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Quantitative assessment of the association between *miR-196a2* rs11614913 polymorphism and gastrointestinal cancer risk

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Abstract Published data on the association between *miR-196a2* rs11614913 polymorphism and risk of gastrointestinal (GI) cancers are inconsistent among studies. To clarify the association, we performed a comprehensive literature search and a meta-analysis. We searched multiple databases to identify genetic association studies investigating the effect of *miR-196a2* rs11614913 polymorphism on GI cancers with the last report up to January 18, 2012. The odds ratio (OR) and its 95 % confidence interval (95 % CI) were calculated to assess the strength of association. A total of 13 studies including 4,947 cases and 5,642 controls based on the search criteria were involved in this meta-analysis. In the overall analysis, it was suggested that variant C allele of *miR-196a2* rs11614913 polymorphism could significantly increase risk of GI cancers in different genetic models (C vs T: OR = 1.17, 95 % CI = 1.07–1.28, $P = 0.0008$; CT + CC vs TT: OR = 1.26, 95 % CI = 1.08–1.48, $P = 0.004$; CC vs CT + TT: OR = 1.23, 95 % CI = 1.08–1.39, $P = 0.002$; CC vs TT: OR = 1.55, 95 % CI = 1.24–1.94, $P = 0.0001$; CT vs TT: OR = 1.20, 95 % CI = 1.02–1.40, $P = 0.03$). When stratified by ethnicity, we found a significant association in Asian population, as well as Caucasian population. When stratified by cancer types, we found a significant association in colorectal cancer, as well as esophageal cancer. We did not find a significant association between *miR-196a2* rs11614913 polymorphism and hepatocellular carcinoma risk. For gastric cancer, a significantly increased cancer risk was observed only in homozygote comparison. This meta-analysis demonstrates that *miR-196a2* rs11614913 polymorphism is significantly associated with risk of GI cancers.

Keywords Gastrointestinal cancers · *miR-196a2* · Genetic polymorphism · Meta-analysis

Introduction

Gastrointestinal (GI) cancers are defined as cancers of the gastrointestinal tract, including the esophagus, stomach, liver, gallbladder, pancreas, bowels, and anus. GI cancers are among the most frequently reported cancers in the world, and are characterized by invasivity, metastatic potential and poor outcomes. A total of 274,330 new cases of GI cancers and approximately 139,580 deaths occurred in the United States in 2010 [1]. Hence, there is a need for identifying high-risk populations as well as novel strategies for early detection. The development and progression of GI cancers is typical of a multistage process. Accumulating evidence support an important role for environmental factors and genetic background in determining risk for GI cancers [2, 3].

MicroRNAs (miRNAs) are endogenous non-coding RNAs of 19–25 nucleotides that inhibit translation or promote degradation of mRNAs of complementary sequences. In human cancer, miRNAs can function as oncogenes or tumor suppressor genes during tumor development and progression [4]. Aberrant expression and structural alteration of miRNAs have been reported to participate in

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tumorigenesis and cancer development [5, 6]. Although they escaped notice until relatively recently, it is appealing to propose that genetic variations in miRNA genes and/or their responsive elements in the target mRNAs might represent a brand-new mechanism of cancer predisposition. Single nucleotide polymorphisms (SNPs) in miRNA regions have been reported to be rare and unlikely to be functionally important. However, evidence indicated that genetic alterations of the miRNA biogenesis pathway may be associated with cancer development and progression, especially in GI cancers [7, 8].

Recently, a number of molecular epidemiological studies have been conducted to examine the association between rs11614913 SNP in *miR-196a2* and the susceptibility of different GI cancers in diverse populations, but the results remain conflicting [8–20]. Meta-analysis is a statistical procedure for combining results from several studies to produce a single estimate of the major effect with enhanced precision [21]. Therefore, we performed this meta-analysis to assess the importance of *miR-196a2* rs11614913 polymorphism for GI cancers susceptibility.

