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TOPIC HIGHLIGHT

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miRNA polymorphisms and risk of gastric cancer in Asian population

Hai-Bing Hua, Ting-Ting Yan, Qing-Min Sun

Hai-Bing Hua, Department of Gastroenterology, Jiangyin Hospital Affiliated to Nanjing University of Traditional Chinese Medicine, Jiangyin 214400, Jiangsu Province, China
Ting-Ting Yan, Nanjing University of Traditional Chinese Medicine, Nanjing 210029, Jiangsu Province, China
Qing-Min Sun, Department of Pharmacy, Affiliated Hospital of Nanjing University of Traditional Chinese Medicine, Nanjing 210029, Jiangsu Province, China
Author contributions: Hua HB and Yan TT contributed equally to this work; Hua HB reviewed the literature and wrote the article; Yan TT contributed to the analysis and interpretation of the data; Sun QM designed the review and revised the article; all authors have read and approved the final version to be published.
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Correspondence to: Qing-Min Sun, MD, Department of Pharmacy, Affiliated Hospital of Nanjing University of Traditional Chinese Medicine, 155 Hanzhong Road, Nanjing 210029, Jiangsu Province, China. qingminsun@gmail.com
Telephone: +86-25-86619821 Fax: +86-25-86619821
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Abstract

miRNAs are endogenous 19- to 25-nt noncoding RNAs that can negatively regulate gene expression by directly cleaving target mRNA or by inhibiting its translation. Recent studies have revealed that miRNA plays a significant role in gastric cancer development either as a tumor suppressor gene or oncogene. miRNA-single-nucleotide polymorphisms (SNPs), as a novel class of functional SNPs/polymorphisms, have been identified as candidate biomarkers for gastric cancer susceptibility. On the basis of recent data, the present review summarizes current knowledge of the functional effects of miRNA-SNPs and their importance as candidate gastric cancer biomarkers. Additionally, this review also includes a meta-analysis of the most frequently studied miRNA-SNPs in gastric cancer.

Key words: miRNA; Polymorphism; Gastric cancer; Risk

Core tip: Host genetic susceptibility plays an important role in gastric carcinogenesis. In this review, we summarize current knowledge about the functional effects of miRNA-single-nucleotide polymorphisms (SNPs) and their importance in gastric cancer susceptibility. Furthermore, we also conduct a simple meta-analysis about most frequently studied miRNA-SNPs (rs11614913 in miR-196a-2, rs895819 in miR-27a and rs2910164 in miR-146a) in gastric cancer.

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INTRODUCTION

miRNAs are small endogenous noncoding RNAs of about 22 nucleotides that negatively regulate post-transcriptional gene expression by pairing with complementary binding sites located in the 3'-untranslated region (UTR) of mRNA[1]. In 1993, Wightman *et al*[2] and Lee *et al*[3] found the first miRNA, lin-4, which controls developmental timing and cell fate specification in *Caenorhabditis elegans*. To date, thousands of miRNA have been characterized in animal and plant genomes[4]. In human malignancies, miRNA have shown important roles

