#### REVIEW

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# 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,<sup>1</sup> lung cancer,<sup>2,3</sup> gastric cancer,<sup>4</sup> breast cancer,<sup>5</sup> glioma,<sup>6</sup> non-small cell lung cancer,<sup>7</sup> hepatocellular carcinoma,<sup>8,9</sup> gallbladder cancer,<sup>10</sup> and head and neck cancer (HNC).<sup>11</sup> 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.<sup>12–14</sup> Studies have shown that almost 10%–30% of all human gene expressions have been regulated by mature miRNAs.<sup>15</sup> MiRNAs could modulate related genes implicated in cellular processes, including cell differentiation, growth, apoptosis, and immune response.<sup>16–18</sup>

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

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polymorphisms (SNPs) provide new sources of genetic variation, which contribute to potential molecular mechanisms of cancer development.<sup>22</sup> 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,<sup>24-26</sup> is crucially associated with cancer risk.<sup>23,27</sup> It is located in the 3'-untranslated region of the miR-196a2 precursor.<sup>28</sup> Hoffman et al<sup>5</sup> 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.<sup>29</sup> Also, a P-value<0.05 was considered statistically significant. In addition, we used stratified metaregression 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<sup>30</sup> and *P* tests<sup>31</sup> were carried out to test the heterogeneity. *P* values describe the percentage of total variation across studies that are due to heterogeneity rather than chance. *P*=0% prompts no heterogeneity observed, with 25% identified as low, 50% as moderate, and 75% as high. If *P* was  $\geq$ 50% or if the *P*-value of heterogeneity was <0.05, indicating significant heterogeneity among these articles, a randomeffect model was used;<sup>32</sup> otherwise, a fixed-effect mode was used.<sup>33</sup> 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.<sup>34</sup> 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,<sup>1–11,26,27,35–100</sup> 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 I The flow diagram of the included and excluded studies.

were subjected to further checking. In the present metaanalysis, we excluded 73 articles (36 articles were metaanalysis, 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), 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 =0.800, 95% CI =0.678–0.944, *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 I Characteristics of studies included in the meta-analys	sis
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Author	Year	Country	Ethnicity	Cancer	Genotyping	Source of	Case	e		Con	trol		HWE
				type	method	control	тт	СТ	сс	тт	СТ	сс	
Hu et al <sup>7</sup>	2008	China	Asian	LC	PCR	РВ	152	264	140	32	52	23	0.827
Hu et al <sup>35</sup>	2009	China	Asian	BRC	PCR-RFLP	PB	287	483	239	358	517	218	0.207
Tian et al³	2009	China	Asian	LC	PCR-RFLP	PB	293	512	253	307	519	209	0.700
Hoffman et al⁵	2009	USA	Caucasian	BRC	TagMan	НВ	71	229	166	36	209	181	0.583
Catucci et al <sup>36</sup>	2010	Italy	Caucasian	BRC	TagMan	РВ	244	842	776	377	1,246	1,116	0.326
Wang et al <sup>38</sup>	2010	China	Asian	ESCC	PCR	PB	48	262	148	111	250	128	0.600
Okubo et al <sup>83</sup>	2010	Japan	Asian	GC	Gel Pictures	НВ	166	281	105	372	592	216	0.466
Peng et al⁴	2010	China	Asian	GC	PCR-RFLP	PB	43	94	76	50	107	56	0.936
Srivastava et al <sup>10</sup>	2010	India	Asian	GLC	PCR-RFLP	РВ	121	97	21	121	94	15	0.566
Dou et al <sup>6</sup>	2010	China	Asian	Glioma	PCR-LDR	НВ	189	343	111	208	305	143	0.119
Li et al <sup>9</sup>	2010	China	Asian	HCC	PCR-RFLP	НВ	82	150	78	78	102	42	0.402
Akkiz et al <sup>8</sup>	2010	Turkey	Caucasian	HCC	PCR-RFLP	НВ	22	86	77	40	87	58	0.492
Liu et al <sup>11</sup>	2010	USA	Caucasian	HNC	PCR-RFLP	PB	194	565	350	202	545	383	0.737
Kim et al <sup>110</sup>	2010	Korea	Asian	LC	PCR-RFLP	НВ	162	305	187	185	300	155	0.126
Catucci et al <sup>36</sup>	2010	Germany	Caucasian	BRC	MassARRAY	PB	216	696	584	157	512	432	0.711
Christensen et al <sup>37</sup>	2010	USA	Caucasian	HNC	AppliedBiosystems	PB	0	302	182	0	367	188	NA
Mittal et al41	2011	India	Asian	BLC	PCR-RFLP	PB	5	131	76	14	127	109	0.003
ledlinski et al40	2011	Australia	Caucasian	BRC	PCR	PB	33	86	68	31	82	58	0.830
Zhan et al42	2011	China	Asian	CRC	PCR-RFLP	НВ	56	128	68	163	267	113	0.849
Zhou et al43	2011	China	Asian	CSCC	PCR-RFLP	PB	57	123	46	82	169	58	0.077
Vinci et al <sup>111</sup>	2011	Italy	Caucasian	LC	TagMan	PB	12	54	35	10	61	58	0.267
