RESEARCH ARTICLE

A Genetic Variant in MiR-146a Modifies Digestive System Cancer Risk: a Meta-analysis

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Abstract

MicroRNAs (miRNAs) negatively regulate gene expression and act as tumor suppressors or oncogenes in oncogenesis. The association between a single nucleotide polymorphism (SNP) in miR-146a rs2910164 and susceptibility to digestive system cancers was inconsistent in previous studies. In this study, we conducted a literature search of PubMed to identify all relevant studies published before August 31, 2013. A total of 21 independent case-control studies were included in this updated meta-analysis with 9,558 cases and 10,614 controls. We found that the miR-146a rs2910164 polymorphism was significantly associated with decreased risk of digestive system cancers in an allele model (OR=0.90, 95%CI 0.87-0.94), homozygote model (OR=0.84, 95%CI 0.77-0.91), dominant model (OR=0.90, 95%CI 0.84-0.96), and recessive model (OR=0.85, 95%CI 0.79-0.91), while in a heterozygous model (OR = 0.99, 95% CI 0.89-1.11) the association showed marginal significance. Subgroup analysis by cancer site revealed decreased risk in colorectal cancer above allele model (OR=0.90, 95%CI 0.83-0.97) and homozygote model (OR=0.85, 95%CI 0.72-1.00). Similarly, decreased cancer risk was observed when compared with allele model (OR=0.87, 95%CI 0.81-0.93) and recessive model (OR=0.81, 95%CI 0.72-0.90) in gastric cancer. When stratified by ethnicity, genotyping methods and quality score, decreased cancer risks were also observed. This current meta-analysis indicated that miR-146a rs2910164 polymorphism may decrease the susceptibility to digestive system cancers, especially in Asian populations.

Keywords: MiR-146a - polymorphism - digestive system cancers risk - meta-analysis - Asians

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Introduction

MicroRNAs (miRNAs) are a class of non-coding, evolutionarily highly conserved, single-stranded endogenous with approximately 18-25 nucleotides in length, which represent a significant mechanism of post transcriptional regulators of gene expression. Emerging evidence indicates that miRNAs are involved in various biological processes, including cell proliferation, differentiation, proliferation, apoptosis, and metabolism, even participated in human carcinogenesis as tumor suppressors or oncogenes by regulating the expression of their target genes (Brennecke et al., 2003; Ambros, 2004; Ruan et al., 2009; Kwak et al., 2010). Although the exact mechanism underlying miRNA deregulation in cancer remains unknown, some key dysregulated miRNAs have already been used as molecular biomarkers, which could improve diagnosis, prognosis, and monitoring of treatment response for cancers (Qu et al., 2011). Single nucleotide polymorphisms (SNPs) are a kind of genetic variations associated with population diversity, disease susceptibility, drug metabolism and genome evolution (Shastry, 2009). SNPs located in miRNA gene region may function as regulator to modify miRNA production and contribute to cancer risk by altering miRNA expression and/or maturation (Saunders et al., 2007; Landi et al., 2012). Thus, SNPs in miRNAs could produce significant functional consequences and represent as an ideal candidate for disease prediction.

MiR-146a rs2910164 is located in the stem region opposite to the mature miR-146a sequence, which is suspected to have an effect on tumor immune responses and ultimately the development of cancer. In recent years, a lot of studies including case-control studies and meta-analyses have been conducted to determine the association between genetic variants in the precursor or mature miRNA sequence of miR-146a and multiple kinds of digestive system cancers at various sites, such as oral cancer (Chu et al., 2012), esophagus cancer (Guo et al., 2010; Wei et al., 2013), pancreatic cancer (Pavlakis et al., 2013), colorectal cancer (Hezova et al., 2012; Min et al., 2012; Lv et al., 2013; Ma et al., 2013), cholangicarcinoma (Mihalache et al., 2012), gallbladder cancer (Srivastava et al., 2010), gastric cancer (Okubo et al., 2010; Zeng et al., 2010; Ahn et al., 2012; Zhou et al., 2012), and liver cancer (Xu et al., 2008; Akkız et al., 2011; Zhang et al., 2011;