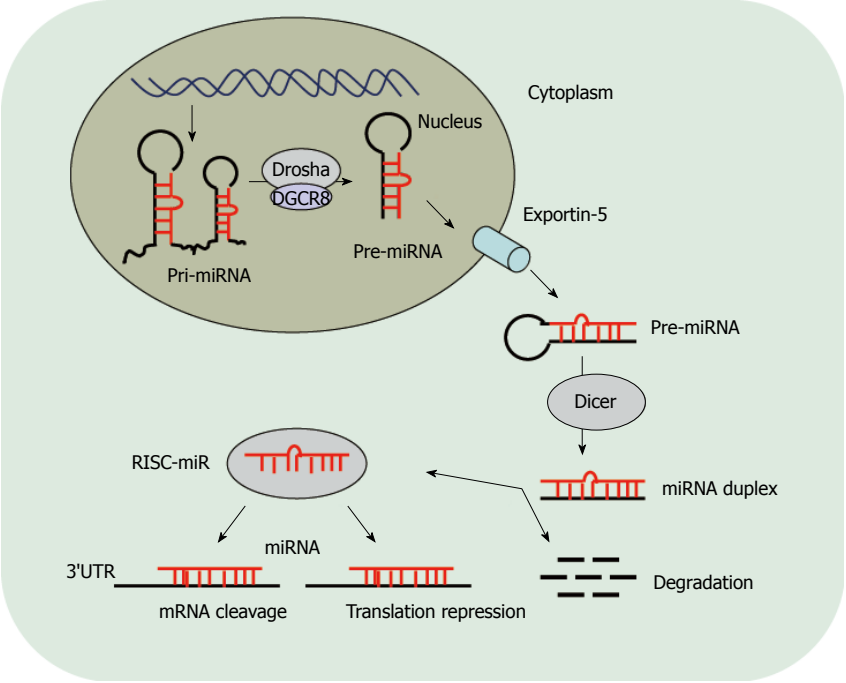

Figure 1 miRNA biogenesis and processing.

in a variety of cellular processes including apoptosis, differentiation, angiogenesis and proliferation[5]. It has been suggested that miRNA regulates almost one-third of the human genes although it represents only a small part of the genome[6]. Moreover, recent evidence shows that more than half of the known human miRNAs are located within cancer-associated genomic regions or fragile sites[7]. Therefore, miRNA can be considered as a potential and ideal biomarker for cancer.

Gastric cancer remains one of the commonest malignant tumors worldwide. In 2013, it was estimated that about 21600 patients were diagnosed with gastric cancer and 10990 died of the disease in the United States[8]. In East Asia, especially in China, gastric cancer has the highest rates of incidence and mortality[9]. Epidemiological studies have identified environmental and lifestyle risk factors that contribute to the development of gastric cancer, such as *Helicobacter pylori* (*H. pylori*) infection or high salt intake[10]. However, only a minority of patients exposed to risk factors such as *H. pylori* infection ultimately develop gastric cancer, which indicates that host genetic susceptibility also plays an important role in gastric carcinogenesis[11-13]. In recent decades, many correlations between single nucleotide polymorphisms (SNPs) in the genome and the risk of various diseases, including gastric cancer, were reported[14,15]. Recently, a class of novel functional polymorphisms in miRNA or its binding sites is the most interesting. Our previous epidemiological studies also provided evidence that the risk of gastric cancer is associated with miRNA-SNPs[16,17]. Therefore, miRNA polymorphisms can be used as specific markers of predisposition for gastric cancer prevention.

In this review, we provide a comprehensive list of potentially functional miRNA-SNPs and have a brief description of miRNA biogenesis, biology and the underlying mechanism of miRNA-SNPs in gastric cancer susceptibility.

miRNA BIOSYNTHESIS AND FUNCTION

miRNA biogenesis is a multistage process[18,19]. Most human miRNA are first transcribed by RNA polymerase II and are encoded by introns[20]. The primary miRNA (pri-miRNA) is excised from the primary transcript of the intron[21]. Then, the pri-miRNA is processed by the RNase Drosha-DGCR8 complex into 70-nucleotide-long precursor hairpin structures (pre-miRNA)[22]. The pre-miRNA is subsequently exported to the cytoplasm by the nuclear membrane protein exportin-5 and cleaved by the RNase Ⅲ enzyme Dicer to produce a transient miRNA duplex composed of a mature miRNA sequence (about 22 nucleotides in length) and its complementary sequence miRNA*[23]. The miRNA duplex is unwound by an RNA helicase and the mature miRNA is incorporated into the targeting miRNA containing RNA induced silencing complex (RISC) together with the argonate (Ago) protein[24,25]. The other strand (or miRNA*) is often degraded. Ago is considered as the heart of the miRNA-induced silencing complex (RISC-miR), which induce the mature miRNA to bind the complementary elements of target mRNA 3' UTR. Lastly, the RISC-miR exerting negatively regulates gene expression function by either mRNA cleavage or inhibiting translation[26] (Figure 1).

