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Original Article

The association between miR-146a polymorphism and cancer susceptibility: a meta-analysis

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Abstract: MicroRNAs (miRNAs) are a class of new non-coding RNA, which play important roles in the pathogenesis of tumor. Rs2910164 in miR-146a is suggested to be associated with the risk of suffering cancer. The present study analyzes the association between the polymorphism of miR-146a rs2910164 and cancer susceptibility through the meta-analysis. We searched the correlative article from PubMed and Embase databases. According to the inclusion and exclusion criteria, we screened all the articles. The strength of associations between microRNA polymorphism and cancer risk were estimated by computing the odds ratios and 95% confidence intervals. All analyses were performed using the Stata software. There are 34 datasets included in the analysis. The results showed that no association was found between the rs2910164 in miR-146a and the risks of overall cancer. A stratified analysis, on the basis of ethnicity for population characteristic, showed that Asians carrying variant genotypes of rs2910164 in miR-146a have lower danger to be attacked by cancer (GC vs. GG: OR=0.90 95% CI=0.83-0.96, P=0.003; CC vs. GG: OR=0.83, 95% CI=0.70-1.00, P=0.047; CC+GC vs. GG: OR=0.89, 95% CI=0.78-0.99, P=0.032). In contrast, Caucasians have higher risk (CC vs. GG: OR=1.17, 95% CI=1.01-1.35, P=0.038; C vs. G: OR=1.06, 95% CI=1.01-1.12, P=0.034). In the subgroup analysis of tumor type, all the genetic model suggested that rs2910164 contribute to reduce the risk of cervical squamous cell carcinoma (GC vs. GG: OR=0.72, 95% CI=0.55-0.95, P=0.022; CC vs. GG: OR=0.50, 95% CI=0.37-0.68, P<0.001; CC+GC vs. GG: OR=0.63, 95% CI=0.49-0.82, P=0.001; CC vs. GG+GC: OR=0.65, 95% CI=0.52-0.82, P<0.001; C vs. G: OR=0.72, 95% CI=0.62-0.84, P<0.001). Rs2910164 CC genotype is the protection factor of hepatocellular carcinoma (CC vs. GG: OR=0.71, 95% CI=0.55-0.92, P=0.010) and prostatic carcinoma (CC vs. GG: OR=0.57, 95% CI=0.35-0.90, P=0.016; C vs. G: OR=0.80, 95% CI=0.66-0.97, P=0.024). The present study suggests that rs2910164 polymorphism in miR-146a may be related to the susceptibility of cancer.

Keywords: Cancer, microRNA, single nucleotide polymorphism, susceptibility, meta-analysis

Introduction

MicroRNAs (miRNAs) are a class of new non-coding RNA, which widely exist in the plants, eelworm and human cell. MiRNAs mainly inhibit the transcription level of gene expression by binding to the 3' end of the translation section on mRNA [1]. The miRNA imperfect paired with target mRNAs of protein-coding genes and transcriptional or posttranscriptional regulated their expression, which may cause the degradation of the target mRNA or inhibit protein synthesis. MicroRNA held a significant effect in a variety of biological processes. It could regulate the growth, differentiation, apoptosis, proliferation of cell, and the process of kinds of cancer [2]. In vivo, about 50% of the mRNA genes in the genomic regions are associated with cancer or fragile site, providing more evidence of in series with the pathogenesis of cancer [3].

Single nucleotide polymorphisms (SNPs) are mainly refers to single nucleotide mutation caused by the level of DNA sequence polymorphism, which affects the susceptibility of the disease. There are studies showing that rs2910164 in miRNA-146a can decrease the expression of the mature mRNAs [4]. Rs2910164 in miRNA-146a could both increase the risk of cervical squamous cell cancer (CSCC) [5]. Meanwhile, rs2910164 was showed to be related with the susceptibility of papillary thy-

roid carcinoma (PTC) [4]. While there are studies did not draw the relationship between rs291016 and the breast cancer, bladder cancer, and kidney cancer in Asian people and white people [6-8]. Tian reported that this polymorphism have no significant correlation with lung cancer [9]. In a population-based case-control study, rs2910164 polymorphism has a tendency to increase the risk of gallbladder cancer in India, but there was no statistical significance [10].

Therefore, the role of rs2910164 in miRNA-146a on cancer susceptibility remains unknown. Although the relationship between miRNA-146a genetic polymorphism and cancer susceptibility has become a hot topic now and there have been many published articles in recent years, there is still not a clear conclusion. In addition, these reported results were contradictory and inconclusive. So we perform an updated meta-analysis on all available studies to assess the overall cancer risk with rs2910164 in miR-146a.