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Kim et al., 2012; Xiang et al., 2012; Zhou et al., 2012), etc. However, the results are conflicting and inconclusive. In addition, an unpublished case-control study on CRC was performed at the Molecular Epidemiology Laboratory in Zhejiang University School of Medicine. Therefore, we conducted the present meta-analysis of all eligible studies to derive a more precise estimation of the association of miR-146a G/C SNP with digestive system cancers risk.

Materials and Methods

Search strategy and study selection

We performed a literature research for all articles that explored the association of miR-146a rs2910164 polymorphism with digestive system cancers on PubMed (up to August 31, 2013) using the following strategy: (pre-miR-146a OR microRNA-146a OR miR-146a OR rs2910164) AND (gene OR polymorphism OR allele OR variation) AND (cancer OR carcinoma OR adenocarcinoma OR neoplasm OR tumour OR tumor), without any restriction on language. All titles and abstracts were reviewed by two of the authors (Li and Zhang) independently. If either author included the study, the full-text paper was obtained for further reviewing. The reference lists of all full-text papers and reviews identified through the above search strategy were manually checked to identify additional publications of interest.

The studies which met the following explicit criteria were included: (1) evaluation of miR-146a rs2910164 polymorphism and digestive cancers; (2) independent case-control studies for human; (3) describing useful genotype frequencies. The digestive caners includes: oropharynx cancer, esophagus cancer, gastric cancer, colorectal cancer, gallbladder cancer, pancreatic cancer, and liver cancer. To ensure the rigor of our meta-analysis, we designed and reported it according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement.

Data extraction and quality assessment

The following information was extracted from each eligible study using a standardized data collection protocol: author, country, ethnicity of the study population, publication year, study size, cancer site, genotyping method, whether verified Hardy-Weinberg equilibrium, and allele as well as genotype frequencies for cases and controls, characteristics of controls. If original genotype frequency data was unavailable in relevant articles, a request for additional data was sent to the corresponding author.

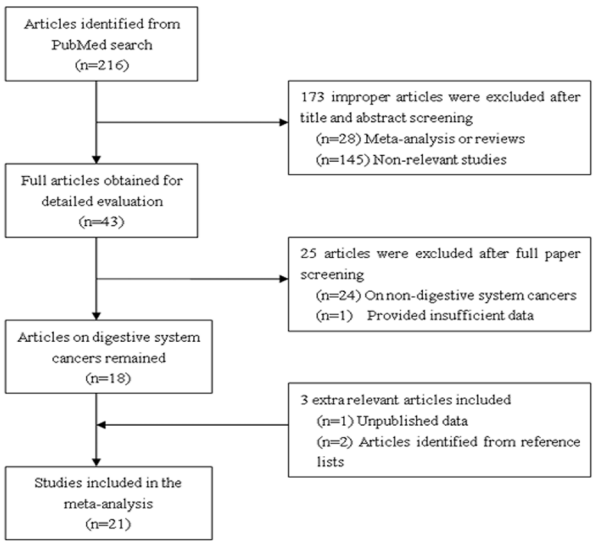

Figure 1. Flowchart of Study Selection

The quality of selected studies was independently assessed by two authors (Li and Zhang) according to a set of predetermined criteria. The score ranges from 0 (the lowest) to 14 (the highest), and a higher score means better quality. The predetermined criteria were developed around the following four aspects: the representation of objects, total sample size, quality control of genotyping methods, and deviation from Hardy-Weinberg equilibrium. The discrepancies were resolved by consensus and discussion.