Hong et al <sup>2</sup>	2011	Korea	Asian	LC	TagMan	НВ	96	224	86	134	198	96	0.163
George et al <sup>39</sup>	2011	Italy	Caucasian	PC	PCR-RFLP	PB	3	101	55	10	114	106	0.002
Linhares et al <sup>45</sup>	2012	Brazil	Mix	BRC	TagMan	НВ	117	177	94	96	165	127	0.005
Chen et al44	2012	China	Asian	CRC	PCR-LDR	НВ	35	64	27	107	206	94	0.788
Min et al <sup>24</sup>	2012	Korea	Asian	CRC	PCR-RFLP	НВ	125	201	120	148	254	100	0.633
Zhu et al47	2012	China	Asian	CRC	TagMan	НВ	130	303	140	172	295	121	0.790
Hezova et al <sup>25</sup>	2012	Czech	Caucasian	CRC	TagMan	НВ	26	89	82	22	103	87	0.291
Zhang et al <sup>100</sup>	2012	China	Asian	CRC	PCR-RFLP	РВ	172	204	79	185	197	81	0.026
Ahn et al <sup>48</sup>	2013	Korea	Asian	GC	PCR-RFLP	PB	119	242	100	128	232	87	0.322
Yoon et al46	2012	Korea	Asian	LC	TagMan	PB	99	186	101	24	32	15	0.480
Zhang et al <sup>104</sup>	2012	China	Asian	BRC	PCR-RFLP	PB	133	93	17	148	89	11	0.893
Chu et al <sup>87</sup>	2012	China	Asian	HNC	PCR-RFLP	НВ	136	277	57	132	206	87	0.690
Vinci et al <sup>113</sup>	2013	Italy	Caucasian	CRC	HRMA	HB	12	86	62	11	84	83	0.087
Lv et al <sup>51</sup>	2013	China	Asian	CRC	PCR-RFLP	PB	114	223	10	91	331	109	0.000
Umar et al <sup>112</sup>	2013	India	Asian	ESCC	PCR-RFLP	НВ	22	121	146	16	122	171	0.330
Wei et al <sup>114</sup>	2013	China	Asian	ESCC	SNPscanTM	HB	106	196	65	113	170	87	0.141
Toraih et al <sup>98</sup>	2016	Egypt	Caucasian	OSCC	PCR	PB	32	93	84	10	35	55	0.221
Wang et al <sup>53</sup>	2013	China	Asian	GC	TaqMan	HB	226	371	152	232	448	220	0.898
Zhang et al <sup>55</sup>	2013	China	Asian	HCC	MassARRAY	HB	294	488	214	328	502	165	0.245
Han et al⁴ <sup>9</sup>	2013	China	Asian	HCC	PCR	PB	305	505	207	304	485	220	0.310
Tong et al <sup>65</sup>	2013	China	Asian	ALL	TaqMan	HB	159	308	103	237	307	129	0.434
Pavlakis et al <sup>93</sup>	2013	Greece	Caucasian	PCC	PCR-RFLP	HB	48	33	12	50	58	14	0.647
Pu et al <sup>84</sup>	2014	China	Asian	GC	PCR-RFLP	НВ	25	95	39	86	324	101	0.000
Bansal et al <sup>56</sup>	2014	India	Asian	BRC	PCR-RFLP	PB	12	41	68	21	59	85	0.042
Kupcinskas et al <sup>62</sup>	2014	Lithuania	Caucasian	CRC	PCR	НВ	27	87	79	54	174	199	0.104
Qu et al <sup>64</sup>	2014	China	Asian	ESCC	PCR	PB	48	207	126	82	211	133	0.918
Wang et al <sup>66</sup>	2014	China	Asian	ESCC	PCR-LDR	PB	162	307	128	154	298	145	0.970
Dikeakos et al <sup>58</sup>	2014	Greece	Caucasian	GC	PCR-RFLP	HB	15	46	102	172	229	79	0.850
Qi et al <sup>∞</sup>	2014	China	Asian	HCC	PCR	HB	60	209	45	121	214	71	0.156
Chu et al <sup>57</sup>	2014	China	Asian	HCC	PCR-RFLP	НВ	66	81	41	100	167	70	0.986
Parlayan et al <sup>115</sup>	2014	Japan	Asian	LC	l aqMan	НВ	38	81	29	146	270	108	0.410
Li et alº	2014	China	Asian	NPC	l aqMan	HB	322	489	209	270	518	218	0.301
Du et al <sup>37,00</sup>	2014	China	Asian	RCC		HB	121	189	43 70	109	1/9	/4	0.9/4
Omrani et al <sup>es</sup>	2014	Iran Chin	Asian	вкс		rв	0	25	78	0	18 204	218	
NOU et al'	2014		Asian	HUU		нв	51	150	84 210	103	304	125	0.001
Koy et al <sup>24</sup>	2014	India	Asian	HNC	AppliedBiosystems	нв	46	187	218	38	168	242	0.250

(Continued)

Table I (Continued)

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

	Control         OR (95% CI)         P-value         P-H $I_1^{*}$ (A)         Total         84         35,80241,541         0.958 (0.911-1.008)         0.096         0.000         81.           Genotyping method         77         9,301/22.204         0.939 (0.871-1.012)         0.1000         0.000         81.           Asian         64         7,321/84,14         0.997 (0.842-1.181)         0.971         0.0000         73.           Caucasian         18         7,321/84,14         0.997 (0.842-1.181)         0.971         0.0000         73.           Asian         64         28.3337/31,932         0.844 (0.816-1.091)         0.431         0.0000         73.           Caucasian         18         7,321/84,14         0.997 (0.865-1.108)         0.626         0.0000         74.           Caucasian         18         7,321/84,14         0.997 (0.865-1.181)         0.917         0.000         75.           Caucasian         18         7,321/84,14         0.997 (0.865-1.103)         0.047         0.000         74.           Caucasian         18         7,321/84,150         0.944 (0.816-1.091)         0.417         0.995         20.           CRC         10         2.968/1.7133 <th>value P-H</th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th> <th></th>	value P-H							
			I²,% OR	(95% CI)	P-value P	-H l <sup>2</sup> ,%	OR (95% CI)	P-value	H-4
$ \begin{array}{c} \mbox{Time} Time$									