Materials and methods

Data sources

We retrieved the articles using the following terms "miRNA or miR-146a" and "cancer" and "polymorphism" from PubMed and Embase datasets (Last search was updated on May 2015). We evaluated potentially relevant publications by examining their titles and abstracts and all studies matching the eligible criteria were retrieved.

Study selection and data extraction

Qualified studies were selected according to the following explicit inclusion standard: (a) evaluation of the rs2910164 and cancer risks, (b) using the methodology of a case-control study or cohort study, (c) there was sufficient published data for the computation of odds ratios (ORs) with 95% confidence intervals (95% CIs).

Duplicate and obviously unrelated articles were eliminated by a single author (Z.Y.). Two authors (Z.C. and Z.Y.) read the abstracts and/or the whole articles independently to decide whether the articles should be excluded. The following information was obtained from each publication: first author's name, publication date, country origin, ethnicity, cancer type, control characteristics, study design, total number of cases and controls, numbers of cases and controls with miR-146a G/C genotypes, quality score, and adjusted co-variables, respectively.

Statistical methods

First the Hardy-Weinberg equilibrium (HWE) in control groups for each included study was analyzed by chi-squared tests. Then Cochran's Q test and I^2 were calculated to assess the between-study heterogeneity for each study. If the heterogeneity was not significant, the summary OR was calculated by the fixed-effect model. Otherwise, the random-effect model was used. The strength of associations between microRNA polymorphism and cancer susceptibility was estimated by computing the pooled ORs and their 95% CIs. ORs were calculated from combination of each study by heterozygote comparison (GC vs. GG), homozygote comparison (CC vs. GG), dominant model (CC+GC vs. GG), recessive model (CC vs. GC+GG) and allelic model (C vs. G), respectively. For each genetic comparison model, subgroup analysis according to ethnicity was investigated to estimate ethnic-specific ORs for Asian population and Caucasian population. Meanwhile, stratified analyses by tumor type, HWE and subjects resource were also applied for each genetic comparison model. The meta-regression was done to analyze the source of the heterogeneity of the included literatures. At last the inverted funnel figures and the egger test method were used to evaluate the publication bias. All of *P* values were two-sided and all analyses were performed using the Stata software version 11.0 (Stata Corp, College station, TX).

Results

Characteristics of included studies

According to above criteria, a total of 55 articles were eligible. Nine of them are reviews and two are comments. Ten of them were excluded because of no cancer risk or data missing. Finally, 33 articles comprising 34 datasets were included and used in quantitative synthesis for meta-analysis. Flow chart of the study selection process was shown in **Figure 1**. Thirty-four datasets were about miR-146a (rs2910164) SNP, including 16142 cases and

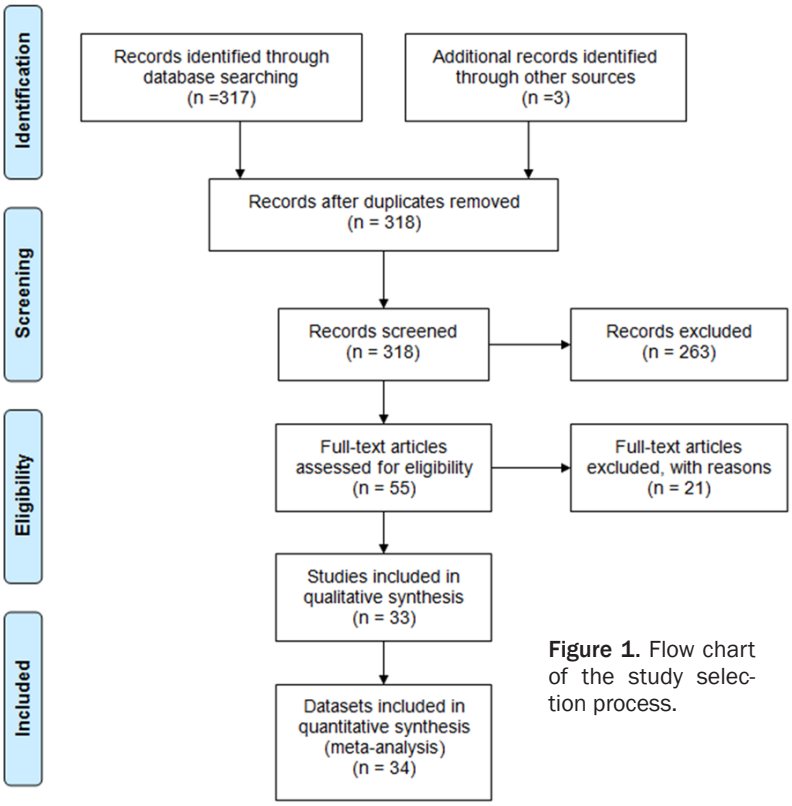

Figure 1. Flow chart of the study selection process.