Data synthesis and statistical analysis

Crude ORs with 95%CIs were used to assess the association between the miRNA gene polymorphisms and digestive system cancers under five genetic models: the allele, dominant, recessive, homozygous and heterozygous models. Meanwhile, stratified analyses were performed by ethnicity, tumor site, gene typing methods, and quality scores. Heterogeneity assumption was checked by the I2-statistics, which represents the proportion of inter-study variability that can be attributed to heterogeneity rather than to chance. And an I2 value of more than 50% was considered as a significant heterogeneity among studies, so the pooled OR estimate of each study was calculated by the random-effects model (the Mantel-Haenszel method). Otherwise, the fixed-effects model (the DerSimonian and Laird method) was used (Lau et al., 1997). Publication bias was determined by Begg's funnel plot and Egger's linear regression method with $P<0.05$ being considered statistically significant (Peters et al., 2006). To assess the stability of the results, sensitivity analyses were performed. Each study in turn was removed from the total, and the remaining studies were reanalyzed (Thakkinstian et al., 2005).

All statistical analyses were carried out using STATA version 11.0 (STATA Corp, College Station, Texas). $P < 0.05$ was considered statistically significant.

Results

Study characteristics

In accordance with the inclusion criteria, 21 eligible studies including 20 published (Xu et al., 2008; Zeng et al., 2010; Okubo et al., 2010; Srivastava et al., 2010; Guo et al., 2010; Akkız et al., 2011; Zhang et al., 2011; Ahn et al., 2012; Chu et al., 2012; Hezova et al., 2012; Mihalache et al., 2012; Xiang et al., 2012; Zhou et al., 2012; Zhou et al., 2012; Min et al., 2012; Kim et al., 2012; Chae et al., 2013; Hu et al., 2013; Lv et al., 2013; Ma et al., 2013; Pavlakis et al., 2013; Wei et al., 2013) and 1 unpublished were collected in this work, with 9,558 cases and 10,614 controls. Two study identified by manually searching reference list of retrieved studies were included (Chu et al., 2012; Kim et al., 2012). The

Table 1. Main Characteristics of Studies Included in the Meta-analysis for miR-146a Rs2910164

Author (reference)	Year	Country	Cancer site	Characteristics of controls(matched by)	Ethnicity	Genotyping methods	Number of cases/controls	Genotypes distribution of cases/ controls		HWE (*P*)
								CC/CG/GG	CC/CG/GG	
Ma et al.	2013	China	CRC	Age, gender	Asian	TaqMan	1147/1203	169/534/444	192/614/397	Yes
Wei et al.	2013	China	ESCC	Age, gender	Asian	MassARRAY	368/370	117/184/67	122/181/67	Yes
Lv et al.	2013	China	CRC	NA	Asian	PCR-RFLP	331/513	47/230/54	143/274/96	Yes
Pavlakis et al.	2013	Greece	PC	NA	Caucasian	PCR-RFLP	122/93	79/39/4	51/38/4	Yes
*Chen et al.	2013	China	CRC	Age, gender	Asian	SNPscan	547/561	186/291/70	205/271/85	Yes
Hezova et al.	2012	Czech Republic	CRC	NA	Caucasian	TaqMan	197/212	12/70/115	9/79/124	Yes
Ahn et al.	2012	Korea	GC	Age, gender	Asian	PCR-RFLP	461/447	159/231/71	164/221/62	Yes
Chu et al.	2012	China	OSCC	NA	Asian	PCR-RFLP	470/425	174/242/54	175/196/54	Yes
Min et al.	2012	Korea	CRC	NA	Asian	PCR-RFLP	446/502	151/233/62	188/245/69	Yes
Xiang et al.	2012	China	HCC	NA	Asian	PCR-RFLP	100/100	28/45/27	33/46/21	Yes
Mihalache et al.	2012	Germany	CC	NA	Caucasian	TaqMan	182/350	11/53/118	17/122/211	Yes
Zhou et al.	2012	China	GC	Age, gender	Asian	TaqMan	1686/1895	286/822/578	393/951/551	Yes
Zhou et al.	2011	China	LC	NA	Asian	PCR-RFLP	186/483	67/86/33	158/254/71	Yes
Okubo et al.	2011	Japan	GC	NA	Asian	PCR-RFLP	552/697	236/243/73	322/254/121	Yes
Akkiz et al.	2011	Turkish	HCC	Age, gender, smoking and alcohol consumption	Caucasian	PCR-RFLP	222/222	10/75/137	11/67/144	Yes
Zhang et al.	2011	China	HCC	Age, gender, smoke, alcohol status	Asian	PIRA-PCR	925/840	319/450/156	303/386/151	Yes
Guo et al.	2010	China	ESCC	Age, gender, residential area	Asian	SNPshot	444/468	20/190/234	42/220/206	Yes
Srivastava et al.	2010	Indian	GBC	Age, gender	Asian	PCR-RFLP	230/224	11/90/129	5/81/138	Yes
Kim et al.	2010	Korea	HCC	NA	Asian	PCR-RFLP	159/201	57/88/14	74/103/24	Yes
Zeng et al.	2010	China	GC	Age, gender	Asian	PCR-RFLP	304/304	89/153/62	119/132/53	Yes
Xu et al.	2008	China	HCC	NA	Asian	PCR-RFLP	479/504	158/241/80	197/249/58	Yes