$ \begin{array}{c} \matrix {\bf P} {\bf$	Carcorypug metricol Taqman         67         13301/22.204         0939 (0.871-1.012)         0.100         0.000         67.           Taqman         16         8.565/10.286         1.021 (0.940-1.101)         0.618         0.000         67.           Ethnicity         64         28.337/31,932         0.847 (0.889-0.997)         0.018         0.000         77.           Asian         64         28.337/31,932         0.847 (0.869-1.088)         0.626         0.000         73.           Caucasian         18         7.321/8,414         0.997 (0.842-1.181)         0.997 (0.000         90.           Exc         10         2.906/4,150         1.051 (0.867-1.276)         0.611         0.000         75.           Exc         10         2.906/4,150         1.051 (0.867-1.276)         0.011         0.000         75.           Exc         6         3.472/556         0.857 (0.66-1.152)         0.001         76.         0.000         77.           Exc         1         4.2         2.066/1/2.533         0.9548 (0.907-1.038)         0.241         0.000         77.           Design         4.2         2.069/1/2.533         0.9548 (0.97-1.038)         0.243         0.000         77.           Perign	000 0.000	81.30 0.90	00 (0.813–0.987)	0.043 0	.000 78.80	1.005 (0.935–1.079)	0.902	0.000
Trans. The staticity is staticitized in the constrained of the staticity in the staticity is staticitized in the staticity is staticity in the staticity	Taqman         6         1,525/10,286         10.21         0.400         0.000         6.7.           Ethnicity         6         8,555/10,286         10.21         0.400         10.071         0.000         6.7.           Asian         64         28,537/13,1932         0.847         0.889-0.997         0.003         0.000         77.           Caucasian         18         7,321/8,414         0.997         0.889-0.997         0.003         0.000         73.           Caucasian         18         7,321/8,414         0.997         0.889-0.997         0.003         0.000         73.           Caucesian         18         7,321/8,414         0.997         0.889-0.997         0.000         74.           Caucesian         18         7,321/5,526         0.897         0.665-1.266         0.000         75.           CC         10         2,966/3,191         0.975         0.800-0.933         0.241         0.000         75.           GC         10.76         0.805         0.805         0.017         0.023         0.228         20           HCC         42         2,6691/2,1533         0.9648         0.971         0.933         0.025         0.000				0 033				0000
Heinicity         <	Ethnicity         0.000         77           Asian         64         28,337/31,932         0.847         0.889-0.997         0.038         0.000         77           Caucasian         18         7,321(8,414         0.997<(0.869-1.089)         0.626         0.000         77           Caucasian         18         7,321(8,414         0.997<(0.869-1.089)         0.624         0.000         79           RC         14         7,760(8,811         0.997<(0.869-1.089)         0.624         0.000         75           RC         14         7,760(8,811         0.997<(0.869-1.089)         0.624         0.000         75           CRC         6         3,492(4,376         0.944 (0.816-1.091)         0.435         0.000         76           CC         10         3,723(5,256         0.897 (0.663-1.109)         0.241         0.000         75           CC         1         4,988(5,962         0.994 (0.800-0.993)         0.013         0.012         0.000         75           HCC         14         4,988(5,962         0.974 (0.816-1.003)         0.334         0.000         77           HCC         14         4,988(5,962         0.974 (0.816-1.0103)         0.334         0.000         77<	0.000	67.40 1.05 67.40 1.05	79 (0.732-0.766)	0.507 0	000 6570	0.767 (0.663–1.102)	0.174	0.000
	Asian         64         28,337/31,932         0.847 (0.889-0.997)         0.038         0.000         77.           Caucasian         18         7,321/8,414         0.997 (0.842-1.181)         0.971         0.000         79.           Exacter type         14         7,760/8,811         0.972 (0.869-1.088)         0.6616         0.000         73.           Exc         19         7,760/8,811         0.972 (0.869-1.089)         0.611         0.000         74.           Exc         10         2,796/4,150         1.076 (1.066-1.1276)         0.611         0.000         75.           Exc         10         3,723/5,545         0.894 (0.800-0.998)         0.001         76.           HC         14         4,988/5,962         0.894 (0.800-0.998)         0.003         77.           HNC         5         3,534/3,554         1.076 (1.006-1.152)         0.033         0.285         20.           HNC         5         3,534/3,554         1.076 (1.006-1.152)         0.0167         0.000         77.           HNC         5         2,786/3,191         0.945 (0.873-1.024)         0.3285         20.           HNC         5         2,554         0.956         0.897 (0.863-1.028)         0.026	0000	2					-	
