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REVIEW

rs11614913 polymorphism in miRNA-196a2 and cancer risk: an updated meta-analysis

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Abstract: Several epidemiological studies have reported that polymorphisms in microRNA-196a2 (miR-196a2) were associated with various cancers. However, the results remained unverified and were inconsistent in different cancers. Therefore, we carried out an updated meta-analysis to elaborate the effects of rs11614913 polymorphism on cancer susceptibility. A total of 84 articles with 35,802 cases and 41,541 controls were included to evaluate the association between the miR-196a2 rs11614913 and cancer risk by pooled odds ratios (ORs) and 95% confidence intervals (CIs). The results showed that miR-196a2 rs11614913 polymorphism is associated with cancer susceptibility, especially in lung cancer (homozygote comparison, OR =0.840, 95% CI =0.734–0.961; recessive model, OR =0.858, 95% CI =0.771–0.955), hepatocellular carcinoma (allelic contrast, OR =0.894, 95% CI =0.800–0.998; homozygote comparison, OR =0.900, 95% CI =0.813–0.997; recessive model, OR =0.800, 95% CI =0.678–0.944), and head and neck cancer (allelic contrast, OR =1.076, 95% CI =1.006–1.152; homozygote comparison, OR =1.214, 95% CI =1.043–1.413). In addition, significant association was found among Asian populations (allele model, OR =0.847, 95% CI =0.899–0.997, P=0.038; homozygote model, OR =0.878, 95% CI =0.788–0.977, P=0.017; recessive model, OR =0.895, 95% CI =0.824–0.972, P=0.008) but not in Caucasians. The updated meta-analysis confirmed the previous results that miR-196a2 rs11614913 polymorphism may serve as a risk factor for patients with cancers.

Keywords: miR-196a2, polymorphisms, cancer risk, meta-analysis

Introduction

The rising morbidity and mortality of cancer has drawn extensive attention worldwide, and finding possible risk factors of tumorigenesis has been a priority task for researchers. Recently, an increasing number of studies have focused on associations between miRNA polymorphisms and cancer susceptibility, which indicated that accumulation of genetic variants may be involved in cancer development, including oral cancer,[1] lung cancer,[2,3] gastric cancer,[4] breast cancer,[5] glioma,[6] non-small cell lung cancer,[7] hepatocellular carcinoma,[8,9] gallbladder cancer,[10] and head and neck cancer (HNC).[11] As the molecular mechanism of cancer remains unclear, further exploration of more accurate cancer treatments and prognosis would be of great importance.

MiRNAs are a class of small non-coding RNAs with 18–25 nucleotides in length, which play as oncogenes or anti-oncogenes in the pathogenesis of tumor by targeting multiple genes.[12–14] Studies have shown that almost 10%–30% of all human gene expressions have been regulated by mature miRNAs.[15] MiRNAs could modulate related genes implicated in cellular processes, including cell differentiation, growth, apoptosis, and immune response.[16–18]

Hsa-microRNA-196a2 (miR-196a2), initially discovered by Lagos-Quintana et al,[19] has been proven to play important roles in various cancers.[20,21] Single nucleotide

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polymorphisms (SNPs) provide new sources of genetic variation, which contribute to potential molecular mechanisms of cancer development.[22] SNPs or mutations in miRNA sequence may transform miRNA expression and/or maturation, related to miRNA function by activating the transcription of the primary transcript, pri-miRNA and pre-miRNA processing, and miRNA–mRNA interactions.[23] MiR-196a2 rs11614913, as a definitional miRNA polymorphism,[24–26] is crucially associated with cancer risk.[23,27] It is located in the 3′-untranslated region of the miR-196a2 precursor.[28] Hoffman et al[5] also showed that miR-196a2 rs11614913 not only influenced the transcription level of mature miR-196a, but also had a biological effect on target gene production. This updated meta-analysis was performed to explore the association between the hsa-miR-196a2 polymorphism and cancer risk and to further estimate the overall cancer risk by pooling all available data.

Materials and methods

Publication search

Two investigators (LYH, HAB) carried out a systematic review on PubMed, Cochrane Library, and Web of Science, by using ("microRNA-196a2" or "miR-196a2", or "miR-196-a-2" or "miR-196-2" or "miR-196-a" or "rs11614913"), and ("cancer" or "tumor" or "carcinoma" or "neoplasm" or "malignancy"), and ("polymorphism" or "variation" or "susceptibility") as the search terms in order to identify potentially eligible studies. We based our dates for literature retrieval from January 2008 to September 2017.

Inclusion and exclusion criteria

Relevant studies had to meet the following inclusion criteria: 1) full-text article; 2) evaluation of a link between miRNA polymorphisms and cancer risks; 3) sufficient data for estimating the odds ratio (OR) with 95% CI and a *P*-value. Studies containing two or more case-control groups were considered as two or more independent studies. Studies that were, 1) review, letters, and comment articles; 2) not for cancer risk; and 3) duplicate samples or publications, were excluded.

Assessment of study quality

The quality of the study was determined by the Newcastle–Ottawa Scale for cohort studies.

Data extraction

Data extraction from the eligible studies were performed independently by two authors (LYH, HAB), based on the inclusion and exclusion criteria. For each publication, the following data were recorded: first author, date of publication, country of origin, ethnicity, type of tumor, source of control groups, total numbers of cases and controls, and genotyping method.

Statistical analysis

The departure of frequencies of miR-196a2 rs11614913 polymorphisms was assessed under the Hardy–Weinberg equilibrium (HWE) for each publication by adopting the goodness-of-fit test (chi-square or Fisher exact test). The association between the miR-196a2 rs11614913 polymorphisms and the risk of cancer was evaluated by calculating pooled OR together with corresponding 95% CI based on the method published by Woolf.[29] Also, a P-value<0.05 was considered statistically significant. In addition, we used stratified meta-regression analyses to explore major causes of heterogeneity among the articles. We respectively examined the association between genetic mutants and cancer risk in allelic contrast (T vs C), homozygote comparisons (TT vs CC), heterozygote comparisons (TC vs CC), recessive model (TT vs TC+CC), and dominant model (TT+TC vs CC). Subgroup analyses were performed by ethnicity (Asian and Caucasian), tumor types (if one tumor type contained less than three individual studies, it was combined into "other cancer" subgroups), and source of control (hospital based and population based).

Q tests[30] and I^2 tests[31] were carried out to test the heterogeneity. I^2 values describe the percentage of total variation across studies that are due to heterogeneity rather than chance. $I^2=0\%$ prompts no heterogeneity observed, with 25% identified as low, 50% as moderate, and 75% as high. If I^2 was $\geq 50\%$ or if the P-value of heterogeneity was <0.05, indicating significant heterogeneity among these articles, a random-effect model was used;[32] otherwise, a fixed-effect mode was used.[33] Sensitivity analyses were conducted to estimate the stability of the meta-analysis result. We adopted Egger's test to assess potential publication bias by visual inspection of the Funnel plot. A P-value <0.05 was regarded as an indication of potential publication bias.[34] All statistical analyses were performed with the Stata software package version 12.0 (Stata Corporation, College Station, TX, USA).

Results

Study identification

Overall, 84 articles,[1–11,26,27,35–100] which were relevant to the search terms, were selected based on the inclusion criteria from PubMed, Cochrane, and Web of Science (Figure 1). These studies with a total of 35,802 cases and 41,541 controls

