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Lack of association of two common polymorphisms rs2910164 and rs11614913 with susceptibility to gastric cancer: A meta-analysis

STOMACH

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Original Article

ABSTRACT

Background/Aims: MicroRNAs post-transcriptionally regulate the expression of their target genes and their function in a wide range of physiological pathways. Aberrant expression of microRNAs has been implicated in the development of human malignant tumors. Recent reports showed that two single nucleotide polymorphisms (SNPs), miR-146a rs2910164 and miR-196a2 rs11614913, are associated with increased risk of human gastric cancer. Nevertheless, results from the published reports are still inconsistent and inconclusive. Thus, we conducted this meta-analysis study to further evaluate the effects of these two SNPs on susceptibility to human gastric cancer.

Materials and Methods: Using specific inclusion and exclusion criteria, we extracted data from selected studies that were identified from electronic databases, such as PubMed, Embase, and Wanfang. Odds ratio (ORs) and 95% CIs were then obtained to determine the impact of the two SNPs on susceptibility to human gastric cancer using the statistical software Stata.

Results: We identified six studies on rs2910164 and five reports regarding rs11614913 for our meta-analysis. Our data demonstrated that the two SNPs rs2910164 and rs11614913 do not produce any effects on the risk of human gastric cancer under all genetic models.

Conclusion: There is no significant association between rs2910164 and rs11614913 and the risk of human gastric cancer. However, future studies with large and homogeneous population of patients with gastric cancer and well-matched controls are needed to validate these findings.

Keywords: Gastric cancer, MicroRNA, single nucleotide polymorphism, susceptibility, meta-analysis

INTRODUCTION

Worldwide, gastric cancer is one of the most common malignant tumors of the gastrointestinal tract. Although the mechanisms underlying the pathogenesis of gastric cancer are still not clear, recent evidence suggests that *Helicobacter pylori* infection, alcohol, smoking, and diet have been implicated in the development of human gastric cancer, although the mechanisms of how these factors contribute to the carcinogenesis of gastric cancer are still not defined (1). Nonetheless, the exposure of these factors only results in the development of gastric cancer in a small population of individuals, indicating that genetic susceptibility may also contribute to the etiology of gastric cancer. Intriguingly, recent studies demonstrated that single nucleotide polymorphisms (SNPs) in certain genes are associated with increased risk of the development of human gastric cancer (2).

MicroRNAs (miRNAs) are ~22 nucleotides, non-coding, single-stranded RNAs. These miRNAs downregulate the expression of their target genes by complementarily binding to target mRNAs and subsequently leading to the degradation of mRNAs or by blocking the translation process of the target mRNAs (3). A large body of evidence has suggested that aberrant expression of miRNAs results in deregulated expression of certain tumor suppressor genes or oncogenes and consequently leads to cancer development (4). Hou et al. (5) has shown that the expression levels of miR-146a are reduced in human gastric cancer, resulting in an increase in tumor size as well as in poor differentiation. Another group further confirmed these findings (6).

Substantial evidence indicates that SNPs in miRNAs may impact the biogenesis and functions of miRNAs,

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thereby influencing susceptibility to human cancers (7). To date, several groups have demonstrated that the SNPs miR-146 rs2910164 and miR-196a2 rs11614913 are closely correlated with susceptibility to human gastric cancer (8-15). However, the relationship between these two SNPs and susceptibility to the development of human gastric cancer are still inconclusive in the literature, probably resulting from the small sample size of an individual study. Thus, meta-analysis may help to increase statistical power and provide more reliable evidence by analyzing the pooled data from published reports. Although several groups have conducted meta-analyses to examine the effects of these two common SNPs on susceptibility to various human cancers (16-18), the reliability of the findings from those reports are limited due to the clinical heterogeneity resulting from diverse histological cancer tissues in the included studies. Furthermore, these meta-analysis studies did not include every eligible article on gastric cancer, thereby limiting their capacities to reveal the true relationships between these two SNPs and the risk of gastric cancer. Here we conducted a meta-analysis study to achieve an updated assessment of the effects of the two SNPs rs2910164 and rs11614913 on the risk of human gastric cancer.