Materials and methods

Identification of eligible studies

We performed an exhaustive search using Pubmed, Embase and Chinese biomedical literature database (CBM). The last search was updated on January 18, 2012. The following key words were used: "microRNA odds ratio (OR) mir OR miRNA", "cancer OR carcinoma OR adenocarcinoma OR neoplasm OR tumour OR tumor", "gene OR polymorphism OR allele OR variation", and "196a OR rs11614913". Searching was done without restriction on language or publication years. References of the retrieved articles were manually screened to identify other relevant publications. Review articles were also inspected to find additional eligible studies. In the current study, data for meta-analysis were available from 13 studies, including 4,947 cases and 5,642 controls for *miR-196a2* rs11614913 polymorphism and GI cancers.

Inclusion and exclusion criteria

Eligible studies had to meet the following criteria: (1) evaluation of *miR-196a2* rs11614913 polymorphism and GI cancers; (2) independent case-control studies for human; (3) sufficient genotype data were showed to calculate the OR with 95 % CI; (4) only full-text manuscripts were included. The exclusion criteria were: (1) no control population; (2) duplication of the previous publications; (3) abstract, comment, review and editorial; (4) studies that focused on hereditary non polyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP). Different ethnicity was categorized as Asian, Caucasian and African. When there were multiple publications from the same population, only the largest study was included.

Data extraction

Two investigators independently extracted the data according to the inclusion criteria listed above. Discrepancies were resolved by discussion with our research team. From each study, we extracted the first author's name, year of publication, source of publication, ethnicity, cancer type, definition and numbers of cases and controls, and genotype frequency for cases and controls. If original genotype frequency data was unavailable in relevant articles, a request for additional data was sent to the corresponding author.

Meta-analysis methods

The OR and its 95 % CI were employed to assess the strength of the association between rs11614913 polymorphism and risk of GI cancers based on genotype frequencies in cases and controls. Ethnicity was categorized as Asian or Caucasian. Subgroup analysis stratified by cancer types was also performed. The pooled ORs were performed for allelic contrast (C vs T), dominant model (CT + CC vs TT), recessive model (CC vs CT + TT), homozygote comparison (CC vs TT) and heterozygote comparison (CT vs TT), respectively. The heterogeneity between the studies was assessed by the Chi square-test based Q-statistic [22]. A significant Q-statistic ($P < 0.10$) indicated heterogeneity across studies. We also measured the effect of heterogeneity by another measure, $I^2 = 100\ \% \times (Q - df)/Q$ [23]. The pooled OR was calculated by a fixed effects model (using the Mantel–Haenszel method) or a random effect model (using the DerSimonian and Laird method) according to the heterogeneity among studies [24, 25]. These two models provide similar results when heterogeneity between studies is absent; otherwise the random-effects model is more appropriate. The significance of the pooled OR was determined by the *Z*-test. Chi square-test was used to determine if observed frequencies of genotypes in controls conformed to Hardy–Weinberg equilibrium expectations.

Evaluation of publication bias

Publication bias was assessed qualitatively by performance of funnel plots and quantitatively by means of Egger's tests ($P < 0.05$ was considered significant) [21].

Analyses were performed using the software Review Manager 4.2 (Cochrane Collaboration, http://www.cc-ims.net/RevMan/relnotes.htm/) and Stata version 10 (StataCorp

LP, College Station, Texas, USA). Two-sided *P* values less than 0.05 were considered statistically significant.

Results

Characteristics of eligible studies (Table 1)

Characteristics of studies investigating the association of *miR-196a2* rs11614913 polymorphism with GI cancers are presented in Table 1. There were 180 articles relevant to the searching word (Pubmed:55; Embase:101; CBM:24). The study selection process is shown in Fig. 1. A total of 13 eligible case-control studies with 4,947 cases and 5,642 controls were included in the current meta-analysis [8–20]. There were four studies about hepatocellular carcinoma [11, 12, 15, 19], four studies about colorectal cancer [9, 10, 13, 14], two studies about esophageal cancer [8, 17], two studies about gastric cancer [16, 20] and one study about gallbladder cancer [18], respectively. Among these studies, 11 studies were performed in Asian population [9, 10, 12–20] and two studies were performed in Caucasian population [8, 11]. The results of Hardy–Weinberg equilibrium test for the distribution of the genotype in control population are shown in Table 1.