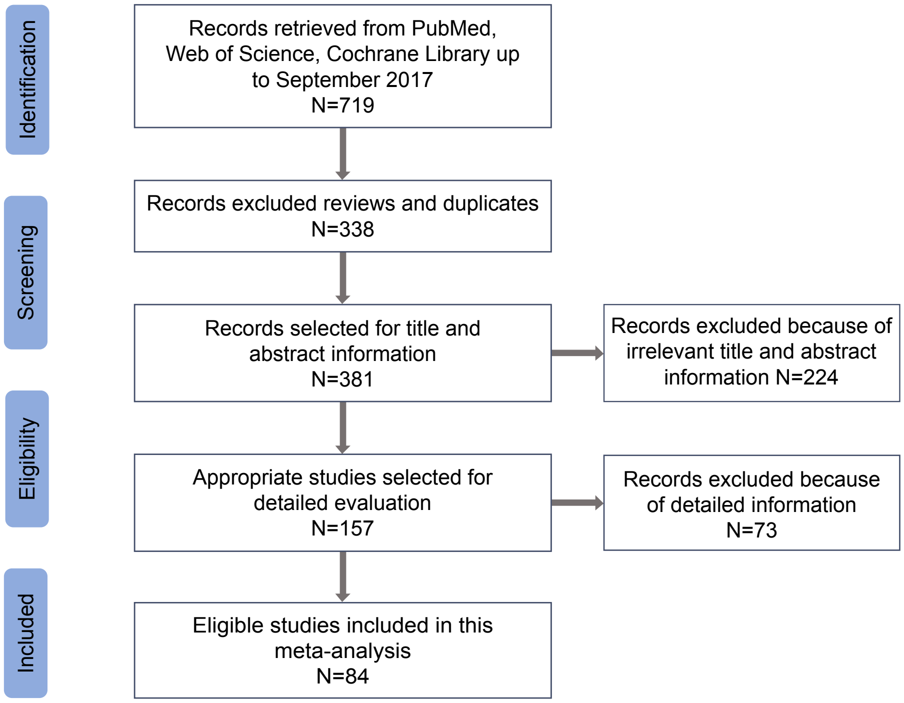

Figure 1 The flow diagram of the included and excluded studies.

were subjected to further checking. In the present meta-analysis, we excluded 73 articles (36 articles were meta-analysis, 22 articles did not express concern about cancer risk, 11 articles lacked detailed allele frequency data or OR calculation, and four articles were incomplete text). The included study characteristics are provided in Table 1.

In total, there were studies on hepatocellular carcinoma (n=14), breast cancer (n=14), colorectal cancer (n=10), gastric cancer (n=10), lung cancer (n=9), esophageal squamous cell carcinoma (ESCC; n=6), HNC (n=5), bladder cancer (n=2), prostate cancer (n=2), oral squamous cell carcinoma (n=2), epithelial ovarian cancer (n=2), renal cell cancer (n=1), glioma (n=1), pancreatic cancer (n=1), cervical cancer (n=1), nasopharyngeal carcinoma (n=1), gallbladder cancer (n=1), acute lymphoblastic leukemia (n=1), and non-Hodgkin lymphoma (n=1). There were 64 studies of Asians and 18 studies of Caucasians.

Among the genotyping methods used in these studies, 57 studies used polymerase chain reaction (including polymerase chain reaction restriction fragment length polymorphism and polymerase chain reaction-ligation detection reaction), 16 studies used Taqman SNP genotyping assay, and others used MassARRAY and DNA sequencing. The controls of 42 studies mainly came from a hospital-based healthy population matched for gender and age, and 42 studies had population-based controls (PB). The distribution of genotypes in the controls of all of the studies was in agreement with HWE ($P>0.05$).

Quantitative synthesis

In this meta-analysis, we analyzed the hsa-miR-196a2 rs11614913 polymorphism in 84 comparisons with 35,802 cases and 41,541 controls. All the studies were pooled into the meta-analysis, and the results showed that the hsa-miR-196a2 rs11614913 polymorphism was significantly associated with the risk of cancer in the following genetic models: TT vs CC: OR =0.900, 95% CI =0.813–0.987, P=0.043; TT vs TC+CC: OR =0.918, 95% CI =0.851–0.989, P=0.025.

Then, we performed the subgroup analysis of different specific cancer types, genotypes, control sources, and ethnicities (Table 2). In the different cancer types, close association between rs11614913 and cancer risk was found for lung cancer (homozygote comparison, OR =0.840, 95% CI =0.734–0.961, P=0.011; recessive model, OR =0.858, 95% CI =0.771–0.955, P=0.005), hepatocellular carcinoma (allelic contrast, OR =0.894, 95% CI =0.800–0.998, P=0.047; homozygote comparison, OR =0.900, 95% CI =0.813–0.997, P=0.039; recessive model, OR =0.800, 95% CI =0.678–0.944, P=0.008), and HNC (allelic contrast, OR =1.076, 95% CI =1.006–1.152, P=0.033; homozygote comparison, OR =1.214, 95% CI =1.043–1.413, P=0.012; Figures 2 and 3). However, the association between rs11614913 and

Table 1 Characteristics of studies included in the meta-analysis

Author	Year	Country	Ethnicity	Cancer type	Genotyping method	Source of control	Case			Control			HWE
							TT	CT	CC	TT	CT	CC	
Hu et al[7]	2008	China	Asian	LC	PCR	PB	152	264	140	32	52	23	0.827
Hu et al[35]	2009	China	Asian	BRC	PCR-RFLP	PB	287	483	239	358	517	218	0.207
Tian et al[3]	2009	China	Asian	LC	PCR-RFLP	PB	293	512	253	307	519	209	0.700
Hoffman et al[5]	2009	USA	Caucasian	BRC	TaqMan	HB	71	229	166	36	209	181	0.583
Catucci et al[36]	2010	Italy	Caucasian	BRC	TaqMan	PB	244	842	776	377	1,246	1,116	0.326
Wang et al[38]	2010	China	Asian	ESCC	PCR	PB	48	262	148	111	250	128	0.600
Okubo et al[83]	2010	Japan	Asian	GC	Gel Pictures	HB	166	281	105	372	592	216	0.466
Peng et al[4]	2010	China	Asian	GC	PCR-RFLP	PB	43	94	76	50	107	56	0.936
Srivastava et al[10]	2010	India	Asian	GLC	PCR-RFLP	PB	121	97	21	121	94	15	0.566
Dou et al[6]	2010	China	Asian	Glioma	PCR-LDR	HB	189	343	111	208	305	143	0.119
Li et al[9]	2010	China	Asian	HCC	PCR-RFLP	HB	82	150	78	78	102	42	0.402
Akkiz et al[8]	2010	Turkey	Caucasian	HCC	PCR-RFLP	HB	22	86	77	40	87	58	0.492
Liu et al[11]	2010	USA	Caucasian	HNC	PCR-RFLP	PB	194	565	350	202	545	383	0.737
Kim et al[110]	2010	Korea	Asian	LC	PCR-RFLP	HB	162	305	187	185	300	155	0.126
Catucci et al[36]	2010	Germany	Caucasian	BRC	MassARRAY	PB	216	696	584	157	512	432	0.711
Christensen et al[37]	2010	USA	Caucasian	HNC	AppliedBiosystems	PB	0	302	182	0	367	188	NA
Mittal et al[41]	2011	India	Asian	BLC	PCR-RFLP	PB	5	131	76	14	127	109	0.003
Jedlinski et al[40]	2011	Australia	Caucasian	BRC	PCR	PB	33	86	68	31	82	58	0.830
Zhan et al[42]	2011	China	Asian	CRC	PCR-RFLP	HB	56	128	68	163	267	113	0.849
Zhou et al[43]	2011	China	Asian	CSCC	PCR-RFLP	PB	57	123	46	82	169	58	0.077
Vinci et al[111]	2011	Italy	Caucasian	LC	TaqMan	PB	12	54	35	10	61	58	0.267
Hong et al[2]	2011	Korea	Asian	LC	TaqMan	HB	96	224	86	134	198	96	0.163
George et al[39]	2011	Italy	Caucasian	PC	PCR-RFLP	PB	3	101	55	10	114	106	0.002
Linhares et al[45]	2012	Brazil	Mix	BRC	TaqMan	HB	117	177	94	96	165	127	0.005
Chen et al[44]	2012	China	Asian	CRC	PCR-LDR	HB	35	64	27	107	206	94	0.788
Min et al[24]	2012	Korea	Asian	CRC	PCR-RFLP	HB	125	201	120	148	254	100	0.633
Zhu et al[47]	2012	China	Asian	CRC	TaqMan	HB	130	303	140	172	295	121	0.790
Hezova et al[25]	2012	Czech	Caucasian	CRC	TaqMan	HB	26	89	82	22	103	87	0.291
Zhang et al[100]	2012	China	Asian	CRC	PCR-RFLP	PB	172	204	79	185	197	81	0.026
Ahn et al[48]	2013	Korea	Asian	GC	PCR-RFLP	PB	119	242	100	128	232	87	0.322
Yoon et al[46]	2012	Korea	Asian	LC	TaqMan	PB	99	186	101	24	32	15	0.480
Zhang et al[104]	2012	China	Asian	BRC	PCR-RFLP	PB	133	93	17	148	89	11	0.893
Chu et al[87]	2012	China	Asian	HNC	PCR-RFLP	HB	136	277	57	132	206	87	0.690
Vinci et al[113]	2013	Italy	Caucasian	CRC	HRMA	HB	12	86	62	11	84	83	0.087
Lv et al[51]	2013	China	Asian	CRC	PCR-RFLP	PB	114	223	10	91	331	109	0.000
Umar et al[112]	2013	India	Asian	ESCC	PCR-RFLP	HB	22	121	146	16	122	171	0.330
Wei et al[114]	2013	China	Asian	ESCC	SNPscanTM	HB	106	196	65	113	170	87	0.141
Toraih et al[98]	2016	Egypt	Caucasian	OSCC	PCR	PB	32	93	84	10	35	55	0.221
Wang et al[53]	2013	China	Asian	GC	TaqMan	HB	226	371	152	232	448	220	0.898
Zhang et al[55]	2013	China	Asian	HCC	MassARRAY	HB	294	488	214	328	502	165	0.245
Han et al[49]	2013	China	Asian	HCC	PCR	PB	305	505	207	304	485	220	0.310
Tong et al[65]	2013	China	Asian	ALL	TaqMan	HB	159	308	103	237	307	129	0.434
Pavlakis et al[93]	2013	Greece	Caucasian	PCC	PCR-RFLP	HB	48	33	12	50	58	14	0.647
Pu et al[84]	2014	China	Asian	GC	PCR-RFLP	HB	25	95	39	86	324	101	0.000
Bansal et al[56]	2014	India	Asian	BRC	PCR-RFLP	PB	12	41	68	21	59	85	0.042
Kupcinskas et al[62]	2014	Lithuania	Caucasian	CRC	PCR	HB	27	87	79	54	174	199	0.104
Qu et al[64]	2014	China	Asian	ESCC	PCR	PB	48	207	126	82	211	133	0.918
Wang et al[66]	2014	China	Asian	ESCC	PCR-LDR	PB	162	307	128	154	298	145	0.970
Dikeakos et al[58]	2014	Greece	Caucasian	GC	PCR-RFLP	HB	15	46	102	172	229	79	0.850
Qi et al[86]	2014	China	Asian	HCC	PCR	HB	60	209	45	121	214	71	0.156
Chu et al[57]	2014	China	Asian	HCC	PCR-RFLP	HB	66	81	41	100	167	70	0.986
Parlayan et al[115]	2014	Japan	Asian	LC	TaqMan	HB	38	81	29	146	270	108	0.410
Li et al[63]	2014	China	Asian	NPC	TaqMan	HB	322	489	209	270	518	218	0.301
Du et al[59,60]	2014	China	Asian	RCC	PCR	HB	121	189	43	109	179	74	0.974
Omrani et al[85]	2014	Iran	Asian	BRC	PCR-RFLP	PB	0	25	78	0	18	218	NA
Kou et al[91]	2014	China	Asian	HCC	PCR	HB	37	150	84	103	304	125	0.001
Roy et al[94]	2014	India	Asian	HNC	AppliedBiosystems	HB	46	187	218	38	168	242	0.250

