMed, EMBASE, and CNKI. In summary, 12 articles [14-25] were identified according to criteria for inclusion and exclusion, as described above (**Figure 1**). After reading the abstracts, detailed reviews, and full-text articles, 64 studies were excluded, including 26 that did not meet inclusion criteria. Moreover, 26 were reviews or meta-analyses, 3 were not relevant to GC or BC, and 9

Table 1. Summary of 12 studies used for analysis

First Author	Year	County	Cancer type	Ethnicity	Case			Control		
					TT	CT	CC	TT	CT	CC
Bodal et al.	2017	Indian	BC	Asian	0	47	48	0	35	64
Bansal et al.	2014	India	BC	Asian	12	41	68	21	59	85
Linhares et al.	2012	Brazil	BC	Non-Caucasian	23	29	11	30	51	33
Zhao et al.	2014	China	BC	Asian	33	50	31	25	61	28
Dai et al.	2016	China	BC	Asian	98	256	197	144	284	155
Jedlinski et al.	2011	Australia	BC	Caucasian	33	86	68	31	82	58
Rogoveanu et al.	2017	Romania	GC	Romania	18	63	61	39	128	121
Li et al.	2015	China	GC	Asian	75	83	24	92	79	11
Ahn et al.	2013	South Korea	GC	Asian	119	242	100	128	232	87
Kupcinskas et al.	2014	Mix	GC	Caucasian	35	184	144	46	145	159
Peng et al.	2010	China	GC	Asian	43	94	76	50	107	56
Yang et al.	2013	China	GC	Asian	21	109	102	42	136	72