As described above, miRNA exert the functionality by sequence-dependent regulation of post-transcriptional gene expression by targeting mRNA for cleavage or translational repression. Target selection is dependent on the extent of Watson-Crick base pairing between the

miRNA and mRNA. Nucleotides 2-8 (from the 5' end of miRNA), also referred to as the "seed sequence", are a major determinant of mRNA target selection[27]. Mutation in either the seed or seed-complementary site could inhibit miRNA activity, which highlights the importance of seed sequence complementarity[28]. Additionally, Grimson *et al*[29] also reported that more than four contiguous Watson-Crick base pairs between nucleotides 12-17 at the 3' end of the miRNA could enhance target recognition. Therefore, miRNA biogenesis and post-transcriptional regulation is highly sequence dependent, and sequence variants (such as SNPs) in either the miRNA sequence or miRNA-target site can have a significant effect on miRNA function. So far, > 1000 miRNAs have been found in humans, which are indicated to regulate up to 30% of all protein-coding genes in the human genome[30]. Moreover, Calin *et al*[7] have suggested that more than half of the human miRNAs are located in cancer-associated fragile regions. This shows that miRNA regulation plays a key regulatory role during development and in various cellular processes such as differentiation, growth and death. These processes are frequently dysregulated in carcinogenesis, implicating miRNA function as oncogenes or tumor suppressors.

miRNA EXPRESSION IN GASTRIC CANCER

Accumulating evidence has strongly indicated that aberrant miRNA expression is an important feature of gastric cancer[31]. In 2012, Wang *et al*[32] summarized 13 miRNA expression profiling studies and suggested that there were 139 miRNAs differentially expressed in gastric cancer tissues compared with neighboring non-cancerous or normal gastric tissues. They also found that the expression levels of miR-21, miR-18a, miR-17 and miR-20a in gastric cancer were significantly upregulated in most studies. Conversely, miR-375 and miR-378 expression levels were downregulated in gastric cancer tissues. Also, expression levels of 29 miRNAs were reported to be inconsistent. In addition, recent evidence using quantitative real-time reverse transcriptase polymerase chain reaction (qRT-PCR) also confirmed that miR-17-5p/20a, miR-181a-5p, miR-214 and miR-23a expression levels were upregulated in human gastric cancer tissues, and overexpression of miR-17-5p/20a could promote gastric cancer cell progression and inhibit apoptosis[31,33-35]. Recent studies have indicated that gastric cancer tissue has significantly lower expression of miR-148a and miR-22 compared to non-tumor tissue, and miR-148a and miR-22 inhibit gastric cancer cell migration and invasion. Moreover, low miR-148a levels are associated with lymph node metastasis, N stage, and blood vessel invasion in gastric cancer patients[36,37]. These miRNA expression profiles analyzed by microarray or qRT-PCR could help us understand better the molecular mechanisms of tumorigenesis and contribute to the development of diagnosis and therapy for gastric cancer.

SNPs IN miRNA

SNPs in the miRNA regulatory pathway, as a novel class of functional polymorphisms in the human genome, have been widely implicated in cancer development[38]. In 2005, Calin *et al*[39] reported the first evidence that mutations in miRNA genes are common and might have functional importance in chronic lymphocytic leukemia (CLL). They identified a germ-line mutation in the miR-16-1-miR-15a primary precursor, which causes low levels of miRNA expression and is associated with prognostic factors and disease progression in CLL[39]. Since then, a series of studies has used systematic sequencing or *in silico* approaches to identify more SNPs in miRNA. In our present study, we focused on the miRNA SNPs in gastric cancer susceptibility. Therefore, we searched PubMed to August 2013 to identify all relevant papers, using the key words miRNA, miRNA polymorphism or variant in combination with gastric cancer or gastric tumor. There were 35 epidemiological studies with a focus on the importance of miRNA-related SNPs in gastric cancer susceptibility. We scanned the titles and abstracts and excluded the studies that were clearly irrelevant to the current topic. The remaining articles were read to determine whether they contained information of interest. In addition, to be eligible, studies had to fulfill the following criteria: (1) a case-control study design or prospective study design; (2) number of subjects with each allele or genotype in cases and controls reported; (3) risk estimates OR and 95%CI, or raw data that allowed us to calculate them; and (4) risk estimate was only with miRNA polymorphism, and not with miRNA binding site SNPs. All searches were performed independently by two investigators. Thirteen epidemiological studies were included in our study. As summarized in Table 1, Peng *et al*[40] suggested a significantly increased risk of gastric cancer in subjects homozygous for the variant C of miR-196a-2 (rs11614913) compared with wild-type homozygote TT and heterozygote CT carriers in a Chinese population (adjusted OR = 1.57, 95%CI: 1.03-2.39). Stratified analyses showed that the subjects homozygous for the variant C genotype of miR-196a-2 had a strong association with lymph node metastasis of gastric cancer (adjusted OR = 2.25, 95%CI: 1.21-4.18). Subsequently, Okubo *et al*[41] evaluated the associations of three SNPs (rs11614913, rs2910164 and rs3746444) in pre-miRNA (miR-196a2, miR-146a and miR-499) with the risk of gastric cancer in the Japanese population. The strongest association was observed only in the miR-146a rs2910164 (G > C) SNP. Our research also indicated that miR-27a A/G (rs895819) and miR-146a C/G (rs2910164) polymorphisms had important significance in gastric cancer susceptibility[16,17]. In addition, an increased risk of gastric cancer was obtained with AA genotype in pre-miR-30c compared with GG genotype in the Chinese population (adjusted OR = 1.83, 95%CI: 1.07-3.15).