(*Continued*)

Table 1 (*Continued*)

Author	Year	Country	Ethnicity	Cancer type	Genotyping method	Source of control	Case			Control			HWE
							TT	CT	CC	TT	CT	CC	
Li et al[63]	2014	China	Asian	HNC	AppliedBiosystems	PB	322	489	209	270	518	218	0.300
Deng et al[67]	2015	China	Asian	BLC	PCR-RFLP	PB	52	66	41	76	166	56	0.040
Qi et al[72]	2015	China	Asian	BRC	PCR	PB	168	119	34	185	88	17	0.141
Dikaiakos et al[68]	2015	Greece	Caucasian	CRC	PCR-RFLP	PB	69	69	19	117	149	33	0.156
Li et al[69]	2015	China	Asian	HCC	PCR	HB	51	131	84	30	123	113	0.689
Li et al[69]	2015	China	Asian	NHL	PCR-RFLP	PB	111	146	61	144	134	42	0.225
Nikolic et al[71]	2015	Serbia	Caucasian	PC	PCR-RFLP	PB	40	161	150	41	147	121	0.728
He et al[90]	2015	China	Asian	BRC	MassARRAY	HB	134	223	93	136	233	81	0.990
Sushma et al[97]	2015	India	Asian	OSCC	PCR-RFLP	PB	68	10	22	81	15	6	0.212
Sodhi et al[95]	2015	India	Asian	LC	PCR-RFLP	PB	19	161	70	8	146	101	0.000
Jiang et al[26]	2016	China	Asian	GC	PCR	HB	300	423	166	290	487	198	0.804
Dai et al[74]	2016	China	Asian	BRC	MassARRAY	HB	98	265	197	144	284	155	0.540
Zhao et al[82]	2016	China	Asian	BRC	TaqMan	PB	33	50	31	25	61	28	0.449
Song et al[79]	2016	China	Asian	OC	PCR	PB	111	247	121	142	203	86	0.385
Shen et al[78]	2016	China	Asian	ESCC	SNaPshot	PB	407	698	295	672	1,121	392	0.043
Li et al[75]	2016	China	Asian	GC	PCR	HB	75	83	24	92	79	11	0.265
Li et al[76]	2016	China	Asian	HCC	PCR	HB	20	64	25	35	52	18	0.861
Xu et al[80]	2016	China	Asian	HCC	PCR-RFLP	HB	56	128	68	163	267	113	0.849
Qiu and Liu[77]	2016	China	Asian	HCC	PCR	PB	61	141	68	70	121	46	0.626
Jiang et al[26]	2016	China	Asian	HCC	TaqMan	PB	159	308	103	237	307	129	0.099
Yin et al[81]	2016	China	Asian	LC	TaqMan	PB	149	298	128	178	297	133	0.664
Zhang et al[99]	2016	China	Asian	HCC	PCR-RFLP	HB	65	85	25	122	138	42	0.770
Sun et al[96]	2016	China	Asian	OC	PCR	HB	39	66	29	77	116	34	0.360
Toraih et al[98]	2016	Egypt	Caucasian	HCC	PCR	PB	11	31	23	17	53	80	0.082
Morales et al[92]	2016	Chile	Mix	BRC	TaqMan	HB	57	191	192	114	351	342	0.121
Gu and Tu[88]	2016	China	Asian	GC	PCR	HB	51	96	39	31	98	57	0.310
Hashemi et al[89]	2016	Iran	Asian	GC	PCR-RFLP	PB	17	88	64	12	93	77	0.021

Abbreviations: ALL, acute lymphoblastic leukemia; BLC, bladder cancer; BRC, breast cancer; CRC, colorectal cancer; CSCC, cervical cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; GLC, gallbladder cancer; HB, hospital based; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HRMA, high-resolution melting analysis; HWE, Hardy–Weinberg equilibrium of controls; LC, lung cancer; NHL, non-Hodgkin lymphoma; NPC, nasopharyngeal carcinoma; NA, not available; OC, ovarian cancer; OSCC, oral squamous cell carcinomas; PB, population based; PC, prostate cancer; PCC, pancreatic cancer; PCR, polymerase chain reaction; PCR-LDR, polymerase chain reaction-ligation detection reaction; PCR-RFLP, polymerase chain reaction restriction fragment length polymorphism; RCC, renal cell carcinoma.

breast cancer, ESCC, gastric cancer (GC), or colorectal cancer (CRC) is not statistically significant.

In ethnic subgroup analysis, a strong association was found between rs11614913 and cancer risk in the allelic contrast (T vs C: OR =0.847, 95% CI =0.899–0.997, P=0.038), the homozygote comparison (TT vs CC: OR =0.878, 95% CI =0.788–0.977, P=0.017), and the recessive model (OR =0.895, 95% CI =0.824–0.972, P=0.008) among Asians, whereas negative results were obtained for Caucasians in all genetic models. Additionally, decreased risk was observed in the polymerase chain reaction (PCR) method for the homozygote comparison (TT vs CC: OR =0.849, 95% CI =0.732–0.986, P=0.032) and the recessive model (TT vs TC+CC: OR =0.880, 95% CI =0.800–0.969, P=0.009), and no significant association of cancer risk was found in Taqman and other methods.

Test of heterogeneity

Among the studies of rs11614913, we found heterogeneity in overall comparisons and subgroup analysis. Moreover, the heterogeneity we evaluated for all genetic models by ethnicity, cancer type, source of controls, as well HWE status was significant. However, we found that heterogeneity could not be explained by the variable ethnicity, cancer type, source of controls, and HWE status (data not shown).