$ \begin{array}{c} \mbox{cmrstyne}    8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.21   8 \ / 7.2   9 \ / 8 \ / 6 \$	Caucasian         18         7,321/8,414         0.997 (0.842-1.181)         0.971         0.000         90.           Cancer type         7,321/8,811         0.977 (0.863-1.088)         0.626         0.000         73.           Cancer type         14         7,760/8,811         0.977 (0.863-1.089)         0.611         0.000         73.           CRC         10         2,760/8,811         0.972 (0.863-1.099)         0.641         0.000         74.           ESCC         6         3,492/4,376         0.934 (0.800-0.998)         0.047         0.000         75.           HCC         14         4,988/5,962         0.894 (0.800-0.998)         0.047         0.000         72.           HCC         14         4,988/5,962         0.894 (0.800-0.998)         0.047         0.000         72.           HCC         14         4,988/5,962         0.894 (0.807-1.033)         0.324         0.025         55.           LC         9         2,786/3,191         0.956 (0.873-1.0263)         0.324         0.000         77.           HNC         5         2,786/3,191         0.956 (0.873-1.024)         0.167         0.000         77.           Persite         42         2,786/3,191         0.956 (0.873-1.024	038 0.000	77.00 0.87	78 (0.788–0.977)	0.017 0.	000 76.00	1.012 (0.936–1.095)	0.759 (	0.000
	Cancer type         Cancer type           BRC         14         7,760(8811         0.972 (0.869-1.088)         0.626         0.000         78.           CRC         10         2,906/4,150         1.051 (0.867-1.276)         0.611         0.000         76.           ESCC         6         3,492/4,356         0.944 (0.816-1.091)         0.435         0.000         73.           GC         10         2,906/4,150         1.051 (0.06-1.152)         0.0147         0.000         73.           HNC         5         3,344/3,564         1.076 (1.006-1.152)         0.033         0.285         20.           HNC         5         3,344/3,564         1.076 (1.006-1.152)         0.033         0.285         20.           HNC         5         3,344/3,564         1.076 (0.87-1.033)         0.324         0.000         77.           PHC         9         2,786/3,191         0.95 (0.854-1.058)         0.354         0.000         77.           Phil         42         20,691/21,533         0.968 (0.907-1.033)         0.324         0.000         77.           Paisin         42         15,111/20,008         0.945 (0.873-1.054)         0.167         0.000         77.           Paisin	971 0.000	90.30 0.97	74 (0.714–1.329)	0.870 0.	000 86.10	0.963 (0.785–1.180)	0.714 (	0.000
RE         (1         2736(081)         0.373 (085-1.126)         0.374         0.000         1.0         0.746 (087)         0.746 (087)         0.746 (087)         0.746 (087)         0.746 (087)         0.746 (087)         0.746 (087)         0.746 (087)         0.746 (087)         0.746 (087)         0.746 (000)         0.746 (087)         0.746 (000)         0.746 (000)         0.746 (087)         0.746 (000)         <	BRC         14         7,760/8811         0.972         0.889         0.626         0.000         79.           CRC         10         2,906/4,150         1.051         0.887/-1.276)         0.611         0.000         73.           ESCC         6         3,492/4,376         0.944         0.816-1.091)         0.435         0.000         73.           CRC         10         2,906/4,150         1.051         0.857         0.6611         70.           HNC         5         3,492/4,376         0.944         0.816         0.000         73.           HNC         5         3,534,562         0.894         0.800-0.998         0.000         73.           HNC         5         3,534,562         0.894         0.800-0.913         0.324         0.000         73.           Design         42         20,691/21,533         0.968         (0.977-1.033)         0.324         0.000         77.           HB         42         20,691/21,533         0.968         (0.877-1.058)         0.354         0.000         77.           HB         42         15,111/20,008         0.945         (0.871-1.058)         0.354         0.000         77.           FI1614913								