PC, pancreatic cancer; ESCC, esophageal cancer; CRC, colorectal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; CC, cholangiocarcinoma; LC, liver cancer; GBC, gallbladder cancer; OSCC, oral squamous cell carcinoma; HB, hospital-based study; PB, population-based study; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; NA, not available

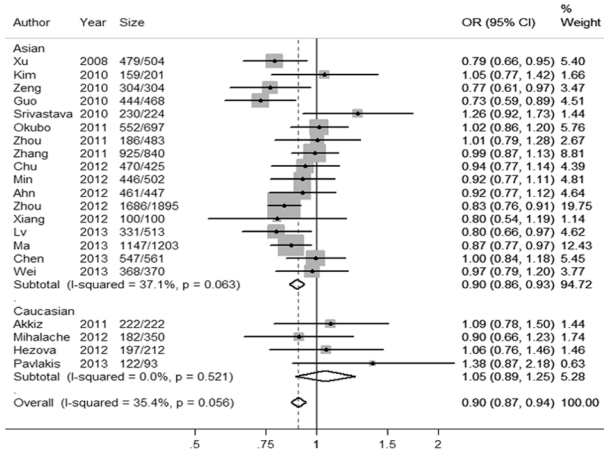

Figure 2. Forest Plot of ORs for the Association of MiR-146a (G>C) Polymorphism with Risk of Digestive System Cancer in Subgroup Analysis by Ethnicity under the Allele Model

details of the selection process were presented in Figure 1. Overall, of the 21 studies, 17 were conducted in Asian population, 4 in Caucasian population. Various cancer site included HCC (6 studies), CRC (5 studies), GC (4 studies), ESCC (2 studies), and other cancers (4 studies). The publication years of the included articles ranged from 2008 to 2013. In addition, a classical polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) method was performed in 13 studies, 4 studies used TaqMan assay, and 4 studies used other genotyping method. Quality scores of included studies ranged from 6.5 to 14. Furthermore, genotype distribution of controls in all studies was consistent with HWE (Table 1).

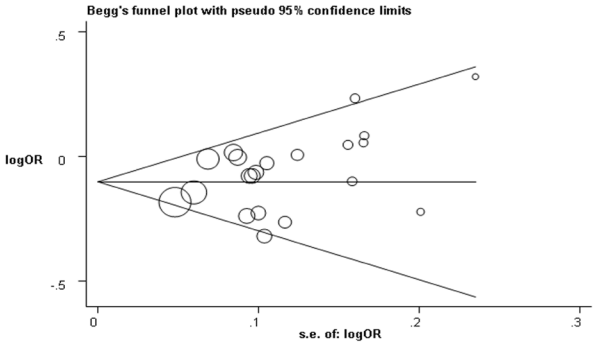

Figure 3. Begg's Funnel Plots under the Allele Model to Identify the Publication Bias. The logarithm values of relative risk (OR) were plotted against their standard errors. One circle dot represents one published study