MATERIALS AND METHODS

Identification and eligibility of included studies

Search terms such as "microRNA-146a," "microRNA-196a2," "rs2910164," "rs11614913," "gastric cancer," "genotype," "polymorphism," and "variant" were used to search the electronic databases PubMed, Embase, and WanFang to identify relevant reports (last search update June 2013). When we identified duplicate reports, the study with the largest sample population was chosen for this meta-analysis. All studies chosen for this meta-analysis were approved by the Ethical Committee of the relevant institutions, as reported in the selected articles. Additionally, all case and control subjects provided written informed consent in the selected studies.

Criteria for inclusion and exclusion

To identify eligible studies for this analysis, we considered the following parameters: (a) the impact of the SNPs rs2910164 or rs11614913 on the risk of human gastric cancers was examined, (b) only case-control studies were included, and (c) the articles that reported clinical data that are sufficient for determining an odds ratio (OR) with their corresponding 95% confidence interval (CI). Criteria for exclusion were as follows: (i) no control subjects were included, (ii) genotype frequency was not available for analysis, and (iii) duplicate studies.

Data extraction

Demographic information, such as first author's name, year of publication, country of origin, race, sources of controls, genotyping method, matched criteria between cases and controls, number of cases and control subjects, and genotype frequencies for cases and control subjects, was collected from selected studies. The extent of the association of the two SNPs miR-146a rs2910164 and miR-196a2 rs11614913 with the risk of gastric cancers was calculated using OR and its corresponding 95% CI. Inconsistency was resolved through discussion between the two authors until an agreement was reached.

Statistical analysis

ORs and 95% CIs were obtained to determine the association of miRNAs SNPs and the risk of gastric cancer. We obtained the pooled ORs by combining the results from a single study under a homozygous model (rs2910164: CC vs. GG; rs11614913: CC vs. TT), heterozygous model (rs2910164: GC vs. GG; rs11614913: CC vs. TT), recessive model (rs2910164: CC vs. GC/GG; rs11614913: CC vs. TC/TT), and dominant model (rs2910164: GC/CC vs. GG; rs11614913: TC/CC vs. TT). To determine the heterogeneity between the included studies, I^2- and the X^2-based Q-statistic tests were conducted (19). The I^2 index indicates the extent of variation across studies due to heterogeneity (low heterogeneity, I^2=25%; moderate heterogeneity, I^2=50%; high heterogeneity, I^2=75%). If the included studies are of moderate or high heterogeneity, the random-effects model was employed to estimate the overall effects; the fixed-effects model was applied when I^2 was less than 50%. Publication bias involving our meta-analysis was evaluated using funnel plots, the Egger's test, and the Begg's test. The significance of the intercept value was calculated by the t-test according to the Egger's test. All analyses with two-sided p values were conducted with the Stata software (Version 11.0; Stata Corp, College Station, TX, USA).

RESULTS

Study characteristics

After an initial extensive literature search of the electronic databases PubMed, EMBASE, and Wanfang, a total of 78 reports was retrieved. Our comprehensive literature search yielded eight case-controlled studies (8-15) that met the inclusion criteria, as described above (Figure 1). The selected studies are of acceptable qualities for our meta-analysis, and we have summarized the characteristics of the chosen studies in Table 1. Genotype frequencies for the SNPs rs2910164 and rs11614913 were separately examined in the studies from Okubo et al. (9) and Ahn et al. (14). Thus, we extracted the data for each SNP separately for this meta-analysis. Wang et al. (15) presented ORs separately according to the different subgroups. Therefore, we included a total of six studies (8-12,14) involving 3.658 cases and 5.036 controls for rs2910164 and five studies (9,13-15) including 2.915 cases and 3.303 controls for rs11614913 in our meta-analysis (Figure 1).