Table 1 List miRNA-single-nucleotide polymorphisms evaluated in gastric cancer

First author year	Population	miRNA	SNP ID	Allele	Case/control	Risk[1] (OR and 95%CI)
Peng *et al*[40] 2010	Chinese	miR-196a-2	rs11614913	T/C	213/213	1.57 (1.03-2.39)
Okubo *et al*[41] 2010	Japanese	miR-146a	rs2910164	G/C	552/697	1.30 (1.02-1.66)
		miR-196a-2	rs11614913	T/C	552/697	NS
		miR-499	rs3746444	A/G	552/697	NS
Sun *et al*[16] 2010	Chinese	miR-27a	rs895819	A/G	304/304	1.48 (1.06-2.05)
Zeng *et al*[17] 2010	Chinese	miR-146a	rs2910164	C/G	304/304	1.58 (1.11-2.20)
Hishida *et al*[56] 2011	Japanese	miR-146a	rs2910164	C/G	583/540	NS
Mu *et al*[42] 2012	Chinese	miR-30c	rs928508	A/G	240/240	1.83 (1.07-3.15)
Zhang *et al*[43] 2012	Chinese	miR-149	rs2292832	T/C	762/757	NS
		miR-605	rs2043556	A/G	762/757	NS
Arisawa *et al*[44] 2012	Japanese	miR-938	rs2505901	T/C	333/574	0.73 (0.55-0.99)
Ahn *et al*[50] 2012	South Korean	miR-146a	rs2910164	C/G	461/447	NS
		miR-149	rs2292832	T/C	461/447	NS
		miR-196a-2	rs11614913	T/C	461/447	NS
		miR-499	rs3746444	A/G	461/447	NS
Zhou *et al*[53] 2012	Chinese	miR-27a	rs895819	A/G	295/413	0.28 (0.12-0.66)
Yang *et al*[54] 2012	Chinese	miR-27a	rs11671784	G/A	892/978	0.76 (0.63–0.92)
		miR-27a	rs895819	A/G	892/978	NS
Zhou *et al*[57] 2012	Chinese	miR-146a	rs2910164	C/G	1686/1895	1.26 (1.01-1.56)
Wang *et al*[51] 2013	Chinese	miR-196a-2	rs11614913	T/C	1689/1946	0.71 (0.60-0.83)

[1]Risk estimate by authors supplied main results in full text.

Moreover, the gastric cancer risk was especially elevated in older individuals (aged > 60 years), men, non-smokers, and *H. pylori*-infected individuals[42]. More interestingly, Zhang *et al*[43] found that lifestyle-related factors, including tea consumption and smoking, might have the potential to modify the associations between miR-149 and miR-605 polymorphisms and gastric cancer risk. One study also suggested that miR-938 polymorphism (rs2505901) C locus carried a decreased risk overall for gastric cancer (OR = 0.73, 95%CI: 0.56-0.99)[44]. Additionally, many epidemiological studies also reported that miRNA binding site polymorphisms were associated with the risk of gastric cancer[45-47]. As shown in Table 1, the most frequently studied SNPs are rs11614913 in miR-196a-2, rs895819 in miR-27a, and rs2910164 in miR-146a. Therefore, we discuss and perform a meta-analysis to evaluate the association between the three polymorphisms and gastric cancer susceptibility based on all eligible case-control published data. We calculated the pooled OR and 95%CI based on the most frequently adopted genetic model in original literature. The *Z* test was used to determine the statistical significance of the pooled OR, and $P < 0.05$ was considered statistically significant. Additionally, Q and I^2 statistics were used to examine possible heterogeneity of study results[48]. If significant heterogeneity existed ($P < 0.10$ was considered representative of statistically significant heterogeneity), the pooled OR estimate of each study was calculated by the random effects model, otherwise the fixed-effects model was used.