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	626 0.000	79.70 0.97	72 (0.869–1.088)	0.341 0.	.000 72.80	0.979 (0.854–1.121)	0.754 (	0.001
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$		611 0.000	86.50 I.05	51 (0.867–1.276)	0.431 0.	000 87.60	1.121 (0.832–1.510)	0.454 (	0.000
CC         10         3723(52.56)         687 (066.3-11.09)         0.241         0.000         9380 (3387-11.93)         0.115         0.000         1013         1013         1013         1013         1013         1013		435 0.001	76.80 0.94	14 (0.816–1.091)	0.385 0.	000 82.40	I.050 (0.878–I.255)	0.594 (	0.040
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	HCC         14         4,988/5,962         0.894 (0.800-0.998)         0.047         0.000         72.           HNC         5         3,534/3,564         1.076 (1.006-1.152)         0.033         0.285         20.           LC         9         2,786/3,191         0.95 (0.854-1.058)         0.354         0.007         75.           Design         42         2,786/3,191         0.95 (0.873-1.023)         0.324         0.000         77.           PB         42         15,111/20,008         0.945 (0.873-1.024)         0.167         0.000         77.           PB         42         15,111/20,008         0.945 (0.873-1.024)         0.167         0.000         77.           FIL614913 $n^a$ TT vs TC+CC         0.167         0.000         84.           FIL614913 $n^a$ TT vs TC+CC $p$ -value         0.055         0.025           Genotyping method         57         0.880 (0.800-0.9690)         0.025         0.005         0.995           FC         57         0.880 (0.800-0.29690)         0.005         0.995         0.005           Famoireity         16         1.000 (0.858-1.166)         0.994         0.996         0.996           Famman<	241 0.000	93.80 0.85	57 (0.663–1.109)	0.276 0.	000 91.50	0.778 (0.552–1.098)	0.153 (	0.000
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	$ \begin{array}{llllllllllllllllllllllllllllllllllll$	047 0.000	72.60 0.90	0 (0.813-0.997)	0.039 0.	000 70.50	0.981 (0.838–1.149)	0.816 (	0.005
		033 0.285	20.40 1.21	4 (1.043–1.413)	0.012 0.	380 2.50	1.157 (0.922–1.451)	0.209	0.003
Design         Design <thdesign< th=""> <thdesign< th=""> <thdesign< t<="" td=""><td>Design PB42<math>20.691/21,533</math> <math>1.5</math><math>0.968</math><math>(0.907-1.033)</math><math>0.324</math><math>0.000</math><math>77</math>PB42<math>15,111/20,008</math><math>0.945</math><math>(0.873-1.024)</math><math>0.167</math><math>0.000</math><math>84.</math>rs11614913<math>\mathbf{n}^3</math><math>\mathbf{TT} vs \mathbf{TC} + \mathbf{CC}</math><math>\mathbf{T} vs \mathbf{TC} + \mathbf{CC}</math><math>\mathbf{P} value</math>rs11614913<math>\mathbf{n}^3</math><math>\mathbf{TT} vs \mathbf{TC} + \mathbf{CC}</math><math>\mathbf{P} value</math>rs11614913<math>\mathbf{n}^3</math><math><b>0</b>.918</math><math>(0.851-0.989)</math><math><b>0</b>.000</math>R0<math>\mathbf{R}</math><math>\mathbf{R}</math><math>\mathbf{R}</math><math>\mathbf{R}</math><math>\mathbf{R}</math>rotad<math><b>57</b></math><math><b>0</b>.800</math><math><b>0</b>.0959</math><math><b>0</b>.025</math>PCR<math>57</math><math>\mathbf{R}</math><math>\mathbf{R}</math><math><b>0</b>.999</math><math><b>0</b>.099</math>PCR<math>57</math><math><b>0</b>.896</math><math><b>0</b>.802-1.166</math><math><b>0</b>.994</math>PCR<math><b>1</b>7</math><math><b>1</b>015</math><math>(<b>0</b>.820-1.256)</math><math><b>0</b>.994</math>Psin<math><b>1</b>7</math><math><b>1</b>015</math><math>(<b>0</b>.820-1.256)</math><math><b>0</b>.894</math>Psin<math><b>1</b>7</math><math><b>1</b>015</math><math>(<b>0</b>.823-1.381)</math><math><b>0</b>.628</math>Psin<math><b>1</b>7</math><math><b>0</b>.943</math><math><b>0</b>.895</math><math><b>0</b>.890</math>PCC<math><b>1</b>0</math><math><b>0</b>.910</math><math>(<b>0</b>.677-1.189)</math><math><b>0</b>.489</math>Psin<math><b>1</b>066</math><math><b>0</b>.890-1.817</math><math><b>0</b>.908</math>Psin<math><b>1</b>000</math><math><b>0</b>.799-1.817</math><math><b>0</b>.908</math>Psin<math><b>1</b>000</math></td><td>354 0.022</td><td>55.30 0.84</td><td>40 (0.734–0.961)</td><td>0.011 0.0</td><td>025 48.10</td><td>0.997 (0.889–1.118)</td><td>0.961</td><td>0.056</td></thdesign<></thdesign<></thdesign<>	Design PB42 $20.691/21,533$ $1.5$ $0.968$ $(0.907-1.033)$ $0.324$ $0.000$ $77$ PB42 $15,111/20,008$ $0.945$ $(0.873-1.024)$ $0.167$ $0.000$ $84.