miR-146a gene polymorphism rs2910164 and the risk of digestive tumors: A meta-analysis of 21 case-control studies

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Abstract. Digestive tumors have the highest incidence among all tumor types worldwide. miR-146a has been shown to play an important role in the development, apoptosis, invasion and metastasis of digestive tumors. Additionally, a miR-146a gene polymorphism has been associated with the risk of a variety of cancer types in the digestive system. Therefore, in order to investigate the correlation, a meta-analysis of reported data was conducted, for which we obtained 21 research studies concerning the association between the miR-146a gene polymorphism and digestive tumors. Odds ratio (OR) values and 95% confidence intervals (95% CI) were used to assess this association. We found that the miR-146a polymorphism rs2910164 might significantly increase the susceptibility of digestive tumors, in particular for esophageal cancer and colorectal cancers. Furthermore, the miR-146a polymorphism might significantly increase the risk of digestive tumors in Asians. However, no obvious correlation between the polymorphism and the risk for digestive tumors was found in Caucasians.

Introduction

According to global cancer statistics, the morbidity and mortality rates of digestive tumors rank first in both male and female populations (1). The etiology and pathogenesis of digestive tumors have a lot in common. To prevent digestive tumors, it is necessary to understand the related predisposing factors. Studies have shown that environmental factors, diet, intake of non-steroidal and anti-inflammatory drugs, and endogenous factors can significantly affect the individual susceptibility to digestive tumors (2,3).

MicroRNAs (miRNAs) are a group of small non-coding RNAs that are ~22 (18-25) nucleotides (nt) long. They have been found to be associated with a variety of diseases, including cancer. An increasing number of findings confirm that miRNAs play essential roles in the development, but also the diagnosis, treatment and prognosis of a variety of tumors. The value of using miRNAs as biomarkers for diagnosis and as target molecules for treatment of cancer is increasingly being recognized (4).

Numerous studies have shown that miR-146a is involved in the development, apoptosis, invasion and metastasis of digestive tumors; studies have reported that miR-146a is downregulated in gastric cancer or gastric cancer cells and that it regulates cell proliferation and apoptosis of gastric cancer cells (5). In addition, Vinci et al (6) studied the distribution of sequence variants of miR-146a in colorectal cancer and the effects of miRNA expression. He *et al* (7) reported that miR-146a modulated TGF-β1-induced hepatic stellate cell proliferation by targeting SMAD4. Tomokuni *et al* (8) demonstrated that miR-146a inhibited the anticancer effect of IFN-α in hepatocellular cancer (HCC) cells, and that this effect was mediated by SMAD4. Another study found that the expression of miR-146a inhibited the invasive capacity of pancreatic cancer cells with concomitant downregulation of EGFR and the NF-κB regulatory kinase interleukin 1 receptor-associated kinase 1 (9). Therefore, miR-146a appears to play a crucial role in the properties of digestive tumors.

Studies have shown that single nucleotide polymorphisms (SNPs) in human miRNAs constitute one of the main forms of genetic variation in human genomic DNA sequences and that they might play central roles in the susceptibility to human disease. miRNA SNPs exhibit interindividual differences that are relevant to disease diagnosis, treatment and prognosis.

A number of recent studies have suggested that the miR-146a expression is deregulated in numerous solid tumors, and it has become evident that miR-146a might act as a tumor-suppressor (5,10,11). The miR-146a rs2910164 G>C

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polymorphism is caused by the miR-146a leader sequence G:U and C:U base pair mismatching. Studies have shown that the miR-146a gene polymorphism rs2910164 is associated with the occurrence of a variety of cancer types, such as prostate, breast and cervical cancer (12-14). From 2008 to 2013, researchers have repeatedly reported associations between the miR-146a rs2910164 polymorphism and the risk for digestive tumors, but the results were mixed or even conflicting. Therefore, we performed a meta-analysis to derive a more precise estimation of the association between the miR-146a G/C SNP and the risks of developing cancer in the digestive system.