Quantitative data synthesis

The association of the miR-146a (G>C) polymorphism and digestive system cancers was investigated in 21 studies. And results of pooled analysis revealed that a decreased risk was observed for the comparison of allele model (OR=0.90, 95%CI 0.87-0.94), homozygote model (OR=0.84, 95%CI 0.77-0.91), dominant model (OR=0.90, 95%CI 0.84-0.96), and recessive model (OR=0.85, 95%CI 0.79-0.91). In the stratified analysis by ethnicity, a remarkable association between miR-146a polymorphism and digestive system cancers was detected in Asian population (allele model: OR=0.90, 95%CI 0.86-0.93; homozygote model: OR=0.82, 95%CI 0.75-0.90; recessive model: OR=0.84, 95%CI 0.78-0.89), but not in Caucasian population. Figure 2 gives the forest plot that provides study-specific and pooled ORs for miR-146a

Table 2. Result of Meta-analysis for miR-146a Rs2910164

Study Groups	N[a]	C vs. G (Allele model)			CC vs. GG (Homozygote model)		
		OR (95%CI)	I^2 (%)	P^b	OR (95%CI)	I^2 (%)	P^b
Total	21	0.90 (0.87, 0.94)	35.4		0.84 (0.77, 0.91)	42.3	
Ethnicity				0.07			0.122
Caucasian	4	1.05 (0.89, 1.25)	0		1.20 (0.75, 1.91)	0	
Asian	17	0.90 (0.86, 0.93)	37.1		0.82 (0.75, 0.90)	49.6	
Cancer site				0.202			0.285
CRC	5	0.90 (0.83, 0.97)	6.5		0.85 (0.72, 1.00)	33.9	
GC	4	0.87 (0.81, 0.93)	47.6		0.82 (0.62, 1.10)	66.7	
LC	6	0.94 (0.86, 1.03)	21.2		0.87 (0.73, 1.05)	28.8	
ESCC	2	0.84 (0.63, 1.12)	74.6		0.65 (0.29, 1.46)	81.1	
Other Cancer	4	1.02 (0.89, 1.17)	36.1		1.16 (0.82, 1.63)	0	
Genotyping methods				0.181			0.171
PCR-RFLP	13	0.92 (0.87, 0.98)	33.8		0.86 (0.75, 0.99)	34.4	
TaqMan	4	0.86 (0.80, 0.92)	0		0.75 (0.65, 0.87)	23.8	
Other methods	4	0.92 (0.80, 1.06)	58.9		0.87 (0.62, 1.22)	66.3	
Quality score				0.175			0.143
>=10	16	0.90 (0.86, 0.94)	41.1		0.82 (0.75, 0.90)	49.9	
<10	5	1.00 (0.86, 1.17)	0		1.10 (0.75, 1.61)	0	