Sensitivity analysis

Sensitivity analysis was conducted to assess the effect by excluding a single study in turn. Sensitivity analysis of the rs11614913 polymorphism in an allelic comparison is presented in Table S1. Overall, we found that no individual study had an influence on the pooled OR. The results demonstrated that the pooled ORs were not materially altered, suggesting the stability of our meta-analysis.

Publication bias

The publication bias of the present meta-analysis was assessed by Begg's funnel plot and Egger's test. The funnel plot for the rs11614913 polymorphism in the allelic comparison is presented

Table 2 Meta-analysis of miR-192a rs11614913 polymorphism with cancer risk

rs11614913	n[a]	Case/ control	T vs C				TT vs CC				TC vs CC			
			OR (95% CI)	***P*-value**	**P–H**	**I^2, %**	**OR (95% CI)**	***P*-value**	**P–H**	**I^2, %**	**OR (95% CI)**	***P*-value**	**P–H**	**I^2, %**
(A)														
Total	84	35,802/41,541	0.958 (0.911–1.008)	0.096	0.000	81.30	0.900 (0.813–0.987)	**0.043**	0.000	78.80	1.005 (0.935–1.079)	0.902	0.000	71.60
Genotyping method														
PCR	57	19,301/22,204	0.939 (0.871–1.012)	0.100	0.000	84.50	0.849 (0.732–0.986)	**0.032**	0.000	81.70	0.987 (0.883–1.102)	0.812	0.000	77.40
Taqman	16	8,565/10,286	1.021 (0.940–1.110)	0.618	0.000	67.40	1.059 (0.894–1.253)	0.507	0.000	65.70	1.053 (0.977–1.134)	0.174	0.410	3.70
Ethnicity														
Asian	64	28,337/31,932	0.847 (0.889–0.997)	**0.038**	0.000	77.00	0.878 (0.788–0.977)	**0.017**	0.000	76.00	1.012 (0.936–1.095)	0.759	0.000	66.90
Caucasian	18	7,321/8,414	0.997 (0.842–1.181)	0.971	0.000	90.30	0.974 (0.714–1.329)	0.870	0.000	86.10	0.963 (0.785–1.180)	0.714	0.000	83.90
Cancer type														
BRC	14	7,760/8,811	0.972 (0.869–1.088)	0.626	0.000	79.70	0.972 (0.869–1.088)	0.341	0.000	72.80	0.979 (0.854–1.121)	0.754	0.001	61.50
CRC	10	2,906/4,150	1.051 (0.867–1.276)	0.611	0.000	86.50	1.051 (0.867–1.276)	0.431	0.000	87.60	1.121 (0.832–1.510)	0.454	0.000	81.10
ESCC	6	3,492/4,376	0.944 (0.816–1.091)	0.435	0.001	76.80	0.944 (0.816–1.091)	0.385	0.000	82.40	1.050 (0.878–1.255)	0.594	0.040	57.20
GC	10	3,723/5,256	0.857 (0.663–1.109)	0.241	0.000	93.80	0.857 (0.663–1.109)	0.276	0.000	91.50	0.778 (0.552–1.098)	0.153	0.000	88.70
HCC	14	4,988/5,962	0.894 (0.800–0.998)	**0.047**	0.000	72.60	0.900 (0.813–0.997)	**0.039**	0.000	70.50	0.981 (0.838–1.149)	0.816	0.005	56.30
HNC	5	3,534/3,564	1.076 (1.006–1.152)	**0.033**	0.285	20.40	1.214 (1.043–1.413)	**0.012**	0.380	2.50	1.157 (0.922–1.451)	0.209	0.003	75.00
LC	9	2,786/3,191	0.95 (0.854–1.058)	0.354	0.022	55.30	0.840 (0.734–0.961)	**0.011**	0.025	48.10	0.997 (0.889–1.118)	0.961	0.056	47.20
Design														
PB	42	20,691/21,533	0.968 (0.907–1.033)	0.324	0.000	77.20	0.899 (0.777–1.017)	0.087	0.000	74.70	1.018 (0.928–1.117)	0.703	0.000	66.60
HB	42	15,111/20,008	0.945 (0.873–1.024)	0.167	0.000	84.50	0.906 (0.813–0.997)	0.211	0.000	81.90	0.987 (0.882–1.104)	0.822	0.000	75.90

rs11614913	n[a]	TT vs TC+CC				TT+TC vs CC			
		OR (95% CI)	***P*-value**	**P–H**	**I^2, %**	**OR (95% CI)**	***P*-value**	**P–H**	**I^2, %**
(B)									
Total	84	0.918 (0.851–0.989)	**0.025**	0.000	75.80	0.974 (0.901–1.052)	0.498	0.000	78.40
Genotyping method									
PCR	57	0.880 (0.800–0.9690)	**0.009**	0.000	73.20	0.949 (0.842–1.069)	0.386	0.000	82.80
Taqman	16	1.000 (0.858–1.166)	0.996	0.000	71.90	1.063 (0.969–1.165)	0.195	0.095	34.10
Ethnicity									
Asian	64	0.895 (0.824–0.972)	**0.008**	0.000	76.50	0.972 (0.8396–1.005)	0.493	0.000	72.90
Caucasian	17	1.015 (0.820–1.256)	0.894	0.000	75.30	0.966 (0.766–1.219)	0.772	0.000	89.30
Cancer type									
BRC	14	0.943 (0.815–1.091)	0.429	0.001	64.40	0.967 (0.830–1.126)	0.663	0.000	73.30
CRC	10	1.066 (0.823–1.381)	0.628	0.000	79.00	1.130 (0.826–1.546)	0.444	0.000	84.70
ESCC	6	0.813 (0.610–1.085)	0.160	0.000	81.30	1.000 (0.822–1.216)	0.997	0.008	67.80
GC	10	0.910 (0.697–1.189)	0.489	0.000	83.90	0.763 (0.507–1.148)	0.194	0.000	92.90
HCC	14	0.800 (0.678–0.944)	**0.008**	0.000	67.40	0.919 (0.776–1.089)	0.332	0.000	66.20
HNC	5	1.205 (0.799–1.817)	0.375	0.000	90.10	1.156 (0.950–1.406)	0.148	0.011	69.10
LC	9	0.858 (0.771–0.955)	**0.005**	0.158	32.50	0.997 (0.834–1.191)	0.973	0.019	56.20
Design									
PB	42	0.924 (0.826–1.034)	0.170	0.000	78.10	0.988 (0.897–1.087)	0.800	0.000	72.40
HB	42	0.912 (0.823–1.010)	0.078	0.000	73.90	0.955 (0.843–1.081)	0.465	0.000	82.70

Notes: Random-effects model was used when *P*-value of *Q*-test for heterogeneity test (P–H) is <0.05; otherwise, fixed-effect model was used. I^2: 0%–25%, no heterogeneity; 25%–50%, modest heterogeneity; ≥50%, high heterogeneity. [a]Number of studies involved. Bold figures indicate statistically significant ($P<0.05$).

Abbreviations: BRC, breast cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HB, hospital based; HCC, hepatocellular carcinoma; HNC, head and neck cancer; LC, lung cancer; OR, odds ratio; PB, population based; PCR, polymerase chain reaction; P–H, *P*-value of heterogeneity test.

in Table S2. No evidence of publication bias was noted in Begg's funnel plot (T vs C [*P*-value for Begg's test =0.660], TT vs CC [*P*-value for Begg's test =0.971, Figure 4], TC vs CC [*P*-value for Begg's test =0.951], TT vs TC+CC [*P*-value for Begg's test =0.908, Figure 4], TC+TT vs CC [*P*-value for Begg's test =0.592]) and Egger's test (allele contrast [*P*=0.923], homozygous model [*P*=0.822], heterozygous model [*P*=0.761], recessive model [*P*=0.899], and dominant model [*P*=0.401]). The quality of included studies is presented in Table 3.

Discussion

MiRNAs are reported as critical posttranscriptional regulators in gene expression and are involved in various diseases. The associations between miR-196a2 rs11614913 polymorphism and susceptibility to different cancers are widely explored. Guo et al[101] found that the C allele had the effect of increasing cancer risk in gastric cancer, and Ma et al[102] found that TT could decrease the risk of colorectal cancer. Moreover, Wang et al[103] and Zhang et al[104] showed that the rs11614913 polymorphism has no association with the risk of hepatocellular carcinoma. However, the regulatory effects of miRNA in carcinogenesis remain unclear. Therefore, we performed this updated meta-analysis to explore the molecular mechanisms of the genetic associations between miRNA and SNPs with cancer risk.