Materials and methods

Screening and identification of relevant studies. Identification and eligibility of relevant studies was performed using the search terms 'miR/microRNA-146a', 'digestive cancer', 'biliary cancer', 'hepatocellular cancer', 'esophageal squamous cell carcinoma', 'gastric cancer', 'colorectal cancer', 'pancreatic cancer', 'rs2910164', 'genotype', 'polymorphism' and 'variant' in the PubMed, Ovid and Embase databases and in the Cochrane Library (last search update: 17 April, 2013). The search was limited to English language articles and only published studies with full-text articles were included. We evaluated potentially relevant publications by manually examining their title and abstract.

Inclusion and exclusion criteria. Inclusion criteria were: i) assessment of miR-146a rs2910164 polymorphism and the risk of suffering from digestive cancer; ii) a separate case-control study on humans; iii) statistically sound genotype data with odds ratio (OR) values and 95% confidence intervals (CI); iv) full-text search. Exclusion criteria were: i) lack of controls in the studies; ii) repetition of previous results; iii) summary, comment, review and editorial articles; iv) a focus on benign tumors of the digestive tract.

Data extraction and study characteristics. Two researchers (Xiaohui Xu and Xiaodong Yang) independently extracted all data that met the above inclusion criteria and the existing differences in the resulting datasets were resolved by team discussions. From each study, the following information was extracted: last name of the first author, year of publication, ethnicity, tumor type, source of research, research methods, the number of cases and controls, the number of various genotypes of cases and controls. If a study did not provide complete data, we sent requests for this information to the corresponding author. A total of 21 eligible studies, comprising 10,318 cases and 12,478 controls met the inclusion criteria (Table I). The studies were published in the period from 2008 to 2013, and all were case-control studies. The case groups were only suffering from one type of cancer (gastrointestinal), while the control groups did not present with any tumor. From these 21 studies, 16 involved individuals of Asian ethnicity and 5 of Caucasian. In addition, the 21 studies used different detection methods, with 14 studies using the traditional method of polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), 1 using the PCR confronting two-pair primer (PCR-CTPP) method, 4 using the TaqMan-polymerase chain reaction (TaqMan-PCR) and another 2 using a SNP assay. All the control groups were selected from a healthy population and the age and gender were consistent with cases. All the above data complied with the Hardy-Weinberg equilibrium (HWE) principles (Table I).

Statistical analysis. According to the case and control genotype frequencies, the correlation between the miR-146a rs2910164 polymorphism and the risk of gastrointestinal cancer was assessed via OR values with 95% CI. In addition, we analyzed whether tumor type and ethnicity may affect the relationship between the miR-146a rs2910164 polymorphism and the risk of gastrointestinal cancer. Statistical analysis was performed on OR values (with 95% CI) for 5 distinct genotypic comparisons: the allelic one (G vs. C), comparison to the dominant genetic model (GC + GG vs. CC), comparison to the recessive genetic model (GG vs. GC + CC), the homozygote (GG vs. CC) and the heterozygote comparison (GC vs. CC). The Chi-square-based Q statistic was used to assess heterogeneity between studies, with a p-value ($P_{heterogeneity}$) <0.05 considered to indicate statistically significant heterogeneity between studies. The I^2 index, expressed as a percentage, quantified the degree of heterogeneity throughout the study, with I^2 values of 25, 50 and 75% referring to low, medium and high heterogeneity, respectively. Funnel plots were used to assess the publication bias. When the effects were assumed to be homogenous, the fixed-effects model was used (Mantel-Haenszel method). If inter-study heterogeneity was detected, the random-effects model was applied (DerSimonian and Laird method) (15). All data analyses were performed using the software Stata 11.0 and all the p-values are derived two-sided tests.

Results

Study characteristics. A total of 545 articles relevant to the used search terms were identified, and only 32 studies concerned the association between digestive cancer and the miR-146a rs2910164 polymorphism. According to the inclusion and exclusion criteria described in Materials and methods, 21 publications (16-36) were included in the final meta-analysis, 8 using population-based controls and 13 using hospital-based controls (Fig. 1). From the 21 publications, 2 concerned esophageal, 4 colorectal, 6 gastric and 6 hepatocellular cancer. The main characteristics of the studies included in the meta-analysis are summarized in Table I.