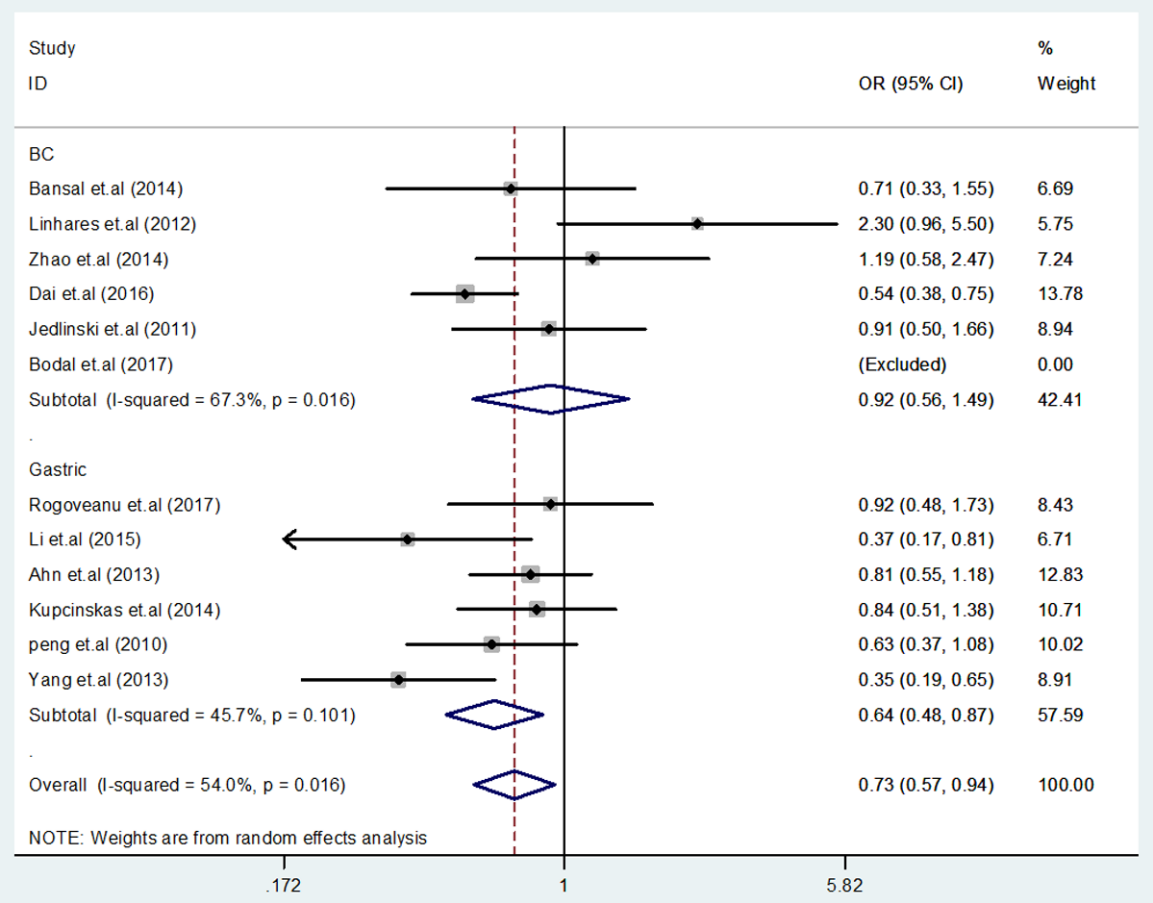

Figure 2. Homozygote comparison (TT VS CC).

studies were not case-control studies. Of these studies, 9 were from PubMed and Embase databases, while the others were from CNKI and wanfang. Characteristics of the selected studies are presented **Table 1**. The present meta-analysis included 12 studies [10-21], involving 2,724 cases and 2,976 controls (**Figure 1**).

Table 2. Summary of ORs for gastric cancer and breast cancer in five models of rs11614913 miR-196a2

	N	TT/CT vs CC		T vs C		TT vs CC		TT vs TC/CC		TC VS CC	
		OR	P_h	OR	P_h	OR	P_h	OR	P_h	OR	P_h
Total	12	0.862 (0.694-1.070)	0.179	0.724 (0.571-0.919)	0.008	0.730 (0.567-0.941)	0.015	1.084 (0.971-1.209)	0.151	0.780 (0.552-1.103)	0.160
BC	6	0.989 (0.705-1.388)	0.949	0.719 (0.490-1.054)	0.091	0.917 (0.563-1.494)	0.727	1.081 (0.918-1.273)	0.349	0.700 (0.406-1.208)	0.200
GC	6	0.767 (0.560-1.052)	0.100	0.733 (0.523-1.028)	0.071	0.644 (0.475-0.874)	0.005	1.086 (0.937-1.258)	0.276	0.861 (0.529-1.403)	0.548

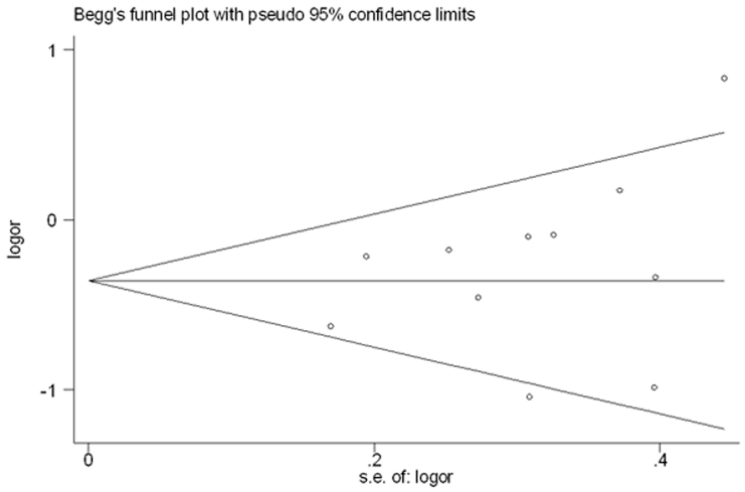

Figure 3. Funnel plot of homozygote comparison (TT VS CC). A: funnel plot of all 12 eligible studies, Egger's test P = 0.276.

Meta-analysis results

This meta-analysis was conducted to investigate the impact of GC and BC. For the type of cancer, decreased cancer risk was found in the homozygote comparison (TT vs CC: OR = 0.644, 95% CI = 0.475-0.874, P = 0.005) for GC (**Figure 2**), whereas negative results were obtained for other genetic models (TT/CT vs CC: OR = 0.767, 95% CI = 0.560 -1.052, P = 0.100; T vs C: OR = 0.733, 95% CI = 0.523-1.028, P = 0.071; TT vs TC/CC: OR = 1.086, 95% CI = 0.937-1.258, P = 0.276; TC VS CC: OR = 0.861, 95% CI = 0.529-1.403, P = 0.548).