MiR-196a2 is composed of two distinct mature miRNAs (miR-196a-3P and miR-196a-5P), which are processed from the same stem loop;[105] thus, the potential targets of miR-196a could be influenced by its altered expression patterns. SNPs in miRNAs could potentially affect the processing or target selection of miRNAs,[106,107] which is identified as a key factor in oncogenesis, and contributes to regulate the translation or degradation of messenger RNA (mRNA).[23] Hoffman et al[5] found that the expression of mature miR-196a2 was increased 9.3-fold in cells transfected with pre-miR-196a2-C but upregulated only by 4.4-fold with pre-miR-196a2-T, and that the C allele of rs11614913 increased mature miR-196a2 levels in lung cancer[7] and CRC[42] tissues. Xu et al[108] have shown that miR-196a2 rs11614913 CC is associated with significantly increased expression of mature miR-196a

Table 3 Methodological quality of the included studies according to the Newcastle–Ottawa scale

Author	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases/ controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate
Hu et al[7]	*	*	*	*	**	*	*	NA
Hu et al[35]	*	*	NA	*	**	*	*	NA
Tian et al[3]	*	*	NA	*	*	*	*	NA
Hoffman et al[5]	*	*	*	*	*	*	*	NA
Catucci et al[36]	*	*	NA	*	**	NA	*	NA
Wang et al[38]	*	*	NA	*	**	*	*	NA
Okubo et al[83]	*	*	*	*	**	*	*	NA
Peng et al[4]	*	*	NA	*	**	NA	*	NA
Srivastava et al[10]	*	*	NA	*	**	*	*	NA
Dou et al[6]	*	*	NA	NA	*	NA	*	NA
Li et al[9]	*	*	*	*	**	NA	*	NA
Akkiz et al[8]	*	*	NA	*	**	NA	*	NA
Liu et al[11]	*	*	NA	*	*	*	*	NA
Kim et al[110]	*	*	NA	NA	*	*	*	NA
Catucci et al[36]	*	*	*	*	**	*	*	NA
Christensen et al[37]	*	*	NA	*	**	*	*	NA
Mittal et al[41]	*	*	NA	*	**	*	*	NA
Jedlinski et al[40]	*	*	*	*	**	NA	*	NA
Zhan et al[42]	*	*	NA	*	*	NA	*	NA
Zhou et al[43]	*	*	NA	*	**	NA	*	NA
Vinci et al[111]	*	*	NA	*	**	*	*	NA
Hong et al[2]	*	*	NA	*	*	*	*	NA
George et al[39]	*	*	NA	*	**	*	*	NA
Linhares et al[45]	*	*	NA	*	**	*	*	NA
Chen et al[44]	*	*	NA	*	**	NA	*	NA
Min et al[24]	*	*	NA	*	**	*	*	NA
Zhu et al[47]	*	*	NA	*	**	*	*	NA
Hezova et al[25]	*	*	NA	*	**	NA	*	NA

(*Continued*)

Table 3 (*Continued*)

Author	Adequacy of case definition	Representativeness of the cases	Selection of controls	Definition of controls	Comparability of cases/ controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate
Zhang et al[100]	*	*	*	*	**	*	*	NA
Ahn et al[48]	*	*	NA	*	**	*	*	NA
Yoon et al[46]	*	*	NA	*	**	*	*	NA
Zhang et al[104]	*	*	*	*	**	NA	*	NA
Chu et al[87]	*	*	NA	*	**	NA	*	NA
Vinci et al[113]	*	*	*	*	**	NA	*	NA
Lv et al[51]	*	*	*	*	**	NA	*	NA
Umar et al[112]	*	*	NA	NA	**	*	*	NA
Wei et al[114]	*	*	NA	*	**	*	*	NA
Toraih et al[98]	*	*	NA	*	**	*	*	NA
Wang et al[53]	*	*	NA	*	**	NA	*	NA
Zhang et al[55]	*	*	NA	NA	**	NA	*	NA
Han et al[49]	*	*	*	*	**	*	*	NA
Tong et al[65]	*	*	NA	*	**	*	*	NA
Pavlakis et al[93]	*	*	NA	*	**	*	*	NA
Pu et al[84]	*	*	*	*	**	NA	*	NA
Bansal et al[56]	*	*	NA	*	**	*	*	NA
Kupcinskas et al[62]	*	*	*	*	**	*	*	NA
Qu et al[64]	*	*	NA	NA	**	*	*	NA
Wang et al[66]	*	*	NA	*	**	*	*	NA
Dikeakos et al[58]	*	*	NA	*	**	*	*	NA
Qi et al[86]	*	*	NA	*	**	NA	*	NA
Chu et al[57]	*	*	*	*	*	*	*	NA
Parlayan et al[115]	*	*	*	*	**	*	*	NA
Li et al[63]	*	*	NA	*	**	*	*	NA
Du et al[59,60]	*	*	NA	*	*	NA	*	NA
Omrani et al[85]	*	*	NA	*	**	*	*	NA
Kou et al[91]	*	*	*	*	**	*	*	NA
Roy et al[94]	*	*	NA	*	**	*	*	NA
Li et al[63]	*	*	NA	*	**	NA	*	NA
Deng et al[67]	*	*	*	*	**	NA	*	NA
Qi et al[72]	*	*	NA	*	**	NA	*	NA
Dikaiakos et al[68]	*	*	*	*	*	*	*	NA
Li et al[69]	*	*	NA	NA	**	*	*	NA
Li et al[69]	*	*	NA	NA	**	*	*	NA
Nikolic et al[71]	*	*	*	*	**	*	*	NA
He et al[90]	*	*	NA	NA	**	NA	*	NA
Sushma et al[97]	*	*	NA	*	**	*	*	NA
Sodhi et al[95]	*	*	*	*	**	*	*	NA
Jiang et al[26]	*	*	NA	*	**	*	*	NA
Dai et al[74]	*	*	NA	*	**	NA	*	NA
Zhao et al[82]	*	*	NA	*	**	*	*	NA
Song et al[79]	*	*	*	*	*	NA	*	NA
Shen et al[78]	*	*	NA	*	**	*	*	NA
Li et al[75]	*	*	NA	*	**	NA	*	NA
Li et al[76]	*	*	NA	*	*	*	*	NA
Xu et al[80]	*	*	NA	NA	*	*	*	NA
Qiu and Liu[77]	*	*	*	*	*	*	*	NA
Jiang et al[26]	*	*	*	*	**	*	*	NA
Yin et al[81]	*	*	NA	*	*	*	*	NA
Zhang et al[99]	*	*	*	*	**	NA	*	NA
Sun et al[96]	*	*	*	*	*	*	*	NA
Toraih et al[98]	*	*	NA	*	**	NA	*	NA
Morales et al[92]	*	*	NA	*	**	*	*	NA
Gu and Tu[88]	*	*	NA	*	*	*	*	NA
Hashemi et al[89]	*	*	NA	*	**	*	*	NA

Notes: This table identified "high"quality choices with a "*". A study can be awarded a maximum of one "*" for each numbered item within the selection and exposure categories. A maximum of two "**" can be given for comparability.

Abbreviation: NA, not available.