Meta-analysis study of the impact of the SNP rs2910164 on the risk of gastric cancer

The impact of rs2910164 on the risk of gastric cancer was examined in six studies with 5.036 controls and 3.658 cases. Because we detected significant heterogeneity among the included studies under all genetic models, we then employed the ran-

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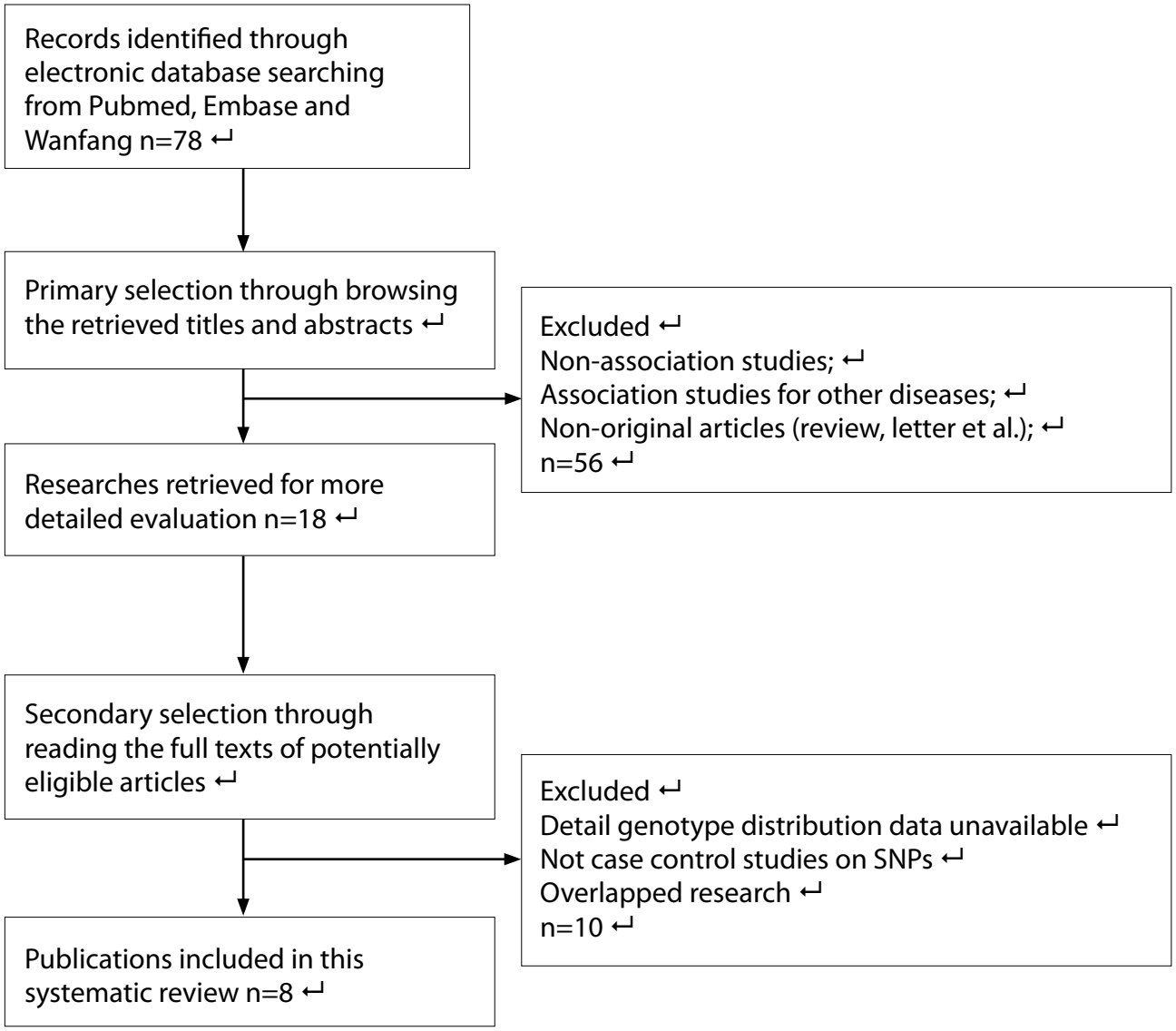

Figure 1. Flow diagram of identification of studies.

dom-effects model to calculate the pooled ORs (Table 2). Our meta-analysis data demonstrated that the SNP rs2910164 is not significantly associated with susceptibility to gastric cancer under all genetic models (heterozygote model: OR=1.08, 95% CI: 0.85–1.37, p=0.515; homozygote model: OR=0.96, 95% CI: 0.73–1.28, p=0.796; recessive model: OR=0.89, 95% CI: 0.76–1.04, p=0.146; dominant model: OR=1.04, 95% CI: 0.82–1.31, p=0.771; Figure 2).