Meta-analysis (Table 2)

The summary of the meta-analysis for *miR-196a2* rs11614913 polymorphism and GI cancers is shown in Table 2. We first analyzed the influence on the overall incidence of GI cancers. Then subgroup analyses were performed on ethnicity and cancer types. When the Q-test of heterogeneity was not significant, we conducted analyses using the fixed effect models. The random effect models were conducted when we detected significant between-study heterogeneity.

Overall effects for meta-analysis

In the overall analysis, we found a significant association between *miR-196a2* rs11614913 polymorphism and risk of GI cancers in different genetic models (C vs T: OR = 1.17, 95 % CI = 1.07–1.28, $P = 0.0008$; CT + CC vs TT: OR = 1.26, 95 % CI = 1.08–1.48, $P = 0.004$; CC vs CT + TT: OR = 1.23, 95 % CI = 1.08–1.39, $P = 0.002$; CC vs TT: OR = 1.55, 95 % CI = 1.24–1.94, $P = 0.0001$; CT vs TT: OR = 1.20, 95 % CI = 1.02–1.40, $P = 0.03$).

Subgroup analysis for ethnicity

Subgroup analysis was stratified by ethnicity. The meta-analysis included 11 studies (4,455 cases and 5,119 controls) in Asian population and two studies (492 cases and 523 controls) in Caucasian population.

We found a significant association between *miR-196a2* rs11614913 polymorphism and risk of GI cancers in Asian population in all genetic models except for heterozygote comparison (C vs T: OR = 1.14, 95 % CI = 1.03–1.26, $P = 0.008$; CT + CC vs TT: OR = 1.23, 95 % CI = 1.04–1.47, $P = 0.02$; CC vs CT + TT: OR = 1.17, 95 % CI = 1.03–1.33, $P = 0.01$; CC vs TT: OR = 1.48, 95 % CI = 1.16–1.90, $P = 0.002$; CT vs TT: OR = 1.19, 95 % CI = 1.00–1.41, $P = 0.05$).

Table 1 Characteristics of studies included in the meta-analysis[a]

ID	Study	Years	Ethnic group	Cancer type	Sample size		*P* for HWE
					Case	Control	
1	Min et al. [9]	2011	Asian	CRC	446	502	0.633
2	Zhu et al. [10]	2011	Asian	CRC	573	588	0.790
3	Akkız et al. [11]	2011	Caucasian	HCC	185	185	0.492
4	Zhang et al. [12]	2011	Asian	HCC	963	852	0.972
5	Zhan et al. [13]	2011	Asian	CRC	252	543	0.849
6	Chen et al. [14]	2011	Asian	CRC	126	407	0.788
7	Li et al. [15]	2010	Asian	HCC	310	222	0.402
8	Okubo et al. [16]	2010	Asian	Gastric cancer	552	697	0.510
9	Wang et al. [17]	2010	Asian	Esophageal cancer	458	489	0.600
10	Srivastava et al. [18]	2010	Asian	Gall bladder cancer	230	230	0.068
11	Qi et al. [19]	2010	Asian	HCC	361	391	0.869
12	Peng et al. [20]	2010	Asian	Gastric cancer	213	213	0.936
13	Ye et al. [8]	2008	Caucasian	Esophageal cancer	307	338	0.420

[a] *CRC* colorectal cancer, *HCC* hepatocellular carcinoma, *HWE* Hardy–Weinberg equilibrium