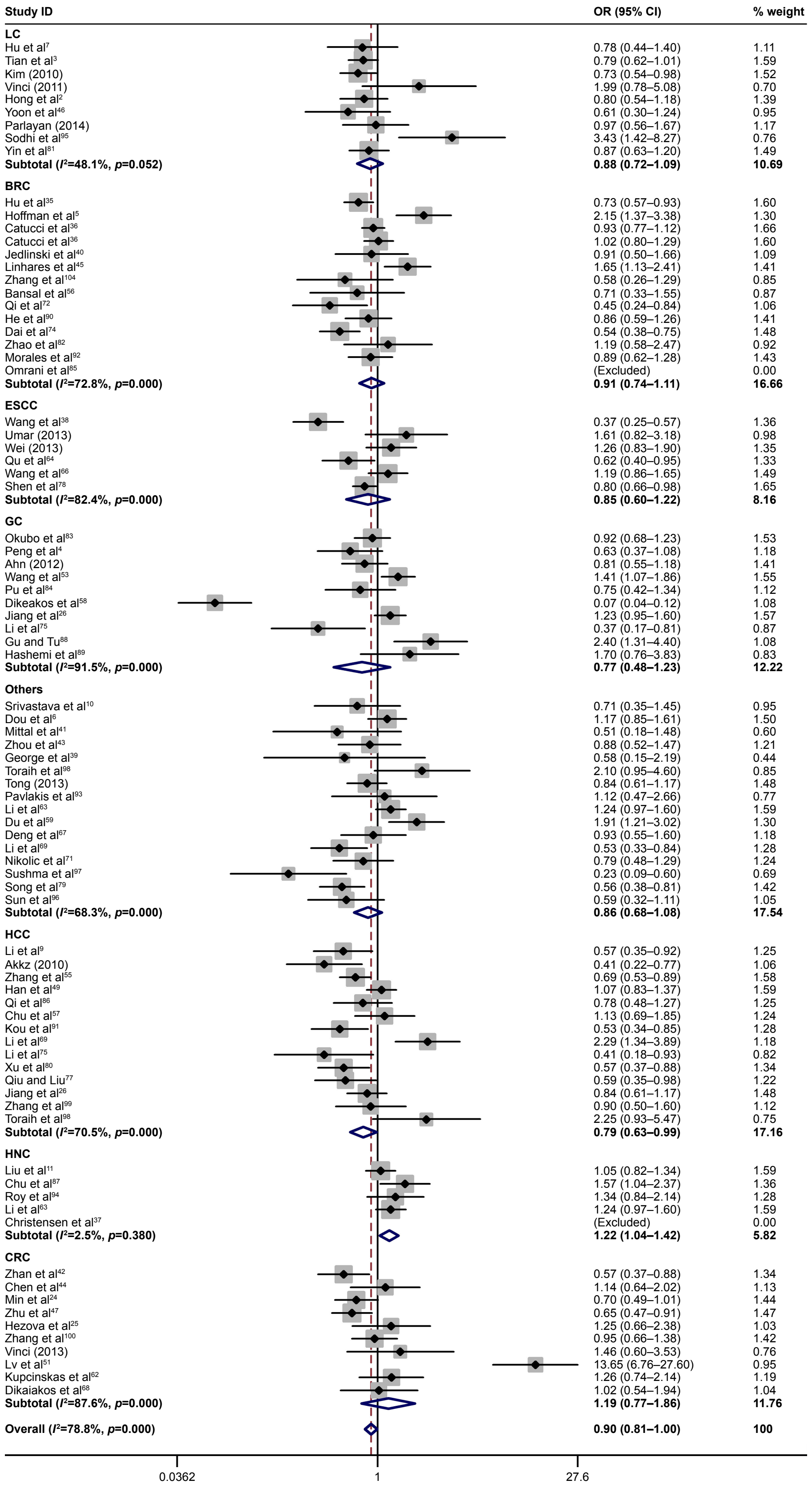

Figure 2 Forest plots of the association between miR-196a2 rs11614913 polymorphism and cancer risk in different cancer types for homozygote comparison (TT vs CC).

Note: Weights are from random effects analysis.

Abbreviations: BRC, breast cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HNC, head and neck cancer; LC, lung cancer; miR-196a2, microRNA-196a2; OR, odds ratio.

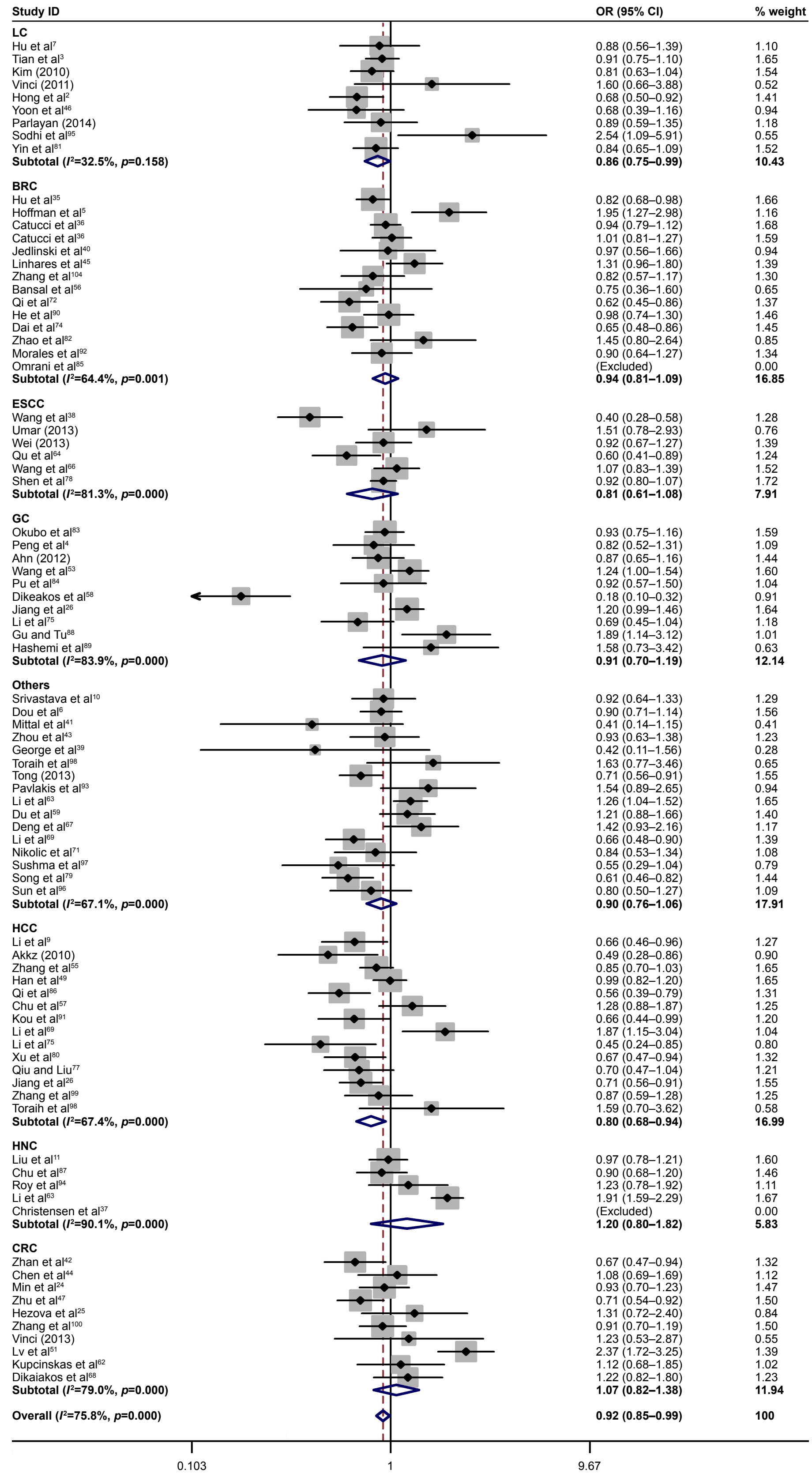

Figure 3 Forest plots of the association between miR-196a2 rs11614913 polymorphism and cancer risk in different cancer types for recessive model (TT vs TC+CC).

Note: Weights are from random effects analysis.

Abbreviations: BRC, breast cancer; CRC, colorectal cancer; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; HCC, hepatocellular carcinoma; HNC, head and neck cancer; LC, lung cancer; miR-196a2, microRNA-196a2; OR, odds ratio.