Overall analyses. The overall analysis of all cases revealed a statistically significant positive association between the miR-146a rs2910164 polymorphism and the risk of developing digestive tumors (Fig. 2).

Allele G vs. C: OR=1.08, 95% CI: 1.04-1.12, $P_{heterogeneity}$=0.001 (Fig. 2A). The results suggested that individuals with the G allele were more susceptible to digestive cancer than those with the C allele.

Dominant genetic model GC + GG vs. CC: OR=1.11, 95% CI: 1.04-1.18, $P_{heterogeneity}$<0.001 (Fig. 2B). The results suggested that individuals following the dominant genetic model GC + GG may show an increased susceptibility to digestive cancer.

Table I. Characteristics of the 21 studies included in the meta-analysis.

Author (ref.)	Year	Ethnicity	Tumor type	Study design	Genotyping method	No. of cases	No. of controls	Cases			Controls			HWE p-value
								CC	CG	GG	CC	CG	GG	
Xu *et al* (16)	2008	Asian	HCC	PB	PCR-RFLP	479	504	158	241	80	197	245	58	0.12
Ye *et al* (17)	2008	Caucasian	ESCC	PB	SNPlex assay	346	346	231	101	14	229	105	12	0.71
Srivastava *et al* (18)	2010	Asian	GBC	PB	PCR-RFLP	230	224	11	90	129	5	81	138	0.08
Guo *et al* (19)	2010	Asian	ESCC	PB	SNPshot	444	468	20	190	234	42	220	206	0.12
Zeng *et al* (20)	2010	Asian	GC	HB	PCR-RFLP	304	304	89	153	62	119	132	53	0.12
Min *et al* (21)	2012	Asian	CRC	PB	PCR-RFLP	446	502	151	233	62	188	245	69	0.443
Akkiz *et al* (22)	2011	Caucasian	HCC	PB	PCR-RFLP	222	222	10	75	137	11	67	144	0.38
Hishida *et al* (23)	2011	Asian	GC	HB	PCR-CTPP	583	1,637	230	271	82	633	825	229	0.12
Okubo *et al* (24)	2010	Asian	GC	HB	PCR-RFLP	552	697	236	243	73	322	254	121	0.28
Zhang *et al* (25)	2011	Asian	HCC	HB	PCR-RFLP	925	840	319	450	156	303	386	151	0.149
Xiang *et al* (26)	2012	Asian	HCC	PB	PCR-RFLP	100	100	28	45	27	33	46	21	0.51
Kim *et al* (27)	2012	Asian	HCC	PB	PCR-RFLP	159	201	57	88	14	74	103	24	0.19
Zhou *et al* (28)	2012	Asian	GC	HB	TaqMan	1,686	1,895	286	822	578	393	951	551	0.64
Ahn *et al* (29)	2012	Asian	GC	HB	PCR-RFLP	461	477	159	231	71	164	221	62	0.36
Hezova *et al* (30)	2012	Caucasian	CRC	HB	TaqMan	212	197	9	79	124	12	70	115	0.41
Mihalache *et al* (31)	2012	Caucasian	CCA	HB	TaqMan	182	350	11	53	118	17	122	211	0.91
Zhou *et al* (32)	2012	Asian	HCC	HB	PCR-RFLP	186	483	67	86	33	158	254	71	0.056
Song *et al* (33)	2013	Asian	GC	HB	PCR-RFLP	1,208	1,166	423	586	199	344	615	207	0.87
Ma *et al* (34)	2013	Asian	CRC	HB	TaqMan	1,147	1,203	169	534	444	192	614	397	0.075
Lv *et al* (35)	2013	Asian	CRC	HB	PCR-RFLP	353	540	47	230	54	143	274	96	0.08
Pavlakis *et al* (36)	2013	Caucasian	PC	HB	PCR-RFLP	93	122	51	38	4	79	39	4	0.76

HCC, hepatocellular cancer; ESCC, esophageal squamous cell carcinoma; GBC, gallbladder cancer; GC, gastric cancer; CRC, colorectal cancer; CCA, cholangiocarcinoma; PC, pancreatic cancer; PB, population-based case-control study; HB, hospital-based case-control study; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; SNP, single nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium.