Study Groups	CG vs. GG (Heterozygous model)			CC+CG vs. GG (Dominant model)			CC vs. CG+GG (Recessive model)		
	OR(95%CI)	I^2 (%)	P^b	OR(95%CI)	I^2 (%)	P^b	OR(95%CI)	I^2 (%)	P^b
Total	0.99 (0.89, 1.11)	50.7		0.90 (0.84, 0.96)	45.2		0.85 (0.79, 0.91)	46.1	
Ethnicity			0.906			0.403			0.016
Caucasian	0.95 (0.76, 1.20)	0		0.98 (0.79, 1.22)	0		1.32 (0.92, 1.90)	0	
Asian	1.00 (0.88, 1.14)	58.4		0.94 (0.84, 1.05)	53.2		0.84 (0.78, 0.89)	47.1	
Cancer site			0.702			0.358			0.365
CRC	1.07 (0.81, 1.40)	70.8		0.99 (0.81, 1.21)	52.2		0.80 (0.60, 1.05)	73.8	
GC	1.03 (0.75, 1.40)	75.2		0.93 (0.71, 1.22)	70.8		0.81 (0.72, 0.90)	0.9	
LC	0.98 (0.83, 1.15)	37.6		0.95 (0.81, 1.11)	42.2		0.91 (0.80, 1.04)	0	
ESCC	0.83 (0.67, 1.04)	29.2		0.81 (0.59, 1.13)	53.7		0.70 (0.36, 1.36)	77.9	
Other Cancer	1.04 (0.83, 1.30)	6.7		1.05 (0.85, 1.31)	0		1.19 (0.78, 1.82)	51.5	
Genotyping methods			0.001			0.006			0.744
PCR-RFLP	1.10 (0.97, 1.24)	35.2		1.02 (0.91, 1.14)	27.9		0.85 (0.73, 0.99)	56.3	
TaqMan	0.81 (0.73, 0.90)	0		0.80 (0.72, 0.88)	0		0.85 (0.74, 0.96)	19.7	
Other methods	1.02 (0.80, 1.29)	56.6		0.97 (0.76, 1.24)	63.1		0.89 (0.78, 1.01)	43.3	
Quality score			0.731			0.762			0.05
>=10	1.01 (0.89, 1.14)	60.4		0.95 (0.84, 1.06)	55.5		0.83 (0.78, 0.89)	49.8	
<10	0.90 (0.71, 1.15)	0		0.93 (0.74, 1.18)	0		1.10 (0.84, 1.43)	0	

[a]The number of studies included; [b]*P* for heterogeneity test between strata. OR, odds ratio; CI, confidence interval; CRC, colorectal cancer; GC, gastric cancer; LC, liver cancer; ESCC, esophageal cancer; HB, hospital-based study; PB, population-based study; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism

polymorphism and digestive system cancers in strata of ethnicity. Further subgroup analysis by cancer site indicated that miR-146a polymorphism may decreased the risk of colorectal cancer (allele model: OR=0.90, 95%CI 0.83-0.97; homozygote model: OR=0.85, 95%CI 0.72-1.00) and gastric cancer (allele model: OR=0.87, 95%CI 0.81-0.93; recessive model: OR=0.81, 95%CI 0.72-0.90), but no evidence of an association with esophagus cancer, liver cancer, and other digestive cancers. Furthermore, subgroup analysis by genotyping method showed that there was significant association between miR-146a polymorphism and decreased cancer risk determined by PCR-RFLP in allele, homozygote, and recessive model, while TaqMan in all five models. Finally, when stratified by quality score, we could observe that significantly decreased risk in the subgroup which quality scores over 10 in allele, homozygote, and recessive model, as summarized in Table 2.

Sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the influence of each individual study on the pooled OR by sequential removal of individual studies. The results suggested that no individual study significantly affected the overall OR dominantly (data not shown).

We also drew the Begg's funnel plots to assess the publication bias of eligible studies (Figure 3). The shapes of the funnel plot for the comparison of the C allele and G allele of rs2910164 appears to be symmetrical, and no significant asymmetry was found by the Egger's and Begg's tests.

Discussion

MiR-146a rs2910164 is located in the stem region opposite to the mature miR-146a sequence. This G-C polymorphism results in a change from G: U pair to C:

U mismatch in the stem structure of miR-146a precursor. Recent studies have provided confirmed evidence on functional role of miR-146a (Jazdzewski et al., 2008; Shen et al., 2008). It has been demonstrated that the deficiency of miR-146a in Treg cells resulted in a breakdown of immunological tolerance manifested in a fatal IFNGγ-dependent immune-mediated lesion in a variety of organs (Lu et al., 2010). Besides, miR-146a acts as a tumor suppressor to down-regulate NFkB activity via targeting TRAF6 (Paik et al., 2011). Therefore, the rs2910164 is suspected to have an effect on tumor immune responses and ultimately the development of cancer.