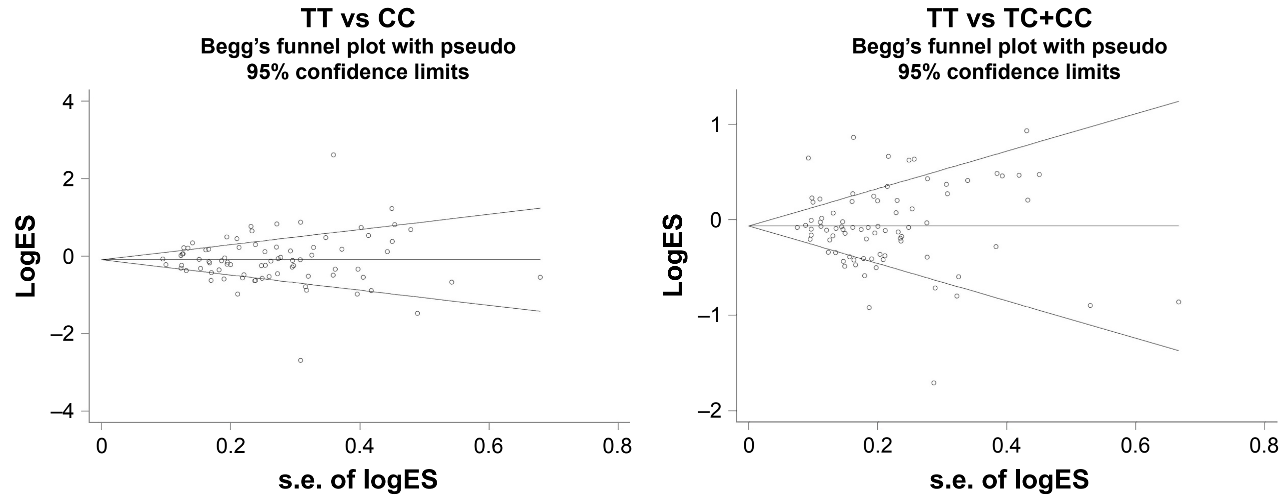

Figure 4 Begg's funnel plot for publication bias of miR-196a2 rs11614913 polymorphism and cancer risk by homozygote comparison and recessive model.
Notes: Each point represents a separate study for the indicated association. LogES represents natural logarithm of OR. Horizontal line means magnitude of the effect. Funnel plot with pseudo 95% confidence limits was used.
Abbreviations: miR-196a2, microRNA-196a2; OR, odds ratio.

(lower cycle threshold corresponding to a higher expression) in cardiac tissue specimens of congenital heart disease, and the increased miR-196a expression could further decrease mRNA target of HOXB8. These results indicated that the rs11614913 polymorphism may affect the processing of the pre-miRNA to its mature form.

Several meta-analyses have been performed to analyse the SNP of this miRNA that is associated with the cancer risk.[104,109] In our present work, we screened out all the studies published to date and included more papers and cancer types than the previously published meta-analyses. For example, Kang et al[109] conducted a meta-analysis encompassing the rs11614913 polymorphism in miR-196a2 and cancer risks, which suggested that the rs11614913 polymorphism may contribute to decreased susceptibility to liver cancer (allele model, homozygous model, dominant model, and heterozygous model) and lung cancer (allele model, homozygous model, and recessive model); however, this was not duplicated in our meta-analysis. In this study, we concluded that the rs11614913 polymorphism conferred a decreased susceptibility to lung cancer (homozygote comparison, recessive model) and hepatocellular carcinoma (allelic contrast, homozygote comparison, recessive model) or an increased susceptibility to HNC (allelic contrast, homozygote comparison). Our study had a larger sample size than the previous ones, which might influence the results. In addition, the previous meta-analyses did not evaluate the quality of the included studies.

According to the procedure of seeking for the source of heterogeneity, we performed subgroup studies according to cancer type, ethnicity, and source of control. A strong association was found between rs11614913 and cancer risk in lung cancers, hepatocellular carcinoma, and HNC, but not in breast cancer, gastric cancer, ESCC, or CRC, which was not similar to the findings of previous studies.[101–103,109] The present meta-analysis showed that homozygote TT had the effect of decreasing the risk of lung cancer or hepatocellular carcinoma compared with that of CC homozygote or C allele carriers. We conducted another subgroup analysis by population to determine the association between these miRNA polymorphisms and tumorigenesis. The results suggested that individuals with alterative T allele could decrease cancer susceptibility in Asians but not in Caucasians, indicating that the difference of ethnic background and the living environment may also be a risk factor.

To determine the hsa-miR-196a2 rs11614913 polymorphism, PCR, Taqman, and other methods have been adopted. We found that the hsa-miR-196a2 rs11614913 polymorphism significantly decreased cancer risk in homozygous models and the recessive model when using the PCR method, but this result was not shown when selecting Taqman and other methods. Therefore, more effort may be necessary for further progress in SNP analysis. We found sources of heterogeneity in the studies from cancer type and ethnicity suggesting cancer and population playing important roles. When detecting the source of control, we observed significant associations in population-based and hospital-based controls. This may be due to the included studies matching age, gender, and residential area to control selection bias.

Nevertheless, several defects of this meta-analysis should be emphasized. Firstly, although we strictly screened articles and precisely extracted the data, the differences in the selection of subjects could not be eliminated. Secondly, in our meta-analysis, only Asian and Caucasian ethnicities were included, and the impact of the differences in racial descent should not be ignored. Thirdly, potential language bias could not be avoided due to limitation of studies published in English or Chinese. Therefore, it is not possible to avoid potential publication bias in this meta-analysis.

In summary, miR-196a2 rs11614913 polymorphism may contribute to the development of cancer, especially in lung cancer, hepatocellular carcinoma, and HNC. It might be useful as a candidate marker for the diagnosis of these cancers, and could also be a potential protective factor for cancer risks in Asians. Furthermore, more significant studies and investigations with larger populations focusing on cancer types or ethnicities should be performed to confirm the results.

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Disclosure

The authors report no conflicts of interest in this work.

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Supplementary materials

Table S1 Details of the sensitivity analyses of the association between rs11614913 polymorphism and cancer risk for homozygous model (TT vs CC) and recessive model (TT vs TC+CC).