22319 controls. In the 34 datasets, there are 21 for Asian and 13 for Caucasians. There were three studies whose distributions of genotypes in the controls were not in Hardy-Weinberg equilibrium. The characteristics of included studies were shown in **Table 1**.

MiR-146a (rs2910164) SNP and overall cancer susceptibility

The C allele frequency of the miR-146a polymorphism (rs2910164) among the controls across different ethnicities ranged from 0.20 to 0.74. The C allele frequencies across different ethnicities were also observed. The average C allele frequencies among Asians and Caucasians are 0.56 and 0.24, respectively. The overall ORs with their 95% CIs didn't show statistically significant association between rs2910164 polymorphism and overall cancer susceptibility (GC vs. GG: OR=0.97, 95% CI=0.92-1.02, P=0.002 for heterogeneity, I^2=46.4%; CC vs. GG: OR=0.94, 95% CI=0.81-1.09, P<0.001 for heterogeneity, I^2=67.5%; CC+GC vs. GG: OR=0.96, 95% CI=0.89-1.04, P<0.001 for heterogeneity, I^2=57.1%; CC vs. GG+GC: OR=0.97, 95% CI=0.87-1.09, P<0.001 for heterogeneity, I^2=65.4%; C vs. G: OR=0.98, 95% CI=0.92-1.04, P<0.001 for heterogeneity, I^2=66.5%) (**Table 2**).

Sensitivity analyses suggested that the present results were stable. Every one single study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset to the pooled ORs. This procedure did not change the pooled ORs supporting the robustness of our findings.

No publication bias was detected by either the inverted funnel plot or Egger's test. The shapes of the funnel plot for the comparison of this polymorphism seemed approximately symmetrical and *P* values of the Egger' tests were not statistically significant (GC vs. GG: t=-0.19, P=0.847; CC vs. GG: t=0.61, P=0.549; CC+GC vs. GG: t=-0.15, P=0.885; CC vs. GG+GC: t=0.20, P=0.840; C vs. G: t=-0.33, P=0.740).

Stratified analyses

In the subsequent stratified analyses, we can see the heterogeneity decreased significantly in groups. In the stratified analysis by ethnicity, the different results were found among the Asian and the Caucasian population (**Table 3**). In Asians, comparing with wild genotype (GG), the heterozygote and homozygote genotypes significantly reduce the susceptibility of cancer (GC vs. GG: OR=0.90, 95% CI=0.83-0.96; CC vs. GG: OR=0.83, 95% CI=0.77-1.00) and the significant result also could be found among the dominant model (CC+GC vs. GG: OR=0.89, 95% CI=0.78-0.99). For the Caucasians, there are two genetic models increasing the risk of cancer (CC vs. GG: OR=1.17, 95% CI=1.01-1.35; C vs. G: OR=1.06, 95% CI=1.01-1.12). In the subgroup analyses by subjects resource, the significant result was found in the hospital-