Furthermore, rs11614913 in miR-196a2 was not associated with a reduced risk of breast cancer in any model (TT/CT vs CC: OR = 0.989, 95% CI = (0.705-1.388, P = 0.949, T vs C: OR = 0.719, 95% CI = 0.490-1.054, P = 0.091, TT vs CC: OR = 0.917, 95% CI = 0.563-1.494, P = 0.727, TT vs TC/CC: OR = 1.081, 95% CI = 0.918-1.273, P = 0.349, TC VS CC: OR = 0.700, 95% CI = 0.406-1.208, P = 0.200). Association strength between rs11614913 in miR-196a2 and cancer risk is revealed in **Table 2**.

Sensitivity analysis

Sensitivity analysis demonstrated that, concerning the association of miR-196a2 with GC and BC, no substantial changes were found (data not shown) after omitting any one study. The present meta-analysis only included published studies.

Publication bias

Begg's test and Egger's test were performed, along with funnel plots, to assess the publication bias of included studies for rs11614913 polymorphism in miR-196a2. Results are shown in **Figure 3**.

Discussion

The present meta-analysis included 12 eligible studies [10-21], involving 2,724 cases and 2,976 controls. Through quantitative analysis, it was shown that rs11614913 in miR-196a2 correlates with a significantly decreased risk of GC. However, there was no significant association between miR-196a2 rs11614913 and susceptibility to BC.

miR-196a2 is composed of two different mature miRNAs (miR-196a-5P and miR-196a-3P). miR-196a-5P and miR-196a-3P are processed from the same stem-loop [25]. Moreover, rs11614913 (C > T) in miR-196a2 is in the mature sequence of miR-196a-3P. It may affect the production levels of mature miR-196a and could affect expression of its target genes [9]. Therefore, changes of miR-196a expression patterns may affect its potential target and may play a role in the regulation of carcinogenesis. Previous studies have suggested an association between rs11614913 and risk of BC. Ying et al. [26] reported that after pre-miR-196a-C introduction, several oncogenes were found to be upregulated in breast cancer cells, such as TP63 and genes encoding two calcium-binding proteins, showing the oncogenic activity of pre-miR-196a-C. Hoffman et al. [27] found that rs11614913 could reduce the risk of breast cancer. However, Linhares et al. [12] found that rs11614913 in miR-196a2 had an increased risk of breast cancer, while Catucci et al. found that miR-196a2 rs11614913 was not associated with risk of breast cancer in Germany and Italy [28]. In addition, the present meta-analysis did not find any association between breast cancer and rs11614913 in any model. However, with the accumulation of more experimental evidence, the association of BC and rs11614913 in miR-196a2 will gradually emerge.

Pre-miR-196a-C has also been documented to be an important risk factor for gastric cancer. Expression of miR-196a and its target gene can be affected by rs11614913. For example, Annexin A1 (ANXA1) and homeobox (HOX) genes [29] and the down regulation of these genes leads to a higher gastric cancer risks. Ma et al. reported that rs11614913 was significantly associated with decreased gastric cancer risk [30]. The present meta-analysis found that rs11614913 in miR-196a2 was associated with a significantly decreased risk of gastric cancer in the homozygous model.

There were some limitations regarding this meta-analysis that should be noted. First, the main source of heterogeneity was found to be small sample size and ethnicity. It is difficult to recruit enough cases of one specific type of cancer. Thus, this heterogeneity was difficult to rule out. Second, this meta-analysis included only published studies and may have publication bias. Third, lifestyle, dietary habits, and environments may have an effect on gene expression, leading to different results. However, many studies did not take these factors into account. Therefore, to obtain more precise results, more studies on the association of rs11614913 in miR-196a2 with BC and GC risks are necessary, evaluating different lifestyles, dietary habits, and environments.

In conclusion, despite the limitations, present results showed that rs11614913 in miR-196a2 might be associated with reduced GC and BC risks in certain genetic models. Further studies with larger sample sizes are necessary to elucidate the impact of this polymorphism on both cancers.

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Disclosure of conflict of interest

None.

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