$ rs11614913 $\mathbf{n}^3$ $\mathbf{TT} vs \mathbf{TC} + \mathbf{CC}$ $\mathbf{T} vs \mathbf{TC} + \mathbf{CC}$ $\mathbf{P} value$ rs11614913 $\mathbf{n}^3$ $\mathbf{TT} vs \mathbf{TC} + \mathbf{CC}$ $\mathbf{P} value$ rs11614913 $\mathbf{n}^3$ $\mathbf{TT} vs \mathbf{TC} + \mathbf{CC}$ $\mathbf{P} value$ rs11614913 $\mathbf{n}^3$ $\mathbf{TT} vs \mathbf{TC} + \mathbf{CC}$ $\mathbf{P} value$ rs11614913 $\mathbf{n}^3$ $\mathbf{TT} vs \mathbf{TC} + \mathbf{CC}$ $\mathbf{P} value$ rs11614913 $\mathbf{n}^3$ $0.918$ $(0.851-0.989)$ $0.000$ R0 $\mathbf{R}$ $\mathbf{R}$ $\mathbf{R}$ $\mathbf{R}$ $\mathbf{R}$ rotad $57$ $0.800$ $0.0959$ $0.025$ PCR $57$ $\mathbf{R}$ $\mathbf{R}$ $0.999$ $0.099$ PCR $57$ $0.896$ $0.802-1.166$ $0.994$ PCR $17$ $1015$ $(0.820-1.256)$ $0.994$ Psin $17$ $1015$ $(0.820-1.256)$ $0.894$ Psin $17$ $1015$ $(0.823-1.381)$ $0.628$ Psin $17$ $0.943$ $0.895$ $0.890$ PCC $10$ $0.910$ $(0.677-1.189)$ $0.489$ Psin $1066$ $0.890-1.817$ $0.908$ Psin $1000$ $0.799-1.817$ $0.908$ Psin $1000$	354 0.022	55.30 0.84	40 (0.734–0.961)	0.011 0.0	025 48.10	0.997 (0.889–1.118)	0.961	0.056
B         42         2064/11233         0.948 (0.977-10.31)         0.324 0.000         645 0.000         647 0.000         74.70         10.16 (0.982-1.104)         0.223 0.000         55 0.000         55 0.000         57 0.0000         57 0.000         57	$ \begin{array}{lcccccccccccccccccccccccccccccccccccc$								
HB         42         IS.111/20.008         0.945 (0.873-1.02.4)         0.167         0.000         84.50         0.987 (0.882-1.104)         0.822         0.000         75           rs1161/913         n*         TT vs TC+CC         Tv vs TC+CC         T+TC vs CC         P-H         P.           rs1161/913         n*         TT vs TC+CC         P-value         P-H         P.         P.           rs1161/913         n*         TT vs TC+CC         P-value         P-H         P.         P.           ors101/0         081         0.0105         0.000         75.80         0.974 (0.901-1052)         0.498         0.000         78           Genotyping method         57         0.800 (0.800-0.959)         0.005         0.000         73.20         0.974 (0.91-1052)         0.498         0.000         73           Taqman         i         1         1.015 (0.801-0.166)         0.900         73.20         0.974 (0.901-1052)         0.498         0.000         73           Taqman         i         0.105 (0.824-1.037)         0.900         0.732         0.974 (0.901-1052)         0.498         0.000         73           Taqman         i         1         1.015 (0.824-1.035)         0.429         0.000	$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	324 0.000	77.20 0.89	(710.1-777.0) 99	0.087 0.	.000 74.70	1.018 (0.928–1.117)	0.703	0.000
rs11614913         rr         Trys TC+CC         Trys TC+CC           R11614913         rr         Trys TC+CC         P-value         P-H         F,%         OR (95% CI)         P-value         P-H         F,           (B)         Trys TC+CC         P-value         P-H         F,%         OR (95% CI)         P-value         P-H         F,           (B)         Total         84         0.918 (0351–0.389)         0.025         0.000         75.80         0.974 (0.901–1.052)         0.498         0.000         23           Coal         57         0.880 (0800–0.9560)         0.000         71.90         1.063 (0.969–1.165)         0.195         0.000         23           Fehnicity         64         0.895 (0824–0.972)         0.000         71.90         1.063 (0.969–1.165)         0.195         0.000         23           Caucestain         17         1.015 (0820–1.256)         0.894         0.000         75.30         0.946 (0.05)         0.473         0.000         23           Caucestain         17         1.015 (0820–1.256)         0.894         0.000         0.772         0.000         0.772         0.000         0.772         0.000         0.772         0.000         0.772         0.000         <	rs11614913         n <sup>a</sup> TT vs TC+CC           OR (95% CI)         P-value           OR (95% CI)         P-value           (B)         0.025           Total         84         0.918 (0.851–0.989)         0.025           (B)         Total         84         0.918 (0.851–0.989)         0.025           (B)         Total         84         0.918 (0.851–0.989)         0.025           Genotyping method         57         0.880 (0.800–0.9690)         0.009           PCR         57         0.880 (0.802–0.9690)         0.009           PCR         57         0.880 (0.802–0.1660)         0.996           Ethnicity         64         0.895 (0.824–0.972)         0.008           Asian         17         1.015 (0.820–1.256)         0.429           Caucastan         17         1.015 (0.820–1.256)         0.429           BRC         14         0.943 (0.815–1.091)         0.429           CRC         10         0.429         0.160           CRC         6         0.813 (0.610–1.085)         0.160           BRC         10         0.823–1.381)         0.489           HCC         14         0.800 (0.678–0.944)         0.160	167 0.000	84.50 0.90	06 (0.813-0.997)	0.211 0.	