Meta-analysis study of the impact of the SNP rs11614913 on the risk of developing gastric cancer

Five studies comprising 3.303 control subjects and 2.915 cases were included to assess the impact of the SNP rs11614913 on the risk of gastric cancer. Under homozygous and recessive genetic models, we used the fixed-effects model to estimate the pooled ORs due to significant heterogeneity between the included studies, whereas we employed the fixed-effects model to pool the ORs in heterozygous and dominant genetic models (Table 2). However, as shown in Figure 3, the SNP rs11614913 does not significantly affect the risk of developing gastric cancer under all genetic models (homozygote model: OR=0.90, 95% CI=0.67–1.21, p=0.08; heterozygote model: OR=0.96, 95% CI=0.85–1.08, p=0.472; recessive model: OR=0.93, 95% CI=0.72–1.21, p=0.067; dominant model: OR=1.01, 95% CI=0.90–1.13, p=0.835).

Publication bias

Next, we generated a funnel plot and performed the Egger's test to investigate the publication bias regarding our meta-analyses. We obtained nearly symmetrical funnel plots for both SNPs under all genetic models (Figure 4). Our result from the Egger's test further indicates that there is no significant publication bias involving this meta-analysis (p>0.05; Figure 5).

Table 1. Characteristics of studies included in the meta-analysis

Study	Country	Ethnicity	Source	Genotype method	Matching criteria	Genotypes distribution (cases/controls)			HWE
						G/G	C/G	C/C	
miR-196a2 rs2910164									
Okubo2010	Japan	Asian	HB	PCR-RFLP	ND	73/121	243/254	236/322	Y
Zeng2011	China	Asian	HB	PCR-RFLP	Age/sex	62/53	153/132	89/119	Y
Hishida2010	Japan	Asian	HB	PCR-confronting	Age/sex	82/229	271/775	230/633	Y
Ahn2012	Korea	Asian	HB	PCR-confronting	Age/sex	62/71	221/231	164/159	Y
Zhou2012	China	Asian	HB	TaqMan	Age/sex	578/551	822/951	286/393	Y
Ma2012	China	Asian	HB	PCR-confronting	ND	22/17	44/19	20/6	N
miR-146a rs11614913					T/T	C/T	C/C		
Okubo2010	Japan	Asian	HB	PCR-RFLP	ND	105/124	281/350	166/223	Y
Peng2010	China	Asian	HB	PCR-RFLP	ND	62/53	153/132	89/119	Y
Hishida2010	Japan	Asian	HB	PCR-confronting	Age/sex	82/229	271/775	230/633	Y
Wang2013(1)	China	Asian	HB	TaqMan	Age/sex	226/232	371/448	152/220	Y
Wang2013(2)	China	Asian	HB	TaqMan	Age/sex	293/292	480/492	167/262	Y

ND: not document; HWE: Hardy-Weinberg equilibrium; Y: genotype frequency distribution agreed to HWE in controls; N: genotype frequency distribution disagreed to HWE in controls; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; HB: hospital-based; PB: population-based

Table 2. Main results of pooled ORs in the meta-analysis

miR-146a rs2910164	Studies	OR (95 % CI)	P_{OR}	Model	I^2 (%)	P_H
Homozygous	6	0.96 (0.73-1.28)	0.796	Random	71.9	0.003
Heterozygous	6	1.08 (0.85-1.37)	0.515	Random	66.8	0.01
Recessive	6	0.89 (0.76-1.04)	0.146	Random	54.7	0.051
Dominant	6	1.04 (0.82-1.31)	0.771	Random	69.8	0.005
miR-196a2 rs11614913	**Studies**	**OR (95 % CI)**	**Model**	**P_{OR}**	**I^2 (%)**	**PH**
Homozygous	5	0.90 (0.67-1.21)	0.08	Random	74	0.004
Heterozygous	5	0.96 (0.85-1.08)	0.472	Fixed	0	0.709
Recessive	5	0.93 (0.72-1.21)	0.067	Random	78.1	0.584
Dominant	5	1.01 (0.90-1.13)	0.835	Fixed	0	0.499

OR: odds ratio; CI: confidence interval; POR: prevalence odds ratio; I2: it is used to measure the degree of heterogeneity; PH: p values for between-study heterogeneity test.