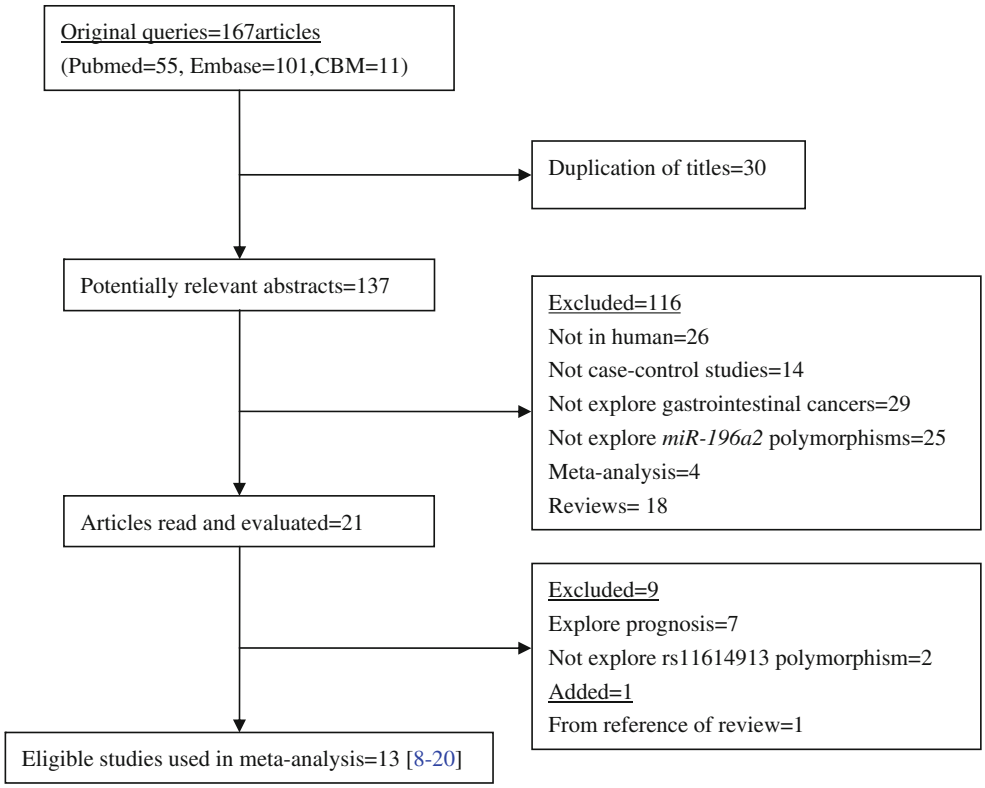

Fig. 1 Flow diagram of the study selection process

Similarly, the results showed that rs11614913 polymorphism was associated with risk of GI cancers in Caucasian population in all genetic models except for heterozygote comparison (C vs T: OR = 1.39, 95 % CI = 1.17–1.66, $P = 0.0003$; CT + CC vs TT: OR = 1.41, 95 % CI = 1.06–1.89, $P = 0.02$; CC vs CT + TT: OR = 1.67, 95 % CI = 1.26–2.21, $P = 0.0004$; CC vs TT: OR = 1.98, 95 % CI = 1.39–2.84, $P = 0.0002$; CT vs TT: OR = 1.21, 95 % CI = 0.89–1.65, $P = 0.23$).

Subgroup analysis for cancer types

Subgroup analysis was also stratified by cancer types. We did not find significant association between *miR-196a2* rs11614913 polymorphism and hepatocellular carcinoma risk (C vs T: OR = 1.15, 95 % CI = 0.94–1.41, $P = 0.18$; CC + CT vs TT: OR = 1.20, 95 % CI = 0.87–1.65, $P = 0.26$; CC vs CT + TT: OR = 1.13, 95 % CI = 0.97–1.33, $P = 0.13$; CC vs TT: OR = 1.32, 95 % CI = 0.88–1.97, $P = 0.18$; CT vs TT: OR = 1.12, 95 % CI = 0.86–1.47, $P = 0.41$).

The results showed that there was a significant association between *miR-196a2* rs11614913 polymorphism and colorectal cancer risk in all genetic models except for heterozygote comparison (C vs T: OR = 1.20, 95 % CI = 1.08–1.32, $P = 0.0004$; CC + CT vs TT: OR = 1.25, 95 % CI = 1.06–1.46, $P = 0.006$; CC vs CT + TT: OR = 1.30, 95 % CI = 1.10–1.53, $P = 0.002$; CC vs TT: OR = 1.44, 95 % CI = 1.18–1.75, $P = 0.0003$; CT vs TT: OR = 1.17, 95 % CI = 0.99–1.38, $P = 0.07$).