000 81.90	0.987 (0.882–1.104)	0.822	0.000
OR (95% CJ)         P-value         P-H         R, %         OR (95% CJ)         P-value         P-H         R, 1           (B)         7 cal         84         0.918 (0.851-0.399)         0.025         0.000         75.80         0.974 (0.901-1.052)         0.498         0.000         23           Total         84         0.918 (0.851-0.369)         0.009         0.000         75.80         0.974 (0.901-1.052)         0.498         0.000         23           Taqman         16         1.000 (0.858-1.166)         0.996         0.000         73.20         0.949 (0.842-1.165)         0.195         0.000         23           Taqman         16         1.000 (0.858-1.166)         0.996         0.000         73.20         0.949 (0.842-1.165)         0.195         0.000         23           Taqman         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.946 (0.76-1.129)         0.77         0.000         23           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.946 (0.76-1.219)         0.772         0.000         23           Caucasian         17         1.015 (0.820-1.126)         0.440         0.966 (0.76-1.219)         0.712	OR (95% CI)         P-value           (B)         Total         84         0.918 (0.851–0.989)         0.025           Genotyping method         57         0.880 (0.800–0.9690)         0.009           PCR         57         0.880 (0.800–0.9690)         0.996           PCR         57         0.880 (0.800–0.9690)         0.996           PCR         54         0.895 (0.824–0.972)         0.996           Asian         64         0.895 (0.824–0.972)         0.908           Asian         64         0.895 (0.820–1.256)         0.894           Caucasian         17         1.015 (0.820–1.256)         0.894           BRC         14         0.943 (0.815–1.091)         0.429           CRC         10         1.066 (0.823–1.381)         0.628           ESCC         6         0.813 (0.610–1.085)         0.160           HCC         14         0.941 (0.657–1.189)         0.489           HNC         5         1.205 (0.799–1.817)         0.375				11+T(	C vs CC			
(B)         75.80         0.974 (0.901-1.052)         0.498         0.000         78           Total         84         0.918 (0.851-0.989) <b>0.025</b> 0.000         75.80         0.974 (0.901-1.052)         0.498         0.000         73           FCR notyping method         57         0.880 (0.800-9.9409) <b>0.003</b> 73.20         0.974 (0.991-1.165)         0.195         0.000         82           FCR notyping method         57         0.880 (0.800-9.9409) <b>0.000</b> 71.90         0.972 (0.839-1.165)         0.195         0.000         82           Fthnicity         16         1.000 (0.838-1.166)         0.996         0.000         75.30         0.972 (0.839-1.165)         0.195         0.000         82           Carcarsian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.956 (0.766-1.219)         0.772         0.000         87           Carcarsian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.956 (0.766-1.219)         0.772         0.000         87           Carcarsian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.956 (0.766-1.219)         0.7722         0.000	(B)         0.918 (0.851-0.989)         0.025           Total         84         0.918 (0.851-0.989)         0.025           Genotyping method         57         0.880 (0.800-0.9690)         0.009           PCR         57         0.880 (0.800-0.9690)         0.009           PT aqman         16         1.000 (0.858-1.166)         0.996           Paraman         16         1.000 (0.858-1.166)         0.996           Asian         64         0.895 (0.824-0.972)         0.008           Asian         64         0.895 (0.820-1.256)         0.894           Caucasian         17         1.015 (0.820-1.256)         0.894           BRC         14         0.943 (0.815-1.091)         0.429           CRC         10         1.066 (0.823-1.381)         0.628           CRC         10         1.066 (0.823-1.381)         0.628           CRC         10         0.943 (0.815-1.091)         0.429           HCC         10         0.910 (0.657-1.189)         0.160 <th>P-value</th> <th>H-4</th> <th>P2, %</th> <th>OR (9</th> <th>5% CI)</th> <th>P-value</th> <th>H-4</th> <th></th>	P-value	H-4	P2, %	OR (9	5% CI)	P-value	H-4	