DISCUSSION

MiRNAs are small, single-stranded, non-coding RNAs that have been implicated in a variety of important biological processes such as apoptosis, differentiation, proliferation, immune responses, and angiogenesis (20). SNPs in miRNA genes can affect the functions of miRNA by influencing the transcription of the primary miRNA transcripts, the maturation of pri-miRNAs and pre-miRNAs, or the interactions of miRNAs and their target mRNAs, which may then contribute to cancer susceptibility (21). In recent years, the roles of certain SNPs in the miRNA-coding regions and their effects on the risk of human gastric cancers have been extensively investigated (22). It has been demonstrated that SNPs in miRNA-coding regions are associated with gastric carcinogenesis and increased susceptibility to the development of gastric cancer (23,24). Better understanding of the association between these SNPS and the risk of gastric cancer may provide novel insights into the prevention and early diagnosis of human gastric cancer in high-risk populations and important guidelines for the management of this malignancy (25,26). miR-146a rs2910164 and miR-196a2 rs11614913 polymorphisms have been reported to be correlated with increased risks to develop gastric cancer. However, the published results regarding these associations are still inconclusive due to inherent limitations such as case selection bias and small sample size. In this meta-analysis study, we analyzed the impact of the two SNPs rs2910164 or rs11614913 on the risk of gastric cancer by pooling the data from eight eligible case-control studies. Thus, our meta-analysis largely increases statistical power.