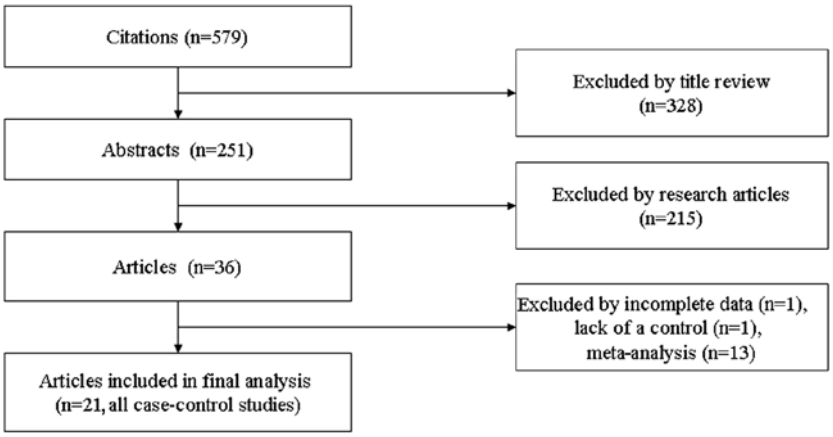

Figure 1. Flowchart of the selection of published studies.

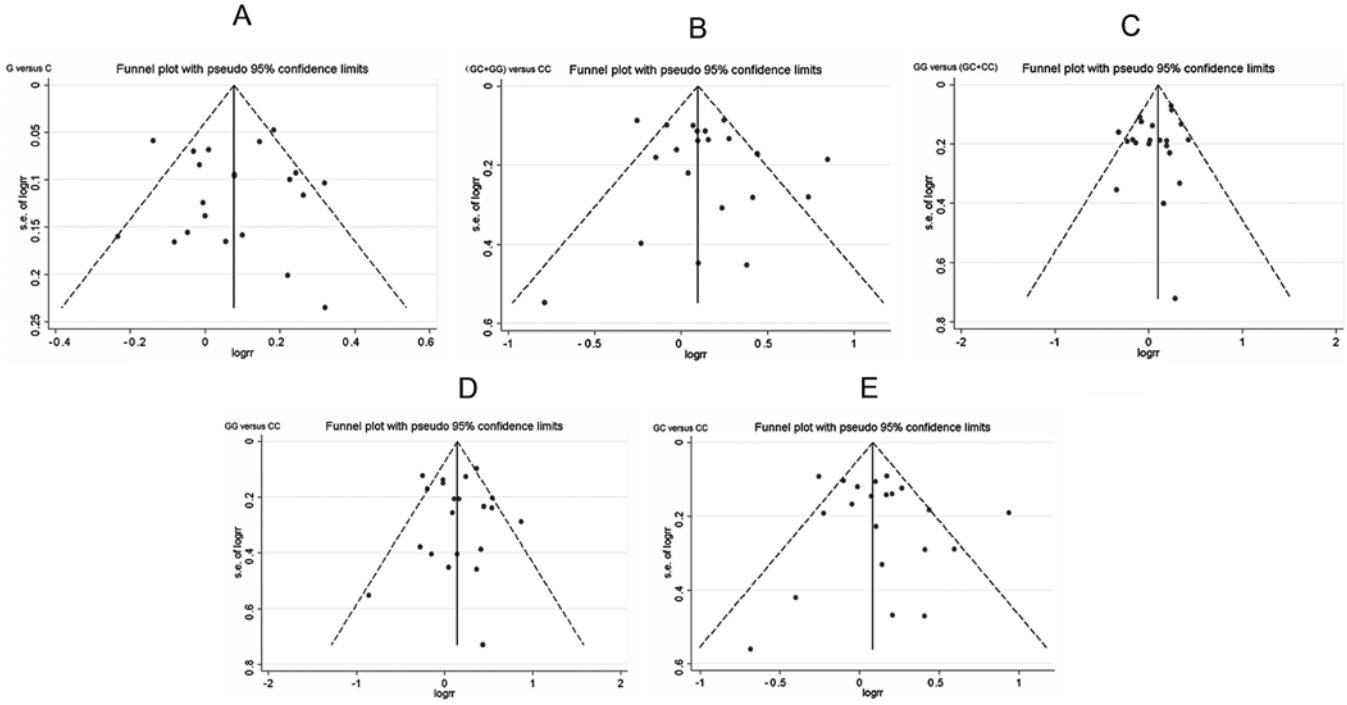

Figure 2. Forest plot for the association between the miR-146a rs2910164 polymorphism and digestive cancer risk in the populations. (A) G vs. C; (B) GC + GG vs. CC; (C) GG vs. GC + CC; (D) GG vs. CC; (E) GC vs. CC.

Recessive genetic model GG vs. CC + GC: OR=1.11, 95% CI: 1.04-1.18, $P_{heterogeneity}$=0.020 (Fig. 2C). The results suggested that compared to CC + GC, individuals following the recessive genetic model GG were more susceptible to digestive cancer.

Homozygous GG vs. CC: OR=1.16, 95% CI: 1.06-1.26, $P_{heterogeneity}$=0.002 (Fig. 2D). The results suggested that individuals following the homozygous GG model showed no significant difference compared to individuals with the CC allele with regards to developing digestive cancer.

Heterozygous GC vs. CC: OR=1.09, 95% CI: 1.02-1.16, $P_{heterogeneity}$<0.001 (Fig. 2E). The results suggested that individuals following the heterozygous model GC were more susceptible to digestive cancer than those with the CC allele.