Table 1. Characteristics of all studies in meta-analysis

Author, year	Country	Ethnicity	Cancer Type	SNP	Study Design	Genotyping Method	Subject resource	No. (case/control)	Case			Control				Quality	Adjusted
									GG/AA	GC/AG	CC/GG	GG/AA	GC/AG	CC/GG	HWE (P)	Score (NOS)	co-variables
Jazdzewskl (2008) [4]	Finland Poland USA	Caucasian	PTC	rs2910164	Case-control	TaqMan	PB	608/901	305	287	16	526	320	55	0.50	8	Crude OR
Horikawa (2008) [8]	US	Caucasian	RCC	rs2910164	Case-control	SNPlex	PB	261/235	144	103	14	126	94	15	0.65	8	Crude OR
Yang (2008) [7]	US	Caucasian	GBC	rs2910164	Case-control	SNPlex	PB	691/674	414	242	35	385	258	31	0.14	8	Crude OR
Hu (2009) [6]	China	Asian	BC	rs2910164	Case-control	PCR-RFLP	PB	1009/1093	165	515	329	180	551	362	0.22	8	Crude OR
Xu (2008) [29]	China	Asian	HCC	rs2910164	Case-control	PCR-RFLP	HB	479/504	80	241	158	58	249	197	0.12	7	Crude OR
Tian (2009) [9]	China	Asian	LC	rs2910164	Case-control	PCR-RFLP	PB	1058/1035	360	510	188	364	502	169	0.85	9	Crude OR
Hoffman (2009) [34]	US	Caucasian	BC	rs2910164	Case-control	Massarray mltiplex	PB	439/478	234	176	29	273	178	27	0.77	8	Crude OR
Srivastava (2010) [10]	India	Caucasian	GBC	rs2910164	Case-control	PCR-RFLP	PB	230/224	129	90	11	138	81	5	0.08	8	Crude OR
Liu (2010) [31]	USA	Caucasian	SCCHN	rs2910164	Case-control	PCR-RFLP	HB	1109/1130	630	411	68	655	405	70	0.49	7	Crude OR
Okubo (2010) [32]	Japan	Asian	GC	rs2910164	Case-control	PCR-RFLP	HB	552/697	73	243	236	121	322	254	0.28	7	Crude OR
Catucci (2010) [33]	Italy, Germany	Caucasian	BC	rs2910164	Case-control	Taqman PCR	PB	1559/2147	860	590	109	1186	838	123	0.11	9	Crude OR
Zeng (2010) [34]	China	Asian	GC	rs2910164	Case-control	PCR-RFLP	HB	304/304	62	153	89	53	132	119	0.12	7	Crude OR
Pastrello (2010) [35]	Italian	Caucasian	BC/OC	rs2910164	Case-control	PCR-direct sequencing	PB	101/155	60	36	5	90	59	6	0.33	8	Crude OR
Guo (2010) [36]	China	Asian	ESCC	rs2910164	Case-control	SNPshot assay	PB	444/468	234	190	20	206	220	42	0.12	8	Crude OR
Xu (2010) [37]	China	Asian	PC	rs2910164	Case-control	PCR-RFLP	HB	251/280	68	135	48	54	150	76	0.19	7	Crude OR
Zhou (2011) [5]	China	Asian	CSCC	rs2910164	Case-control	PCR-RFLP	PB	226/309	43	113	70	34	159	116	0.06	8	Crude OR
George (2011) [38]	India	Caucasian	PC	rs2910164	Case-control	PCR-RFLP	PB	159/230	4	79	76	7	107	116	0.002	8	Crude OR
Mittal (2011) [39]	India	Caucasian	BC	rs2910164	Case-control	PCR-RFLP	PB	212/250	127	79	6	135	108	7	0.007	8	Crude OR
Permuth (2011) [40]	US	Caucasian	Glioma	rs2910164	Case-control	Illumina's GoldenGate technology	PB	593/614	345	198	50	375	214	25	0.42	8	Crude OR
Hishida (2011) [14]	Japan	Asian	GC	rs2910164	Case-control	PCR-confronting two-pair primers	HB	583/1637	82	271	230	229	775	633	0.12	7	Crude OR
Akkiz (2011) [41]	Turkish	Caucasian	HCC	rs2910164	Case-control	PCR-RFLP	PB	222/222	137	75	10	144	67	11	0.38	8	Crude OR
Yue (2011) [42]	China	Asian	CSCC	rs2910164	Case-control	PCR-RFLP	HB	447/443	118	224	105	87	206	150	0.29	7	Crude OR
Garcia (2011) [27]	French	Caucasian	BC	rs2910164	Case-control	TaqMan	HB	1130/596	676	388	66	352	220	24	0.15	7	Crude OR
Zhou (2012) [43]	China	Asian	GC	rs2910164	Case-control	Taqman PCR	HB	1686/1895	578	822	286	551	951	393	0.64	7	Crude OR
Lung (2012) [44]	China	Asian	NC	rs2910164	Case-control	Tm-shift allele-specific genotyping	PB	229/3776	24	88	117	497	1807	1472	0.12	8	Crude OR
Zhou (2012) [45]	China	Asian	HCC	rs2910164	Case-control	PCR-RFLP	PB	186/483	33	86	67	71	254	158	0.06	8	Crude OR
Xiang (2012) [46]	China	Asian	HCC	rs2910164	Case-control	PCR-RFLP	HB	100/100	27	45	28	21	46	33	0.51	6	Crude OR
Kim (2012) [47]	Korean	Asian	HCC	rs2910164	Case-control	PCR-RFLP	PB	159/201	57	88	14	74	103	24	0.19	7	Crude OR
Wei (2013) [17]	China	Asian	ESCC	miR-146a	Case-control	PCR	HB	368/369	67	184	117	67	181	122	1.00	7	Crude OR
Vinci (2013) [18]	Italy	Caucasian	CRC	miR-146a	Case-control	TaqMan PCR	HB	160/178	86	57	17	100	65	13	0.87	6	Crude OR
Hu (2014) [19]	China	Asian	CRC	miR-146a	Case-control	PCR-RFLP	HB	276/373	34	82	84	44	187	142	0.33	7	Crude OR
Hasani (2014) [20]	Iran	Asian	ALL	miR-146a	Case-control	TARMS-	HB	75/115	7	49	22	27	50	20	0.94	6	Crude OR
Omrani (2014) [21]	Iran	Asian	BC	miR-146a	Case-control	PCR	HB	236/203	183	45	8	155	39	9	0.02	7	Crude OR