Furthermore, there was a significant association between *miR-196a2* rs11614913 polymorphism and esophageal cancer risk in different tested models except for dominant model and heterozygote comparison (C vs T: OR = 1.40, 95 % CI = 1.22–1.61, $P < 0.00001$; CC + CT vs TT: OR = 1.75, 95 % CI = 0.87–3.52, $P = 0.11$; CC vs CT + TT: OR = 1.48, 95 % CI = 1.18–1.85, $P = 0.0006$; CC vs TT: OR = 2.23, 95 % CI = 1.65–3.00, $P < 0.00001$; CT vs TT: OR = 1.59, 95 % CI = 0.69–3.63, $P = 0.28$).

For analysis in gastric cancer, a significantly increased cancer risk was observed only in homozygote comparison (C vs T: OR = 1.12, 95 % CI = 0.98–1.28, $P = 0.10$; CC + CT vs TT: OR = 1.12, 95 % CI = 0.90–1.39, $P = 0.30$; CC vs CT + TT: OR = 1.22, 95 % CI = 0.96–1.55, $P = 0.10$; CC vs TT: OR = 2.19, 95 % CI = 1.23–3.91, $P = 0.008$; CT vs TT: OR = 1.07, 95 % CI = 0.85–1.34, $P = 0.58$).

Evaluation of publication bias (Table 3)

We assessed funnel plot asymmetry by the method of Egger's linear regression test. If there is asymmetry, the regression line

Table 2 Meta-analysis of *miR-196a2* rs11614913 polymorphism with gastrointestinal cancers[a]

Comparsions	Sample size		No. of studies	Test of association				Test of heterogeneity		
	Case	Control		OR (95 % CI)	Z	*P* value	Model	χ^2	*P* value	I^2 (%)
Overall										
C vs T	9894	11284	13	1.17 (1.07–1.28)	3.36	0.0008	R	31.07	0.002	61.4
CC + CT vs TT	4947	5642	13	1.26 (1.08–1.48)	2.90	0.004	R	33.47	0.0008	64.1
CC vs CT + TT	4947	5642	13	1.23 (1.08–1.39)	3.14	0.002	R	22.47	0.03	46.6
CC vs TT	2414	2862	13	1.55 (1.24–1.94)	3.86	0.0001	R	42.38	<0.0001	71.7
CT vs TT	3616	4338	13	1.20 (1.02–1.40)	2.24	0.03	R	29.12	0.004	58.8
Asian										
C vs T	8910	10238	11	1.14 (1.03–1.26)	2.64	0.008	R	25.93	0.004	61.4
CC + CT vs TT	4455	5119	11	1.23 (1.04–1.47)	2.39	0.02	R	30.03	0.0008	66.7
CC vs CT + TT	4455	5119	11	1.17 (1.03–1.33)	2.45	0.01	R	16.96	0.08	41.0
CC vs TT	2149	2599	11	1.48 (1.16–1.90)	3.12	0.002	R	39.27	<0.0001	74.5
CT vs TT	3284	3932	11	1.19 (1.00–1.41)	1.95	0.05	R	26.69	0.003	62.5
Caucasian										
C vs T	984	1046	2	1.39 (1.17–1.66)	3.66	0.0003	F	0.54	0.46	0.0
CC + CT vs TT	492	523	2	1.41 (1.06–1.89)	2.34	0.02	F	2.25	0.13	55.5
CC vs CT + TT	492	523	2	1.67 (1.26–2.21)	3.54	0.0004	F	0.16	0.69	0.0
CC vs TT	265	263	2	1.98 (1.39–2.84)	3.74	0.0002	F	0.58	0.45	0.0
CT vs TT	332	406	2	1.21 (0.89–1.65)	1.20	0.23	F	2.33	0.13	57.1
HCC										
C vs T	3580	3270	4	1.15 (0.94–1.41)	1.33	0.18	R	11.42	0.01	73.7
CC + CT vs TT	1790	1635	4	1.20 (0.87–1.65)	1.13	0.26	R	10.39	0.02	71.1
CC vs CT + TT	1790	1635	4	1.13 (0.97–1.33)	1.53	0.13	F	4.96	0.17	39.5
CC vs TT	926	832	4	1.32 (0.88–1.97)	1.34	0.18	R	10.95	0.01	72.6
CT vs TT	1345	1262	4	1.12 (0.86–1.47)	0.83	0.41	R	6.78	0.08	55.7
CRC										
C vs T	2794	4080	4	1.20 (1.08–1.32)	3.57	0.0004	F	3.83	0.28	21.6
CC + CT vs TT	1397	2040	4	1.25 (1.06–1.46)	2.74	0.006	F	4.67	0.20	35.7
CC vs CT + TT	1397	2040	4	1.30 (1.10–1.53)	3.10	0.002	F	3.09	0.38	3.1
CC vs TT	701	1018	4	1.44 (1.18–1.75)	3.61	0.0003	F	3.80	0.28	21.1
CT vs TT	1042	1612	4	1.17 (0.99–1.38)	1.80	0.07	F	4.81	0.19	37.6
Esophageal cancer										
C vs T	1530	1654	2	1.40 (1.22–1.61)	4.69	<0.00001	F	0.42	0.52	0.0
CC + CT vs TT	765	827	2	1.75 (0.87–3.52)	1.58	0.11	R	7.74	0.005	87.1
CC vs CT + TT	765	827	2	1.48 (1.18–1.85)	3.41	0.0006	F	1.20	0.27	17.0
CC vs TT	362	404	2	2.23 (1.65–3.00)	5.22	<0.00001	F	1.67	0.20	40.0
CT vs TT	534	640	2	1.59 (0.69–3.63)	1.09	0.28	R	9.92	0.002	89.9
Gastric cancer										
C vs T	1530	1820	2	1.12 (0.98–1.28)	1.62	0.10	F	1.44	0.23	30.5
CC + CT vs TT	765	910	2	1.12 (0.90–1.39)	1.03	0.30	F	0.15	0.70	0.0
CC vs CT + TT	765	910	2	1.22 (0.96–1.55)	1.66	0.10	F	1.95	0.16	48.8
CC vs TT	290	453	2	2.19 (1.23–3.91)	2.65	0.008	R	3.18	0.07	68.5
CT vs TT	584	730	2	1.07 (0.85–1.34)	0.56	0.58	F	0.04	0.85	0.0