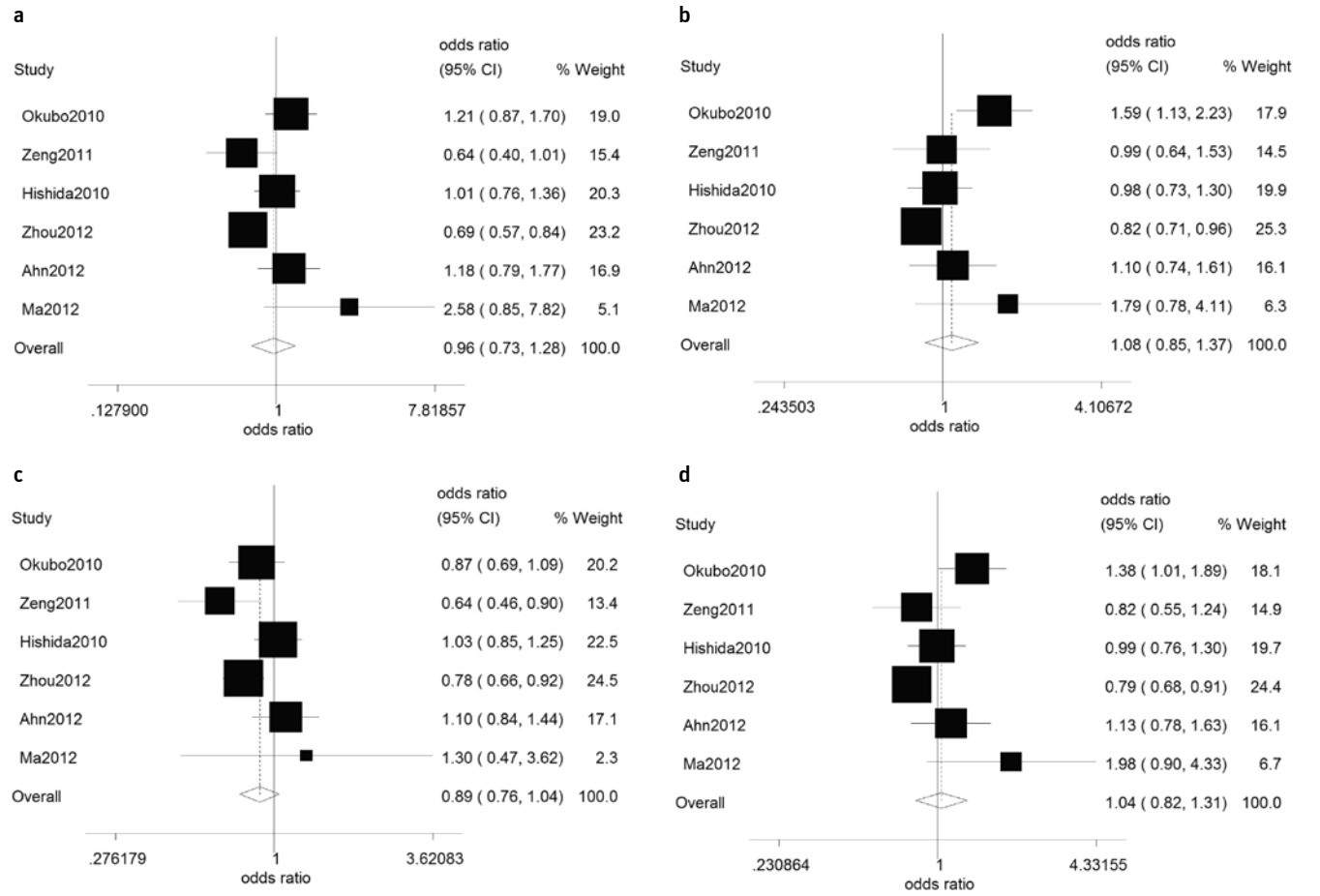

Figure 2. a-d. Meta-analysis of the association between gastric cancer risk and the miR-146a rs2910164 polymorphism for the homozygous model **(a)**, heterozygous model **(b)**, recessive model **(c)**, and dominant model **(d)**.

Despite its implication in the regulation of immune responses, it remains controversial whether miR-146a plays any role in the pathogenesis and progression of human cancers (27,28). The expression levels of miR-146a have been found to be elevated in papillary thyroid cancer (29) and cervical cancer (30). However, miR-146a expression is reduced or absent in prostate cancer (31), gastric cancer (32), and pancreatic cancer (33). Additionally, ectopic expression of miR-146a downregulates the expression levels of interleukin 1 receptor-associated kinase 1, nuclear factor-kappaB (NF-kb), and epidermal growth factor receptor (EGFR) in breast cancer cells, thereby inhibiting the invasion and metastasis of these cancers (34). These controversial findings suggest that miR-146a exhibits completely different functions in various human cancers. In this meta-analysis, the data extracted from six eligible reports were analyzed to achieve a better estimate of the impact of the SNP rs2910164 on the risk of gastric cancer. However, our data show that miR-146a rs2910164 is not associated with the risk of human gastric cancer, indicating that rs2910164 polymorphism may not participate in the pathogenesis of human gastric cancer.

Another SNP rs11614913 in miR-196a2 has also been documented to be an important risk factor for gastric cancer. This SNP can influence the expression of miR-196a and its target genes such as homeobox (HOX) genes and Annexin A1 (ANXA1) (35,36). The expression of the homeobox genes, including HOXA4, HOXA5, HOXA7, HOXA9, and HOXA13, is elevated in human gastric cancers, and the deregulated expression of these genes have been implicated in the pathogenesis of gastric cancer (37). Intriguingly, miR-196a, which functions to mediate apoptosis and inhibit cell proliferation, has been found to regulate the expression of its target gene ANXA1 (36). Further evidence suggests that the deregulated expression of ANXA1 is closely associated with the degree of aggressiveness and advanced disease stage of gastric cancer, including lymph node metastasis and poor histological differentiation (38). Therefore, SNPs in miR-196a2 may lead to increased susceptibility to gastric cancer through the deregulated expression of its target genes, such as HOX and ANXA1. The data from the five included studies of the impact of rs11614913 on susceptibility to gastric cancer were identified and pooled for our meta-analysis. However, our data showed that the SNP rs11614913 is not significantly correlated with the risk of developing gastric cancer under all genetic models. In fact, the inconsistency between epidemiological findings and functional studies may result from different genetic