Furthermore, in the stratified analysis exploring the contributions from the type of digestive cancer (Table II), significantly increased risks for esophageal squamous cell carcinoma were found [(for G vs. C: 1.23 (1.04-1.44), $P_{heterogeneity}$=0.054; for GG vs. CC + GC: 1.39 (1.09-1.78), $P_{heterogeneity}$=0.655; for GG vs. CC: 1.88 (1.19-2.97), $P_{heterogeneity}$=0.145)], as well as risks for colorectal cancer [(for G vs. C: 1.15 (1.06-1.25), $P_{heterogeneity}$=0.697; for (GC + GG) vs. CC: 1.31 (1.12-1.52), $P_{heterogeneity}$=0.005, for GG vs. CC + GC: 1.14 (1.00-1.31), $P_{heterogeneity}$=0.16; for GG vs. CC: 1.30 (1.08-1.57), $P_{heterogeneity}$=0.587, for GC vs. CC: 1.28 (1.09-1.50), $P_{heterogeneity}$<0.001)], but not for biliary, hepatocellular, gastric and pancreatic cancer.

However, in the subgroup analysis where ethnicity was analyzed, significantly increased risks were found for Asians

Table II. Subgroup analysis of the association between the miR-146a rs2910164 polymorphism and the risk of digestive cancer.