BC: breast cancer, CSCC: cervical squamous cell carcinoma, ESCC: esophageal squamous cell carcinoma, GBC: gallbladder cancer, GC: gastric cancer, HCC: hepatocellular carcinoma, LC: lung cancer, NC: nasopharyngeal carcinoma, OC: ovarian cancer, PC: prostate cancer, PTC: papillary thyroid carcinoma, RCC: renal cell carcinoma, SCCHN: cell carcinoma of head and neck, PB: Population-based, HB: Hospital based, HWE: Hardy-Weinberg equilibrium, NOS: the Newcastle-Ottawa Scale.

Table 2. Association between miR-146a (rs2910164) and cancer susceptibility

	Data set number	Fixed effect*	Random effect*	Phet#	I-squared (%)
rs2910164					
GC vs. GG	34	0.97 [0.92, 1.02]	0.96 [0.89, 1.04]	0.002	46.4
CC vs. GG	34	0.92 [0.86, 1.00]	0.94 [0.81, 1.09]	0.000	67.5
CC+GC vs. GG	34	0.97 [0.92, 1.01]	0.96 [0.89, 1.04]	0.000	57.1
CC vs. GC+GG	34	0.97 [0.91, 1.03]	0.97 [0.87, 1.09]	0.000	65.4
C vs. G	34	0.98 [0.94, 1.01]	0.98 [0.92, 1.04]	0.000	66.5

*All of the ORs were crude ORs. #Phet: *P* value of heterogeneity.

Table 3. Stratified analyses of miR-146a (rs2910164) and cancer susceptibility by ethnicity, HWE and control population

		Data set number	Association results		Model	Heterogeneity	
			OR (95% CI)*	*P* value		*P* value	I^2 (%)
Asians	GC vs. GG	21	0.90 [0.83, 0.96]	0.003	F	0.041	37.8
	CC vs. GG	21	0.83 [0.70, 1.00]	0.047	R	0.000	71.0
	CC+GC vs. GG	21	0.89 [0.78, 0.99]	0.032	R	0.003	58.5
	CC vs. GC+GG	21	0.91 [0.80, 1.04]	0.163	R	0.000	69.2
	C vs. G	21	0.93 [0.85, 1.01]	0.086	R	0.000	73.6
Caucasians	GC vs. GG	13	1.04 [0.97, 1.12]	0.231	F	0.062	40.8
	CC vs. GG	13	1.17 [1.01, 1.35]	0.038	F	0.093	36.3
	CC+GC vs. GG	13	1.06 [0.99, 1.13]	0.087	F	0.341	10.4
	CC vs. GC+GG	13	1.15 [1.00, 1.32]	0.056	F	0.023	49.2
	C vs. G	13	1.06 [1.01, 1.12]	0.034	F	0.777	0.0
HWE (P>0.05)	GC vs. GG	31	0.97 [0.89, 1.05]	0.406	R	0.001	50.1
	CC vs. GG	31	0.94 [0.81, 1.09]	0.423	R	0.000	70.4
	CC+GC vs. GG	31	0.96 [0.87, 1.05]	0.395	R	0.000	60.3
	CC vs. GC+GG	31	0.98 [0.94, 1.03]	0.450	F	0.625	0.0
	C vs. G	31	0.98 [0.92, 1.05]	0.625	R	0.000	69.2
HWE (P<0.05)	GC vs. GG	3	0.87 [0.65, 1.16]	0.336	F	0.624	0.0
	CC vs. GG	3	0.89 [0.47, 1.68]	0.723	F	0.874	0.0
	CC+GC vs. GG	3	0.86 [0.65, 1.13]	0.284	F	0.718	0.0
	CC vs. GC+GG	3	0.96 [0.78, 1.18]	0.681	F	0.811	0.0
	C vs. G	3	0.90 [0.74, 1.09]	0.271	F	0.882	0.0
PB	GC vs. GG	18	1.01 [0.89, 1.13]	0.915	R	0.001	58.5
	CC vs. GG	18	1.04 [0.82, 1.32]	0.724	R	0.000	65.5
	CC+GC vs. GG	18	1.02 [0.91, 1.15]	0.734	R	0.001	59.2
	CC vs. GC+GG	18	1.01 [0.95, 1.06]	0.850	F	0.486	0.0
	C vs. G	18	1.03 [0.95, 1.12	0.455	R	0.001	60.3
HB	GC vs. GG	16	0.92 [0.85, 0.99]	0.024	F	0.319	11.8
	CC vs. GG	16	0.86 [0.72, 1.02]	0.084	R	0.000	64.9
	CC+GC vs. GG	16	0.90 [0.81, 1.00]	0.050	R	0.021	46.7
	CC vs. GC+GG	16	0.95 [0.89, 1.02]	0.142	F	0.853	0.0
	C vs. G	16	0.93 [0.85, 1.01]	0.073	R	0.000	66.2