SNP rs11614913 in miR-196a-2

The SNP (rs11614913) in the pre-miRNA region of miR-196a-2 was first identified in a case-control study of 1009 breast cancer cases and 1093 cancer-free controls in a population of Chinese women[49]. In gastric cancer, Peng *et al*[40] suggested a significantly increased risk of gastric cancer in subjects homozygous for the variant C of miR-196a-2 (rs11614913) compared with TT + CT carriers. However, one study conducted in a Japanese population only found the rs11614913 SNP in the miR-196a2 was associated with the degree of *H. pylori*-induced mononuclear cell infiltration, and not gastric cancer risk[41]. To understand this effect better, the SNP was genotyped again in a study conducted on 461 Korean patients with gastric cancer and 447 matched controls. They revealed that miR-196a-2 CC genotype was associated with elevated gastric cancer risk among women (adjusted OR = 1.86, 95%CI: 1.09-3.19)[50]. On the contrary, Wang *et al*[51] recently found that the CC genotype was significantly associated with a reduced risk of gastric cancer compared with the CT + TT genotypes in larger samples of the Chinese population (adjusted OR = 0.71, 95%CI: 0.60-0.83). Therefore, to determine further whether there is an association between rs11614913 and risk of gastric cancer, we summarized the published data from these studies using a recessive model, and showed no significant association between SNP rs11614913 in miR-196a-2 and gastric cancer risk (OR = 1.06, 95%CI: 0.74-1.50, $Z = 0.30$, $P = 0.77$; $Q = 18.85$, $P < 0.01$, Table 2).

SNP rs895819 in miR-27a

A recent study has suggested that miR-27a expression is significantly upregulated in gastric cancer tissues, and high expression levels of miR-27a are associated with poor tumor histological grade[52]. These findings indicate the important role of miR-27a in the development and progression of gastric cancer. Our recent research including 304 gastric cancer cases and 304 cancer-free controls indicated that miR-27a A/G polymorphism

Table 2 miR-196a-2 single-nucleotide polymorphism (rs11614913) in gastric cancer

First author year	Study design	Case/control	Case			Control			Risk[1] (OR and 95%CI)
			TT	CT	CC	TT	CT	CC	
Peng *et al*[40] 2010	HB	213/213	43	94	76	50	107	56	1.56 (1.03-2.35)
Okubo *et al*[41] 2010	HB	552/697	166	281	105	223	350	124	1.09 (0.81-1.45)
Ahn *et al*[50] 2012	HB	461/447	119	242	100	128	232	87	1.15 (0.83-1.58)
Wang *et al*[51] 2013	HB	1689/1946	519	851	319	524	940	482	0.71 (0.60-0.83)
Overall		2915/3303	847	1468	600	925	1629	749	1.06 (0.74-1.50)

[1]OR and 95%CI were calculated under a recessive genetic model (CC *vs* CT + TT). HB: Hospital based.

Table 3 MiR-27a single-nucleotide polymorphism (rs895819) in gastric cancer

First author year	Study design	Case/control	Case			Control			Risk[1] (OR and 95%CI)
			AA	AG	GG	AA	AG	GG	
Sun *et al*[16] 2010	HB	304/304	115	135	54	145	119	40	1.50 (1.08-2.07)
Zhou *et al*[53] 2012	HB	295/413	166	122	7	214	167	32	0.84 (0.62-1.12)
Yang *et al*[54] 2012	HB	892/978	349	437	106	367	472	139	0.93 (0.76-1.13)
Overall		1491/1695	630	694	167	726	758	211	1.04 (0.76-1.42)

[1]OR and 95%CI were calculated under a dominant genetic model (AG + GG *vs* AA). HB: Hospital based.