Comparison	Subgroup	No.[a]	OR (95% CI)	I^2 (%)	P-value[b]
G vs. C	Ethnicity				
	Asian	16	1.08 (1.04-1.13)	65.1	<0.001
	Caucasian	5	1.05 (0.91-1.21)	0.0	0.701
	Digestive cancer type				
	Biliary cancer	2	0.94 (0.75-1.17)		
	Hepatocellular cancer	6	1.06 (0.97-1.16)	23.4	0.258
	Esophageal squamous cell carcinoma	2	1.23 (1.04-1.44)	70.8	0.054
	Gastric cancer	6	1.05 (0.99-1.11)	78.6	<0.001
	Colorectal cancer	4	1.15 (1.06-1.25)	0.0	0.697
	Pancreatic cancer	1	1.38 (0.87-2.18)		
GC + GG vs. CC	Ethnicity				
	Asian	16	1.11 (1.04-1.18)	72.5	<0.001
	Caucasian	5	1.08 (0.85-1.37)	0.0	0.576
	Digestive cancer type				
	Biliary cancer	2	0.65 (0.35-1.23)		
	Hepatocellular cancer	6	1.10 (0.97-1.26)	0.0	0.549
	Esophageal squamous cell carcinoma	2	1.19 (0.91-1.56)	82.1	0.018
	Gastric cancer	6	1.04 (0.96-1.14)	79.7	<0.001
	Colorectal cancer	4	1.31 (1.12-1.52)	76.5	0.005
	Pancreatic cancer	1	1.51 (0.87-2.63)		
GG vs. CC + GC	Ethnicity				
	Asian	16	1.12 (1.04-1.19)	54.6	0.005
	Caucasian	5	1.04 (0.84-1.29)	0.0	0.792
	Digestive cancer type				
	Biliary cancer	2	0.98 (0.76-1.28)		
	Hepatocellular cancer	6	1.06 (0.90-1.24)	40.8	0.133
	Esophageal squamous cell carcinoma	2	1.39 (1.09-1.78)	0.0	0.655
	Gastric cancer	6	1.09 (0.99-1.20)	64.5	0.015
	Colorectal cancer	4	1.14 (1.00-1.31)	42	0.16
	Pancreatic cancer	1	1.33 (0.32-5.45)		
GG vs. CC	Ethnicity				
	Asian	16	1.16 (1.06-1.26)	64.1	<0.001
	Caucasian	5	1.12 (0.75-1.68)	0.0	0.92
	Digestive cancer type				
	Biliary cancer	2	0.68 (0.36-1.28)		
	Hepatocellular cancer	6	1.14 (0.95-1.38)	28.8	0.219
	Esophageal squamous cell carcinoma	2	1.88 (1.19-2.97)	53	0.145
	Gastric cancer	6	1.10 (0.98-1.23)	76.3	0.001
	Colorectal cancer	4	1.30 (1.08-1.57)	0.0	0.587
	Pancreatic cancer	1	1.55 (0.37-6.47)		
GC vs. CC	Ethnicity				
	Asian	16	1.09 (1.02-1.17)	71.6	<0.001
	Caucasian	5	1.06 (0.83-1.36)	0.0	0.446
	Digestive cancer type				
	Biliary cancer	2	0.61 (0.31-1.17)		
	Hepatocellular cancer	6	1.09 (0.95-1.25)	0.0	0.629
	Esophageal squamous cell carcinoma	2	1.13 (0.85-1.50)	73	0.054
	Gastric cancer	6	1.03 (0.94-1.13)	77.4	<0.001
	Colorectal cancer	4	1.28 (1.09-1.50)	83.5	<0.001
	Pancreatic cancer	1	1.51 (0.85-2.67)		

[a]Number of comparisons; [b]P-value of test for the overall effect. OR, odds ratio; CI, confidence interval.