*All of the ORs were crude ORs. HWE: Hardy-Weinberg equilibrium. PB: Population-based. HB: Hospital based. F: Fixed effect; R: Random effect.

based case-control study (GC vs. GG, OR=0.92, 95% CI=0.85-0.99). There were no significant associations in the stratified analysis results by HWE.

Table 4. Stratified analyses of miR-146a (rs2910164) and cancer susceptibility by cancer type

		Data set number	Association results		Model	Heterogeneity	
			OR (95% CI)*	*P* value		*P* value	I^2 (%)
Prostate cancer	GC vs. GG	2	0.76 [0.51, 1.14]	0.182	F	0.384	0.0
	CC vs. GG	2	0.57 [0.35, 0.90]	0.016	F	0.234	29.5
	CC+GC vs. GG	2	0.69 [0.47, 1.01]	0.054	F	0.340	0.0
	CC vs. GC+GG	2	0.76 [0.57, 1.01]	0.057	F	0.235	29.1
	C vs. G	2	0.80 [0.66, 0.97]	0.024	F	0.200	39.1
Gastric cancer	GC vs. GG	4	0.91 [0.81, 1.02]	0.104	F	0.136	45.8
	CC vs. GG	4	0.92 [0.63, 1.34]	0.648	R	0.000	84.1
	CC+GC vs. GG	4	0.96 [0.74, 1.24]	0.753	R	0.011	73.1
	CC vs. GC+GG	4	0.92 [0.70, 1.21]	0.543	R	0.000	83.5
	C vs. G	4	0.95 [0.78, 1.16]	0.633	R	0.000	86.4
Hepatocellular carcinoma	GC vs. GG	5	0.89 [0.73, 1.09]	0.260	F	0.276	21.8
	CC vs. GG	5	0.71 [0.55, 0.92]	0.010	F	0.659	0.0
	CC+GC vs. GG	5	0.86 [0.71, 1.04]	0.128	F	0.233	28.3
	CC vs. GC+GG	5	0.86 [0.72, 1.04]	0.122	F	0.432	0.0
	C vs. G	5	0.89 [0.80, 1.00]*	0.059	F	0.333	12.7
Cervical squamous cell carcinoma	GC vs. GG	2	0.72 [0.55, 0.95]*	0.022	F	0.254	23.1
	CC vs. GG	2	0.50 [0.37, 0.68]*	0.000	F	0.814	0.0
	CC+GC vs. GG	2	0.63 [0.49, 0.82]*	0.001	F	0.382	0.0
	CC vs. GC+GG	2	0.65 [0.52, 0.82]*	0.000	F	0.359	0.0
	C vs. G	2	0.72 [0.62, 0.84]*	0.000	F	0.796	0.0
Breast cancer	GC vs. GG	7	0.97 [0.89, 1.07]	0.576	F	0.729	0.0
	CC vs. GG	7	1.12 [0.96, 1.32]	0.162	F	0.812	0.0
	CC+GC vs. GG	7	1.00 [0.91, 1.09]	0.950	F	0.752	0.0
	CC vs. GC+GG	7	1.08 [0.95, 1.24]	0.261	F	0.648	0.0
	C vs. G	7	1.02 [0.95, 1.09]	0.619	F	0.794	0.0
Gallbladder cancer	GC vs. GG	2	0.94 [0.78, 1.14]	0.554	F	0.173	46.2
	CC vs. GG	2	1.22 [0.78, 1.92]	0.382	F	0.185	43.0
	CC+GC vs. GG	2	1.02 [0.74, 1.42]	0.901	R	0.120	58.7
	CC vs. GC+GG	2	1.26 [0.81, 1.97]	0.312	F	0.254	23.0
	C vs. G	2	1.06 [0.79, 1.41]	0.708	R	0.105	62.0
Colorectal cancer	GC vs. GG	2	0.77 [0.43, 1.37]	0.373	R	0.096	63.8
	CC vs. GG	2	1.01 [0.52, 1.96]	0.969	R	0.151	51.5
	CC+GC vs. GG	2	0.86 [0.51, 1.44]	0.563	R	0.112	60.3
	CC vs. GC+GG	2	1.23 [0.90, 1.69]	0.199	F	0.560	0.0
	C vs. G	2	1.03 [0.85, 1.27]	0.742	F	0.422	0.0