Several meta-analyses were conducted to investigate the association between miR-146a rs2910164 polymorphism and risks of various cancers (Wang et al., 2012; Wu et al., 2013; Xu et al., 2013; Yin et al., 2013), including liver cancer, gastric cancer, gallbladder cancer, breast cancer, and other cancers. However, the results were contradictory and inconclusive, and several studies about the relationship between rs2910164 polymorphisms and risks of digestive system cancers were published recently (Lv et al., 2013; Ma et al., 2013; Pavlakis et al., 2013). To better understanding of the association between miR-146a rs2910164 polymorphism and digestive system cancers risk, a meta-analysis with larger sample and subgroup analysis is necessary. The current study is the largest meta-analysis of the association between miR-146a rs2910164 polymorphism with the risk of digestive system cancers.

Our study showed that the presence of C allele significantly decreased the risk of digestive system cancers with the comparison to G allele. This finding indicates that the genetic variant in miR-146a may crucially modify the susceptibility of digestive system cancers. When stratified by cancer site, protection effect was found in CRC and GC, but not in ESCC, LC and other digestive cancers in allele model. This may be explained by the effect of gene polymorphism on cancer susceptibility varies by specific cancer site. Otherwise, the relatively small amount of eligible studies in stratified analysis might induce statistically significant or insignificant association by chance due to insufficient statistical power (Tapia et al., 2008).

In the subgroup of ethnicity, we found statistically significant association between miR-146a polymorphism and decreased risk of digestive system cancers in Asians but not in Caucasians. A former meta-analysis reported a parallel observation to us (Ma et al., 2013). The inconsistency between the two ethnicities can be explained by the possibility that different ethnic groups live with multiple life styles and environmental factors and thus yield diverse gene-environment interactions (Dick, 2011). Moreover, different populations carry different genotype and allele frequencies of miR-146a polymorphism, and may lead to various degrees of cancer susceptibility (Gao et al., 2010). Meanwhile, relative small sample size in Caucasians might also be the reason of the inconspicuousness.

We found statistically significant differences between subgroups stratified by genotyping methods in heterozygous model and dominant model. Disagreements in the stratification of genotyping methods might attribute to different technical principles of genotyping. Furthermore, a significant association between miR-146a polymorphism and the decreased digestive system cancers was found in group that quality score over 10, which indicated the importance of the quality of study.

Some advantages can be highlighted in our study. On one hand, this meta-analysis shed light on the association between miR-146a polymorphism and decreased risks of digestive system cancers, colorectal cancer, gastric cancer, and esophagus cancer comprehensively and systematically. On the other hand, the inclusion of an unpublished study on CRC strengthened the power and persuasion of our inference. Furthermore, all included studies had acceptable quality (scored at least 6.5). However, limitations of this meta-analysis should also be discussed as they may affect the interpretation of the results. Firstly, most of the patients were Asians, which limited the general application of the findings from the meta-analysis. Secondly, genetic factors, tumor biological characteristics, and their interactions with environmental factors exert diverse influences to the cancer susceptibility and tumorigenesis. For instance, Heliobacter pylori infections and smoking may increase the incidence of gastric cancer. And hepatitis B, C virus infections and exposure of aflatoxin in food are risk to liver cancer (Wallace et al., 2011). However, studies included in this meta-analysis contained various cancer site, different ethnicity, and multifactor such as gender, age, and lifestyle-related factors. Thus, these factors may become potential determinants to influence the evaluation of the associations between SNPs and susceptibility to digestive system cancers by interacting with genetic factors. Finally, the number of studies on specific cancer site, such as pancreatic cancer and cholangiocarcinoma is limited.

In summary, this meta-analysis indicated that miR-146a rs2910164 polymorphism may decrease the susceptibility of digestive system cancers, especially in Asian population. Well-designed studies with larger sample size and more ethnic groups are of great value to clarify these findings.

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