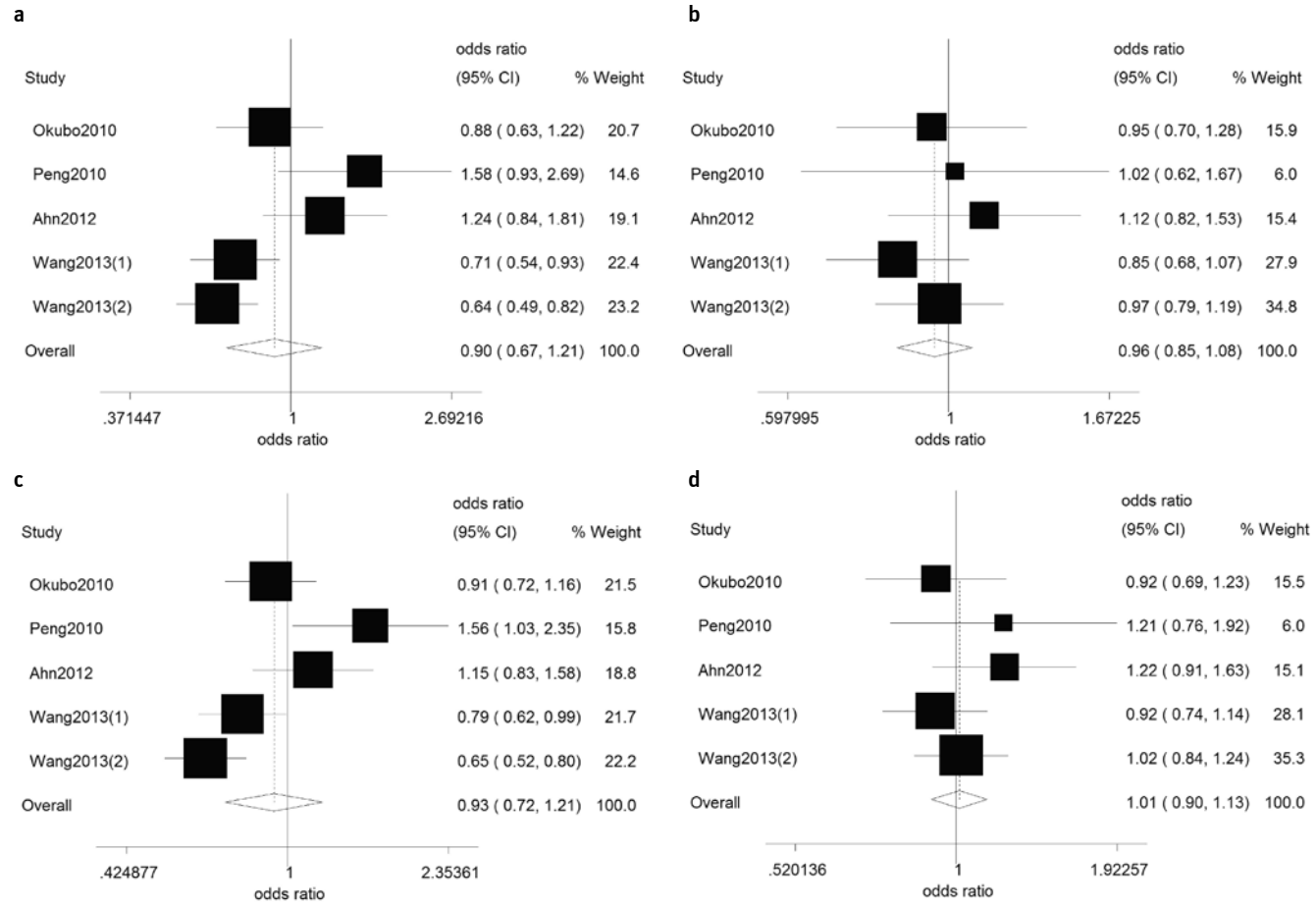

Figure 3. a-d. Meta-analysis of the association between gastric cancer risk and the miR-196a2 polymorphism for the homozygous model **(a)**, heterozygous model **(b)**, recessive model **(c)**, and dominant model **(d)**.