*All of the ORs were crude ORs.

In the stratified analysis by tumor type, we could found the susceptibility decreased for cervical squamous cell carcinoma in all the genotype models (GC vs. GG: OR=0.72, 95% CI=0.55-0.9; CC vs. GG: OR=0.50, 95% CI=0.37-0.68; CC+GC vs. GG: OR=0.63, 95% CI=0.49-0.82; CC vs. GG+GC: OR=0.65, 95% CI=0.52-0.82; C vs. G: OR=0.72, 95% CI=0.62-0.84). In the analyses for prostate cancer, comparing with the individuals with GG genotype, the subjects carrying the CC genotype were in lower risks to develop cancer and the significant result also existed in the additive model (CC vs. GG: OR=0.57, 95% CI=0.35-0.90; C vs. G: OR=0.80, 95% CI=0.66-0.97). For hepatocellular carcinoma, the individuals carrying the CC genotype were not likely to develop cancer compared with those carrying GG genotype (CC vs. GG: OR=0.71, 95% CI=0.55-0.92). **Table 4** shows the stratified analyses results of miR-

146a (rs2910164) and cancer susceptibility by cancer type.

Every one single study involved in the meta-analysis was deleted each time to reflect the influence of the individual dataset to the pooled ORs. This procedure did not change the pooled ORs supporting the robustness of our findings.

No publication bias was detected by either the inverted funnel plot or Egger's test. The shapes of the funnel plot for the comparison of the G allelic and the C allelic of rs2910164 SNP seemed approximately symmetrical and *P* values of the Egger' tests were not statistically significant.

Meta-regression results

Because the heterogeneity was observed in the overall analyses, we use meta-regression to analyze the sources of heterogeneity. Meta-regression included the ethnicity and the type of cancer. The significant result was found for the factor of the ethnicity ($P<0.05$) but not for the factor of cancer type ($P>0.05$), suggesting that the source of heterogeneity in the present meta-analysis may be the type of ethnicity.

Discussion

Individual susceptibility plays important role in the development of most cancers. Polymorphisms of genes involved in carcinogenesis may have accounted for the susceptibility. SNP is one of the human most common genetic variations which could affect the cancer susceptibility of individuals. Much research effort has been directed toward understanding the role of SNPs present in precursor and mature miRNA and their influence on susceptibility and progression of various diseases. Studies have pointed out that these SNPs might affect different cancer susceptibility and development, thus play an important role in cancer. Recently, genetic variants of the miR-146a gene in the etiology of several cancers have drawn increasing attention. The studies suggested that the most common SNP, rs2910164, in miR-146a was likely to alter mature miRNA expression and affect regulation of target mRNAs, further change cancer risk [4-6]. Although there are many researches on the study of miR-146a polymorphism and cancer, there is still no exact result. In order to better understand the relationship between miR-146a polymorphism and cancer susceptibility, a meta-analysis with larger sample and subgroup analysis is necessary. So far there are some similar meta-analyses. For instance, in 2011, there have been studies on the relationship between miR-146a and all cancer by meta-analysis [10-13]. At the beginning of 2012, researchers analyzed the relationship of rs2910164 and the susceptibility of liver cancer [14], gastric carcinoma [15], thymic carcinoma [16]. However the relationship between this SNP and cancer risk is the hot topic, many studies have been published since then [17-21]. In addition, these reported results were contradictory and inconclusive. So we performed the present update meta-analyses. The current study is the largest meta-analysis of the association between miR-146a rs2910164 polymorphism and the susceptibility of overall cancer and different types of cancer.