Comparison	Study omitted	Estimate	(95% Conf Interval)	
			Lower CI	Upper CI
TT vs CC	Hu et al[7]	0.902	0.814	0.999
	Hu et al[35]	0.904	0.815	1.002
	Tian et al[3]	0.902	0.814	1.001
	Hoffman et al[5]	0.890	0.805	0.985
	Catucci et al[36]	0.900	0.811	1.000
	Wang et al[38]	0.911	0.824	1.008
	Okubo et al[83]	0.900	0.812	0.998
	Peng et al[4]	0.904	0.816	1.002
	Srivastava et al[10]	0.903	0.815	1.000
	Dou et al[6]	0.897	0.809	0.994
	Li et al[9]	0.906	0.818	1.003
	Akkiz et al[8]	0.908	0.820	1.005
	Liu et al[11]	0.898	0.810	0.997
	Kim et al[101]	0.904	0.815	1.002
	Catucci et al[36]	0.899	0.810	0.997
	Christensen et al[37]	0.900	0.813	0.997
	Mittal et al[41]	0.904	0.816	1.001
	Jedlinski et al[40]	0.900	0.813	0.998
	Zhan et al[42]	0.906	0.818	1.004
	Zhou et al[43]	0.901	0.813	0.998
	Vinci et al[102]	0.895	0.809	0.992
	Hong et al[2]	0.902	0.814	1.000
	George et al[39]	0.902	0.815	0.999
	Linhares et al[45]	0.893	0.806	0.988
	Chen et al[44]	0.898	0.811	0.995
	Min et al[24]	0.904	0.815	1.002
	Zhu et al[47]	0.905	0.816	1.003
	Hezova et al[25]	0.897	0.810	0.994
	Zhang et al[100]	0.900	0.812	0.998
	Yoon et al[46]	0.904	0.816	1.001
	Zhang et al[99]	0.904	0.816	1.001
	Chu et al[87]	0.894	0.807	0.990
	Vinci et al[105]	0.897	0.810	0.994
	Ahn et al[103]	0.902	0.814	1.000
	Lv et al[51]	0.878	0.798	0.965
	Umar et al[104]	0.895	0.808	0.992
	Wei et al[106]	0.896	0.809	0.993
	Wang et al[53]	0.894	0.807	0.990
	Zhang et al[55]	0.904	0.816	1.003
	Han et al[49]	0.898	0.810	0.996
	Pavlakis et al[93]	0.899	0.812	0.996
	Tong et al[65]	0.901	0.813	1.000
	Pu et al[84]	0.902	0.814	1.000
	Bansal et al[56]	0.902	0.815	1.000
	Kupcinskas et al[62]	0.897	0.809	0.994
	Qu et al[64]	0.905	0.817	1.003
	Wang et al[66]	0.897	0.809	0.994
	Dikeakos et al[58]	0.925	0.843	1.015
	Qi et al[86]	0.902	0.814	1.000
	Chu et al[57]	0.898	0.810	0.995
	Parlayan et al[107]	0.900	0.812	0.997
	Li et al[63]	0.896	0.808	0.993
	Du et al[59]	0.892	0.806	0.987
	Omrani et al[85]	0.900	0.813	0.997
	Kou et al[91]	0.907	0.819	1.004
	Roy et al[94]	0.896	0.809	0.993
	Li et al[63]	0.896	0.808	0.993
	Deng et al[67]	0.900	0.812	0.997
	Qi et al[72]	0.907	0.819	1.005
	Dikaiakos et al[68]	0.899	0.812	0.996
	Li et al[69]	0.890	0.805	0.985
	Li et al[69]	0.907	0.819	1.004
	Nikolic et al[71]	0.902	0.814	1.000
	He et al[90]	0.901	0.813	0.999
	Sushma et al[97]	0.909	0.821	1.006
	Sodhi et al[95]	0.891	0.806	0.986
	Jiang et al[26]	0.896	0.808	0.993
	Toraih et al[98]	0.894	0.807	0.990
	Dai et al[74]	0.908	0.820	1.005
	Zhao et al[82]	0.898	0.811	0.995
	Song et al[79]	0.907	0.819	1.004
	Shen et al[78]	0.902	0.813	1.002
	Li et al[75]	0.907	0.820	1.005
	Li et al[76]	0.906	0.819	1.004
	Xu et al[80]	0.906	0.818	1.004
	Qiu et al[77]	0.905	0.817	1.003
	Jiang et al[26]	0.901	0.813	1.000
	Yin et al[81]	0.901	0.813	0.999
	Zhang et al[99]	0.901	0.813	0.998
	Sun et al[96]	0.904	0.817	1.002
	Toraih et al[98]	0.894	0.808	0.990
	Morales et al[92]	0.901	0.812	0.999
	Gu et al[88]	0.891	0.805	0.986
	Hashemi et al[89]	0.896	0.809	0.992
	Combined[2–10,25,26,35–107]	0.900	0.813	0.997
TT vs TC+CC	Hu et al[7]	0.918	0.851	0.991
	Hu et al[35]	0.920	0.852	0.993
	Tian et al[3]	0.918	0.850	0.991
	Hoffman et al[5]	0.910	0.844	0.980
	Catucci et al[36]	0.917	0.849	0.991
	Wang et al[38]	0.928	0.862	0.999
	Okubo et al[83]	0.917	0.850	0.991
	Peng et al[4]	0.919	0.852	0.991
	Srivastava et al[10]	0.918	0.850	0.990
	Dou et al[6]	0.918	0.850	0.991
	Li et al[9]	0.922	0.854	0.994
	Akkiz et al[8]	0.923	0.856	0.995
	Liu et al[11]	0.917	0.849	0.990
	Kim et al[101]	0.920	0.852	0.992
	Catucci et al[36]	0.916	0.849	0.989
	Christensen et al[37]	0.918	0.851	0.989
	Mittal et al[41]	0.921	0.854	0.993
	Jedlinski et al[40]	0.917	0.850	0.989
	Zhan et al[42]	0.922	0.854	0.994
	Zhou et al[43]	0.918	0.850	0.990
	Vinci et al[102]	0.915	0.849	0.987
	Hong et al[2]	0.922	0.854	0.994
	George et al[39]	0.920	0.853	0.992

(*Continued*)

Table S1 *(Continued)*

Comparison	Study omitted	Estimate	(95% Conf Interval)	
			Lower CI	Upper CI
	Linhares et al[45]	0.913	0.847	0.985
	Chen et al[44]	0.916	0.849	0.988
	Min et al[24]	0.918	0.850	0.990
	Zhu et al[47]	0.921	0.854	0.994
	Hezova et al[25]	0.915	0.848	0.987
	Zhang et al[100]	0.918	0.850	0.991
	Yoon et al[46]	0.920	0.853	0.993
	Zhang et al[99]	0.919	0.852	0.992
	Chu et al[87]	0.918	0.851	0.991
	Vinci et al[105]	0.919	0.851	0.991
	Ahn et al[103]	0.916	0.850	0.988
	Lv et al[51]	0.905	0.842	0.974
	Umar et al[104]	0.914	0.848	0.986
	Wei et al[106]	0.918	0.850	0.990
	Wang et al[53]	0.913	0.846	0.985
	Zhang et al[55]	0.919	0.851	0.992
	Han et al[49]	0.917	0.849	0.990
	Pavlakis et al[93]	0.921	0.854	0.994
	Tong et al[65]	0.913	0.847	0.985
	Pu et al[84]	0.918	0.851	0.990
	Bansal et al[56]	0.919	0.852	0.991
	Kupcinskas et al[62]	0.916	0.849	0.988
	Qu et al[64]	0.923	0.855	0.995
	Wang et al[66]	0.916	0.848	0.988
	Dikeakos et al[58]	0.931	0.866	1.001
	Qi et al[86]	0.924	0.857	0.996
	Chu et al[57]	0.914	0.847	0.986
	Parlayan et al[107]	0.918	0.851	0.990
	Li et al[63]	0.913	0.846	0.985
	Du et al[59]	0.914	0.847	0.986
	Omrani et al[85]	0.918	0.851	0.989
	Kou et al[91]	0.921	0.854	0.994
	Roy et al[94]	0.915	0.848	0.987
	Li et al[63]	0.906	0.845	0.971
	Deng et al[67]	0.913	0.847	0.985
	Qi et al[72]	0.923	0.856	0.995
	Dikaiakos et al[68]	0.914	0.848	0.987
	Li et al[69]	0.911	0.845	0.982
	Li et al[69]	0.922	0.855	0.995
	Nikolic et al[71]	0.919	0.852	0.991
	He et al[90]	0.917	0.850	0.990
	Sushma et al[97]	0.921	0.855	0.994
	Sodhi et al[95]	0.913	0.847	0.984
	Jiang et al[26]	0.914	0.847	0.986
	Toraih et al[98]	0.914	0.848	0.986
	Dai et al[74]	0.922	0.855	0.995
	Zhao et al[82]	0.914	0.848	0.986
	Song et al[79]	0.923	0.856	0.995
	Shen et al[78]	0.918	0.849	0.992
	Li et al[75]	0.921	0.854	0.993
	Li et al[76]	0.923	0.856	0.995
	Xu et al[80]	0.922	0.854	0.994
	Qiu et al[77]	0.921	0.854	0.993
	Jiang et al[26]	0.921	0.854	0.994
	Yin et al[81]	0.919	0.851	0.992
	Zhang et al[99]	0.918	0.851	0.991
	Sun et al[96]	0.919	0.852	0.992
	Toraih et al[98]	0.915	0.848	0.986
	Morales et al[92]	0.918	0.851	0.991
	Gu et al[88]	0.911	0.845	0.982
	Hashemi et al[89]	0.915	0.848	0.986
	Combined[2–10,25,26,35–107]	0.918	0.851	0.989

Table S2 *P*-values of Begg's and Egger's test for the polymorphism rs11614913

Polymorphism	Comparison	Subgroup	Begg's test ($P>z$)	Egger's test ($P>t$)
rs11614913	T vs C	Overall	0.660	0.923
		Taqman	0.368	0.723
		PCR	0.640	0.859
		Asian	0.946	0.854
		Caucasian	0.147	0.969
		HB	0.509	0.386
		PB	0.251	0.579
	TT vs CC	Overall	0.971	0.822
		Taqman	0.719	0.606
		PCR	0.832	0.762
		Asian	0.578	0.758
		Caucasian	0.163	0.971
		HB	0.721	0.489
		PB	0.666	0.880
	TC vs CC	Overall	0.951	0.761
		Taqman	0.418	0.289
		PCR	0.839	0.933
		Asian	0.991	0.546
		Caucasian	0.902	0.767
		HB	0.721	0.601
		PB	0.965	0.453
	TT+TC vs CC	Overall	0.592	0.401
		Taqman	0.418	0.613
		PCR	0.734	0.598
		Asian	0.986	0.185
		Caucasian	0.300	0.770
		HB	0.737	0.543
		PB	0.584	0.593
	TT vs TC+CC	Overall	0.908	0.899
		Taqman	0.719	0.440
		PCR	0.912	0.917
		Asian	0.795	0.688
		Caucasian	0.537	0.857
		HB	0.673	0.503
		PB	0.914	0.508

Abbreviations: HB, hospital based; PB, population based; PCR, polymerase chain reaction.

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