(rs895819) polymorphism was associated with an elevated risk of gastric cancer. We observed that the patients with variant genotypes (AG + GG) of miR-27a showed a significantly increased risk of gastric cancer relative to AA carriers (adjusted OR = 1.48, 95%CI: 1.06-2.05). The elevated risk was especially evident in older subjects (age > 58 years), men, non-smokers and rural residents. Moreover, we also found that polymorphism of miR-27a might be responsible for elevated miR-27a levels and reduced target gene zinc finger and BTB domain containing 10 (ZBTB10) mRNA[16]. However, another study showed that the SNP rs895819 in miR-27a with the minor allele C (C corresponds to G in the opposite strand) presented a significantly reduced risk of gastric cancer (adjusted OR = 0.77, 95%CI: 0.60-0.99)[53]. Similarly, in the Chinese population, Yang *et al*[54] found that the G/A polymorphism in miR-27a (rs11671784) reduced gastric cancer risk, but not the association with rs895819. Therefore, we extracted the genotypes from the above studies, and calculated the overall OR based on the dominant model (Table 3). There was no significant risk association in the overall pooled analysis (OR = 1.04, 95%CI: 0.76-1.42, Z = 0.25, P = 0.81; Q = 7.82, P = 0.02).

SNP rs2910164 in miR-146a

A G to C polymorphism (rs2910164) located within the sequence of an miR-146a precursor was identified by Shen *et al*[55]. They revealed that the variant predisposed to an earlier age of onset of familial breast and ovarian cancers. In a Japanese population study, Okubo *et al*[41] revealed that rs2910164 CC genotype held a significantly higher risk of gastric cancer when compared to non-cancer subjects (adjusted OR = 1.30, 95%CI: 1.02-1.66). However, we showed that subjects with the variant genotypes (GC + GG) in miR-146a had a significantly higher risk of gastric cancer when compared with CC genotype carriers in the Chinese population (adjusted OR = 1.58, 95%CI: 1.11-2.20)[17]. Additionally, in other stratified analyses for gastric cancer risk, Ahn *et al*[50] found that subjects with miR-146a GG and (CG + GG) genotypes were associated with increased risk of gastric cancer among the non-smokers in a Korean population. In contrast, the study conducted by Hishida *et al*[56] on 583 gastric cancer cases and 540 gastric atrophy cases suggested a lack of association between SNP rs2910164 and gastric cancer risk. These observations were validated by Zhou *et al*[57] in a large sample of the Chinese population (1686 gastric cancer patients and 1895 cancer-free subjects). Their logistic regression suggested a significant association between rs2910164 polymorphism and increased gastric cancer risk (OR = 1.26, 95%CI = 1.01-1.56; GG *vs* CC + CG]. Apparently, these conclusions of the relevant studies are inconsistent, in part because of the small sample size, and the different genetic model and ethnicity of the patients. So, we performed a comprehensive analysis based on published data using a recessive model (Table 4). The combined results indicated that subjects homozygous for the variant C genotype in miR-146a had no statistically significant risk of gastric cancer when compared with (CC + CG) genotypes carrier (OR = 1.08, 95%CI: 0.87-1.33, Z = 0.68, P = 0.50; Q = 10.13, P = 0.04).

CONCLUSION

This review includes a summary and discussion of the current findings evaluating the role of SNPs of miRNA in gastric cancer occurrence and development. Furthermore, we performed a meta-analysis of the most frequently studied miRNA-SNPs (rs11614913 in miR-196a-2, rs895819 in miR-27a and rs2910164 in miR-146a) in gastric cancer.

Table 4 MiR-146a single-nucleotide polymorphism (rs2910164) in gastric cancer

First author year	Study design	Case/control	Case			Control			Risk[1] (OR and 95%CI)
			CC	CG	GG	CC	CG	GG	
Okubo *et al*[41] 2010	HB	552/697	236	243	73	254	322	121	0.73 (0.53-0.99)
Zeng *et al*[17] 2010	HB	304/304	89	153	62	119	132	53	1.21 (0.81-1.82)
Hishida *et al*[56] 2011	HB	583/540	230	271	82	215	254	71	1.08 (0.77-1.52)
Ahn *et al*[50] 2012	HB	461/447	159	231	71	164	221	62	1.13 (0.78-1.63)
Zhou *et al*[57] 2012	HB	1686/1895	286	822	578	393	951	551	1.27 (1.10-1.47)
Overall		3586/3913	1000	1720	866	1145	1880	858	1.08 (0.87-1.33)

[1]OR and 95%CI were calculated under a recessive genetic model (GG *vs* CC + CG). HB: Hospital based.

Based on current data, there was no significant association between these miRNA-SNPs and gastric cancer risk in our meta-analysis. Future studies based on larger samples and independent cohorts are still needed to confirm the predictive signature of miRNA-SNPs in gastric cancer, for a better understanding of gastric cancer carcinogenesis.

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