In this meta-analysis, we did not find statistical evidence for the associations between rs2910164 in miR-146a and the susceptibility of overall cancer before performing subgroup analysis and sensitivity analysis. However, based on larger sample sizes and increased statistical power, our data indicated this polymorphism might play different roles in Asian individuals (protective role) and Caucasian individuals (risk role). Furthermore, rs2910164 C allele may decrease the risk of prostate cancer, cervical squamous cell carcinoma and hepatocellular carcinoma. These results add the new information about the rs2910164 in miR-146a and cancer susceptibility.

It is known that the incidence of genetic polymorphism in different ethnicity is also different. In this meta-analysis, we find that the prevalence of the rs2910164 C allele is highly significant different among the control group between Asians (0.56) and Caucasians (0.24). In the stratified analyses by ethnicity, significantly affected cancer risks were found for both Asians and Caucasians, but the effects were diverse. It showed that there may be ethnicity difference for association between miR-146a rs2910164 polymorphism and cancer risks.

Considering the number of studies included in this article, we performed the stratified analyses by cancer types for breast cancer, hepatocellular carcinoma, gastric cancer, colorectal cancer, cervical squamous cell carcinoma, gallbladder cancer and prostate cancer. Our results

suggested that rs2910164 C allele might decrease the risk of prostate cancer, hepatocellular carcinoma and cervical squamous cell carcinoma, but not in other cancer types. The reason may be that the rs2910164 polymorphism may have different effect on carcinogenesis in different organs, reflecting the diversities of the susceptible factors for different tumor types.

There are contentious results of the effect of rs2910164 polymorphism on miR-146a expression in various cancer tissues and cell lines. Some studies showed elevated expression in papillary thyroid cancer [22] and cervical cancer [23]. In other studies, reduced or absent expression level of miR-146a was found in prostate cancer [24], gastric cancer [25], pancreatic cancer [26] and breast cancer [27]. The researchers found that the GG genotype of rs2910164 might be associated with increased expression level of miR-146a in hepatocellular cancer cells [8] and prostate cancer cells [24]. However, another study showed the allele C of this polymorphism increased the expression level of mature miR-146a [28]. Thus, the results about the association between miR-146a rs2910164 polymorphism and miR-146a production are different in various cancers. In this meta-analysis, we found a significant association between miR-146a (rs2910164) with prostate cancer, cervical squamous cell carcinoma and hepatocellular carcinoma, but not with overall cancer risk, indicating that rs2910164 polymorphism may play different roles in various types of human cancers.

In addition, the observed different effects for different types of cancers could be likely due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated fluctuated risk estimation. So studies with larger sample size in different types of cancer are necessary to fully understand the relationship between the polymorphism and the susceptibility of cancer.

Although we are in our best effort to perform a comprehensive analysis, but there are still some defects in the meta-analysis. First, although the study's publication bias did not have statistical significance, we used the published English literatures to do the meta-analysis, so certain publication bias will still exist. Second, the lack of original data of available included studies limited us to continue studying some potential interactions, such as age, gender, family history, environmental factors and life style. Third, this study lacks the data of other ethnic populations.

In conclusion, our meta-analysis suggested that rs2910164 polymorphism in miR-146a is likely to affect the susceptibility of cancer; however the effects were diverse in different types of ethnicity. In addition, C allele of rs2910163 in miR-146a is related to the risk of hepatocellular carcinoma, cervical squamous cell carcinoma and prostate cancer. Considering the limited quality of the included case-control studies, future well-designed and larger population studies, especially in other ethnic populations are of great value to confirm these findings. Moreover, combination of genetic factors together with environmental exposures should also be considered.

Conclusion

Rs2910164 in miR-146a might be associated with cancer susceptibility; however, the effects were disagreed in different types of ethnicity and diverse types of cancers.

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Disclosure of conflict of interest

None.

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