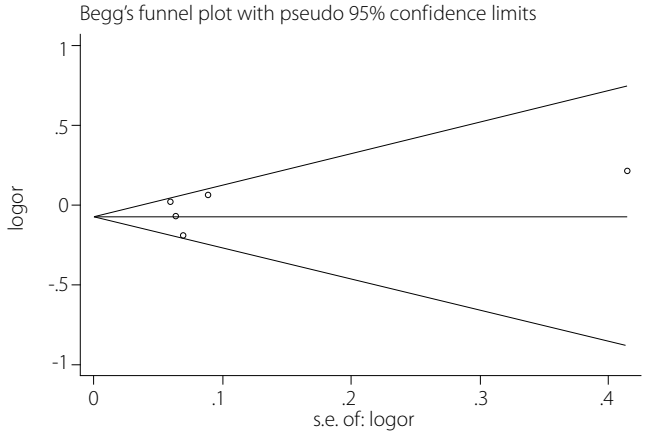

Figure 4. Egger's publication bias of miR-146a rs2910164 polymorphism and gastric cancer risk (Egger's test for publication bias was not significant: CC vs. GC+GG; p=0.573).

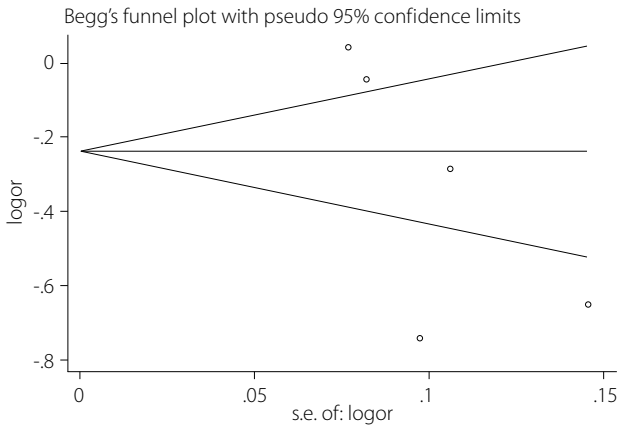

Figure 5. Egger's publication bias of miR-196a2 polymorphism and gastric cancer risk (Egger's test for publication bias was not significant: TT vs. CT+CC; p=0.142).

backgrounds of cancer patients because human cancer is a complex multi-genetic disease (39). Hence, we cannot rule out the possibility that the impact of the SNP rs11614913 on the risk of gastric cancer may be masked by the dysregulation of some other unidentified causal genes that are implicated in the pathogenesis of gastric cancer.

It is noteworthy that there are some limitations regarding this meta-analysis that we would like to discuss here. Firstly, the control subjects were not absolutely uniform because some may suffer from certain benign diseases, although they were mainly chosen from healthy populations. Therefore, the reliability of our meta-analysis may be compromised by the non-

differential misclassification bias because the studies that are included in our meta-analysis may have recruited the control subjects who had been exposed to other confounding risk factors for gastric cancer. Secondly, the relatively small number of included studies limited our capacity to conduct the subgroup analysis. Despite these limitations, as discussed above, there are some advantages regarding our meta-analysis that we would like to highlight. First, although we included relatively small number of studies in this meta-analysis, the total number of cases and control subjects from the chosen studies were substantial, which dramatically boosts the statistical power of our meta-analysis. Second, all case and control subjects from the included studies were Asians; thus, there are no issues regarding heterogeneity that may result from different ethnicity of recruited subjects. Third, we detected no publication biases regarding our meta-analysis, suggesting that the overall pooled effects may not be biased.

Taken together, despite certain limitations as discussed above, our meta-analysis demonstrates that there is no significant association between the two SNPs rs2910164 and rs11614913 and the risk of gastric cancer. Nevertheless, it is important to conduct additional independent studies with larger sample sizes using well-matched control subjects, homogeneous patients with gastric cancer, and standardized genotyping techniques. Additionally, it will also be important to consider the confounding effects of gene–gene and gene–environment interactions in the development of human gastric cancer in future studies. Such studies that will take these factors into account may provide novel insights into our understanding of the association between the two SNPs rs2910164 and rs11614913 and the risk of gastric cancer in the future.

Ethics Committee Approval: Ethics committee approval was received for this study.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author contributions: Concept - L.Z.; Design - L.Z., F.B.; Supervision - L.Z., F.B.; Resource - L.Z., J.G., F.B.; Materials - L.Z., J.G., F.B.; Data Collection &/or Processing - L.Z., J.G., D.Z.; Analysis &/or Interpretation - L.Z., J.G., D.Z.; Literature Search - L.Z., J.G.; Writing - L.Z.; Critical Reviews - J.G., D.Z., F.B.

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