[a] *HCC* hepatocellular carcinoma, *CRC* colorectal cancer, *OR* odds ratio, *vs* versus, *R* random effect model, *F* fixed effect model

will not run through the origin. The intercept *a* provides a measure of asymmetry, and the larger its deviation from zero the more pronounced the asymmetry. The results of Egger's linear regression test are shown in Table 3. For all the comparisons, *P* values from Egger's test were greater than 0.05 and the latter 95 % CI also included zero, indicating no publication bias.

Table 3 Egger's linear regression test to measure the funnel plot asymmetric[a]

Groups	Y axis intercept: *a* (95 % CI)				
	C vs T	CC + CT vs TT	CC vs TT + CT	CC vs TT	CT vs TT
Overall	1.39 (−2.66 to 5.45)	2.26 (−0.96 to 5.49)	1.27 (−2.80 to 5.34)	1.52 (−3.08 to 6.12)	2.05 (−0.98 to 5.08)
Asian	0.41 (−4.36 to 5.18)	1.88 (−2.14 to 5.90)	0.18 (−4.30 to 4.66)	0.90 (−4.72 to 6.52)	1.88 (−1.89 to 5.64)
Caucasian	–	–	–	–	–
HCC	4.61 (−12.75 to 7.42)	4.03 (−3.45 to 11.51)	3.06 (−5.29 to 11.41)	4.37 (−4.73 to 13.47)	3.33 (−2.32 to 8.98)
CRC	−3.46 (−14.84 to 7.92)	−2.28 (−17.93 to 13.37)	−3.09 (−13.32 to 7.13)	−3.50 (−14.67 to 7.68)	−1.51 (−18.33 to 15.32)
Esophageal cancer	–	–	–	–	–
Gastric cancer	–	–	–	–	–

[a] *CRC* colorectal cancer, *HCC* hepatocellular carcinoma, *vs* versus

Discussion

A total of 13 case-control studies with 10,589 subjects (4,947 cases and 5,642 controls) were finally included in this meta-analysis. Through quantitative analysis, it was suggested that variant C allele of *miR-196a2* rs11614913 polymorphism could significantly increase risk of GI cancers.