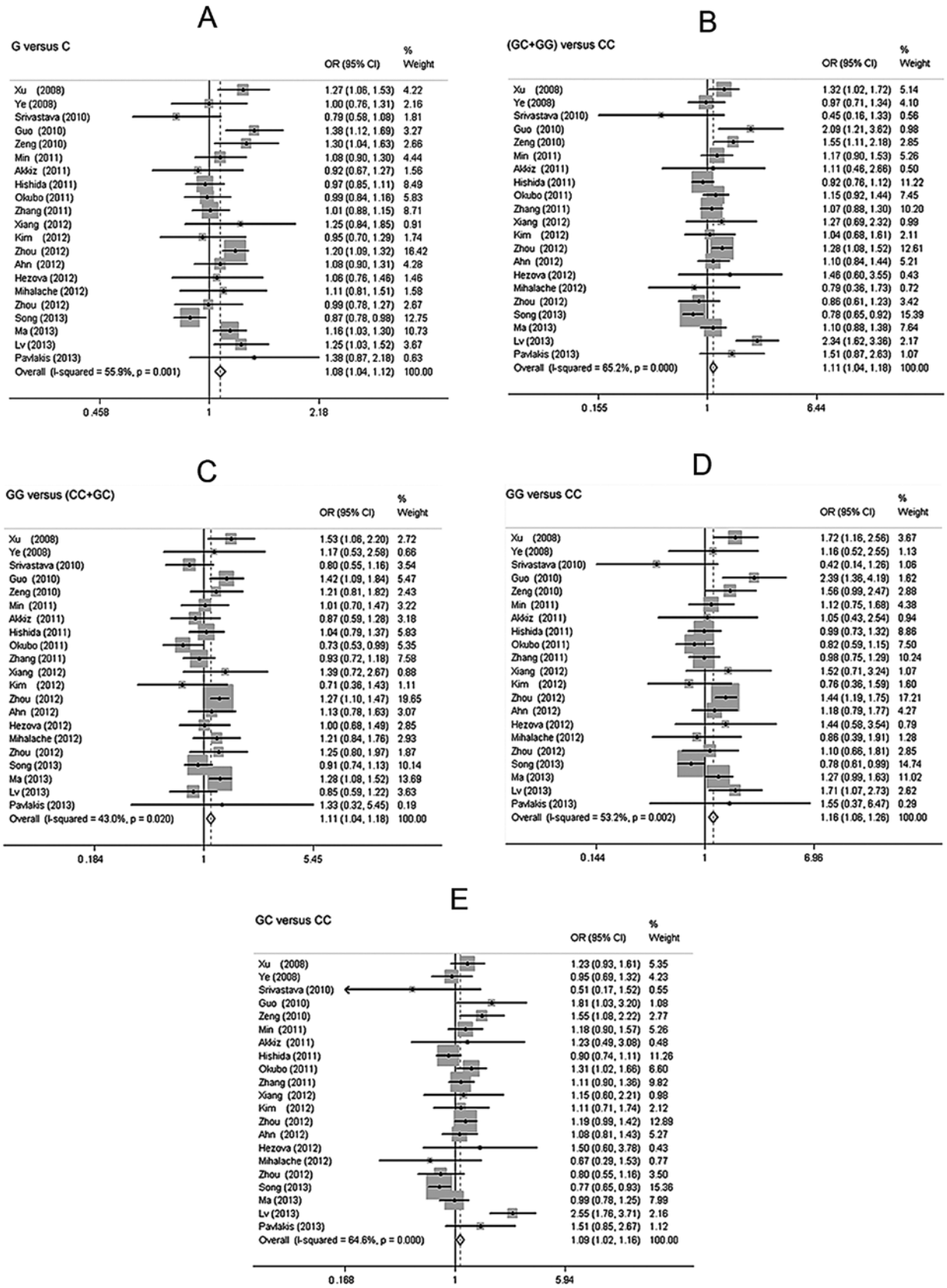

Figure 3. Funnel plot for all studies included in the meta-analysis studying associations of the miR-146a rs2910164 polymorphism with digestive cancer risk in the populations. (A) G vs. C; (B) GC + GG vs. CC; (C) GG vs. GC + CC; (D) GG vs. CC; (E) GC vs. CC.

[(for G vs. C: 1.08 (1.04-1.13), $P_{heterogeneity}$<0.001; for GC + GG vs. CC: 1.11 (1.04-1.18), $P_{heterogeneity}$<0.001; for GG vs. CC + GC: 1.12 (1.04-1.19), $P_{heterogeneity}$=0.005; for GG vs. CC: 1.16 (1.06-1.26), $P_{heterogeneity}$<0.001; for GC vs. CC: 1.09 (1.02-1.17), $P_{heterogeneity}$<0.001)]. No significant risk was found to be associated with any of the genetic models for Caucasians (Table II).