Sequence variations in miRNAs region have an important influence on the expression and transcriptional regulation of miRNAs. *MiR-196a2* is comprised of two different mature miRNAs (*miR-196a* and *miR196a**) which are processed from the same stem-loop. The rs11614913 SNP lies in the mature sequence of *miR-196a**, and may influence either miRNA by affecting processing of the pre-miRNA to its mature form [26]. Genetic polymorphism of *miR-196a2* has been shown to alter the expression of mature miR-196a and binding activity of target mRNA. A previous study found that several members of the homeobox (HOX) gene family were targeted by *miR-196a* [27]. HOXB2, HOXB3, HOXC13, and HOXB5 were significantly downregulated in cells treated with *pre-miR-196a-C* [27]. Hoffman et al. [26] reported that *pre-miR-196a-C* introduction could downregulate some tumor suppressors (GADD45G, INHBB) and upregulate some oncogenes (TP63, S100A8, S100A9) in breast cancer cells. Of course, development of GI cancers is a multistep process with many genes and SNPs involved. The candidate gene approach that considers one gene/SNP at a time may not be able to detect the modest effect associated with each SNP. This highlights the importance of taking a multigenic approach to identify interactions between genetic variations [8].

Studies on the association of *miR-196a2* rs11614913 polymorphism with GI cancers were predominantly conducted in East Asian countries; only a few were conducted in Western countries. Thus, possible ethnic differences in the association of rs11614913 polymorphism with GI cancers should be investigated further and confirmed as more studies are conducted in Western countries. In addition, our results showed that significantly increased risk in *miR-196a2* C allele carriers was found in colorectal cancer and esophageal cancer, but not in hepatocellular carcinoma. We conducted power calculation in subgroup analysis of hepatocellular carcinoma. The result showed that the statistical power to detect a significant association in dominant and recessive model was 64.9 and 32.7 %, respectively. Thus, further studies based on larger sample size are still needed in hepatocellular carcinoma. Meanwhile, the tendency toward significant association in gastric cancer could be verified with accumulation of more data over time. Several meta-analyses were performed to address the relationship between this polymorphism and cancer risks [28–31]. Their results suggest that *miR-196a2* rs11614913 polymorphism contributes to genetic susceptibility for increased cancer risk. At the same time, Gao et al. [32] found that individuals carrying CC genotype of *miR-196a2* rs11614913 polymorphism was associated with an increased breast cancer risk using meta-analysis. Recently, Guo et al. [33] found a significant association between *miR-196a2* polymorphism and increased susceptibility of digestive system cancers using meta-analysis. Compared with their meta-analysis, the current meta-analysis focused on GI cancer and had a more comprehensive searching result. A case-control study of HCC [12] and another study of esophageal cancer [8] were both omitted by Guo's meta-analysis. The two studies include 2,460 subjects (1,270 cases and 1,190 controls) which may somewhat affect the result. For example, they found a significant association between SNP rs11614913 and increased risk of HCC, while we did not find a significant association between *miR-196a2* rs11614913 polymorphism and HCC risk. Thus we believe that conducting this comprehensive meta-analysis focused on GI cancers might be helpful in illuminating precisely how this variant genotype confers risk of GI cancers.

The present study has some potential limitations that should be considered. First, significant between-study heterogeneity was detected in some comparisons, and may distort the meta-analysis. Second, our results were based on unadjusted estimates, whereas a more precise analysis could be performed if individual data were available. Third, only published studies were included in this meta-analysis, and publication bias may occur. Fourth, lacking of data regarding African population limited our further evaluation focus on this race. Further research should focus on this race. Finally, interactions between gene–gene, gene-environment and even different polymorphic loci of the same gene may modulate GI cancers susceptibility.

In conclusion, our meta-analysis suggests that the *miR-196a2* rs11614913 C allele is associated with increased GI cancers risk. More well-designed studies based on larger sample sizes are still needed in future research.

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Conflict of interest The authors declare that there is no conflict of interest.

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