Statistical sensitivity. Data from one study were omitted and the rest was analyzed, and the pooled RRs were similar with the overall pooled RRs (data not shown), supporting the robustness of our results.

Publication bias. Begg's funnel plot and Egger's test were used to assess the publication bias of the included studies. However, the results from all the comparisons and from Egger's test showed no evidence for a publication bias (Fig. 3): P=0.354 for G vs. C, P=0.912 for GC + GG vs. CC, P=0.352 for GG vs. CC, P=0.795 for GC vs. CC (except P=0.045<0.1 for GG vs. CC + GC).

Discussion

In the present study, we conducted a comprehensive statistical analysis of the relationship between the miR-146a polymorphism rs2910164 and digestive tumors. The results of the stratified analysis are the following: allele G vs. C (OR=1.08, 95% CI: 1.04-1.12), dominant genetic model GC + GG vs. CC comparison (OR=1.11, 95% CI: 1.04-1.18), recessive genetic model GG vs. CC + GC comparison (OR=1.11, 95% CI: 1.04-1.18), homozygous GG vs. CC comparison (OR=1.11, 95% CI: 1.04-1.18), heterozygous GC vs. CC comparison (OR=1.09, 95% CI: 1.02-1.16). We found that the miR-146a polymorphism rs2910164 might significantly increase the susceptibility to digestive tumors, especially for esophageal and colorectal cancer. In addition, the miR-146a polymorphism might significantly increase the risk for developing digestive tumors in Asian individuals, while for Caucasians, no obvious correlation between the polymorphism and the risk for digestive tumors was found.

miRNAs are small single-stranded regulatory RNAs the abnormal expression of which has been associated with the susceptibility to many human diseases, including cancer in the lung, prostate and bladder, cervical squamous cell carcinoma (37-40), autoimmune diseases such as systemic lupus erythematosus, Sjogren's syndrome and lupus nephritis (41-43), as well as cardiovascular diseases such as heart disease, heart failure and myocardial infarction (44-46).

The miR-146a polymorphism rs2910164 is associated with the susceptibility to a variety of tumors. Jazdzewski et al (47) found a significantly different distribution of genotypes among patients with papillary thyroid carcinomas as compared to normal subjects, with the GC genotype being associated with an increased risk of papillary thyroid carcinoma. Another study indicated that miR-146a might be involved in the pathogenesis of malignant melanoma, and individuals with the CG genotype showed an increased risk of developing malignant melanoma (48). Orsós *et al* (49) found that the pre-miR/146a C allele might contribute to an increased susceptibility to head and neck cancer. Therefore, the miR-146a polymorphism rs2910164 appears to be associated with the risk of developing cancer in a cancer type-specific manner.

The association between miR-146a polymorphisms and susceptibility to digestive tumors has attracted increased research in recent years. However, numerous studies on the topic were characterized by small sample size and thus, might not possess sufficient statistical power to detect effects of small magnitude or might have generated a fluctuated risk estimate. Moreover, conclusions from all these studies have not been uniform, and have even been contradicting for different types of tumors. Therefore, it is necessary to collect previously-generated research data and obtain a large number of samples to get reliable results.

Nevertheless, the present meta-analysis had a number of limitations. First, our study only concerned the analysis of unvaried factors. Second, the population characteristics of the experimental and the control groups were not uniform. Age, gender, HBV and potentially, other features, might have affected the reliability of the results. Third, the present study included only Caucasian and Asian populations; the absence of other ethnicities in the sample considerably reduces the universal validity of the results. Furthermore, unconsidered non-neoplastic disease factors might have impacted on the conclusions. Therefore, a more precise analysis might need to be performed.

In conclusion, our analysis demonstrated that there is an apparent association between the miR-146a polymorphism rs2910164 and digestive cancer. However, the association is inconsistent with regards to susceptibility to different types of gastrointestinal cancer. Therefore, it is necessary to collect large samples of data, perform stratified analyses and gather data from additional ethnicities to clarify the association between the miR-146a G/C rs2910164 polymorphism and the susceptibility to digestive cancer.

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