Total         84         0.918 (0.851-0.989)         0.025         0.000         7580         0.974 (0.901-1.052)         0.498         0.000         78           Genotyping method         5         0.880 (0.800-0.9690)         0.009         0.000         73.20         0.949 (0.842-1.069)         0.338         0.000         82           Reinvicty         5         0.880 (0.800-0.9690)         0.009         0.000         73.20         0.949 (0.842-1.165)         0.138         0.000         82           Reinvicty         6         0.895 (0.84-0.972)         0.009         0.000         73.20         0.947 (0.961-1.165)         0.195         0.000         82           Asian         64         0.895 (0.84-0.972)         0.008         0.000         73.20         0.947 (0.959-1.165)         0.195         0.000         73           Asian         64         0.895 (0.84-0.972)         0.008         0.000         75.30         0.946 (0.766-1.219)         0.772         0.000         73           Asian         64         0.943 (0.815-1.091)         0.423         0.000         75.30         0.946 (0.766-1.219)         0.772         0.000         73           Ruce type         14         0.943 (0.815-1.166)         0.433         0.00	Total840.918 (0.851-0.989) <b>0.025</b> Genotyping method570.880 (0.800-0.9690) <b>0.009</b> PCR570.880 (0.800-0.9690) <b>0.009</b> PCR570.880 (0.805-0.9690) <b>0.009</b> PCR641.000 (0.858-1.166)0.996Ethnicity640.895 (0.820-1.256)0.908Asian640.895 (0.820-1.256)0.908Caucastian171.015 (0.820-1.256)0.894BRC140.943 (0.815-1.091)0.429CRC160.943 (0.815-1.091)0.429BRC140.910 (0.678-0.944)0.160CRC100.910 (0.678-0.944)0.060HCC121.205 (0.799-1.817)0.375								
Genotyping method         0.388         0.309         0.000         73.20         0.348         0.336         0.000         82           Taqman         16         1.000         0.388-1.166         0.395         0.306         0.000         73.20         0.346         0.365         0.000         82           Taqman         16         1.000         0.383-1.166         0.395         0.000         73.20         0.346         0.365         0.195         0.005         82           Taqman         16         1.0015         0.3824         0.306         0.000         75.30         0.395         0.385         0.000         82           Asian         17         1.015         0.824         0.300         0.000         75.30         0.366         0.766         1.219         0.772         0.000         73           Caucasian         17         1.015         0.824         0.000         0.429         0.000         73         0.772         0.000         0.772         0.000         0.772         0.000         0.772         0.000         0.772         0.000         73         0.000         0.772         0.000         0.772         0.000         0.772         0.772         0.0100 <t< td=""><td>Genotyping method         0.880 (0.800-0.9690)         0.009           PCR         57         0.880 (0.800-0.9690)         0.009           Taqman         16         1.000 (0.858-1.166)         0.996           Ethnicity         64         0.895 (0.824-0.972)         0.008           Asian         64         0.895 (0.820-1.256)         0.894           Caucasian         17         1.015 (0.820-1.256)         0.894           BRC         14         0.943 (0.815-1.091)         0.429           CRC         10         1.066 (0.823-1.381)         0.628           CRC         10         1.066 (0.823-1.381)         0.489           FSCC         6         0.813 (0.610-1.085)         0.160           HCC         19         0.910 (0.678-0.944)         0.489           HNC         5         1.205 (0.799-1.817)         0.375</td><td>0.025</td><td>0.000</td><td>75.80</td><td>0.974 ((</td><td>0.901-1.052)</td><td>0.498</td><td>0.000</td><td></td></t<>	Genotyping method         0.880 (0.800-0.9690)         0.009           PCR         57         0.880 (0.800-0.9690)         0.009           Taqman         16         1.000 (0.858-1.166)         0.996           Ethnicity         64         0.895 (0.824-0.972)         0.008           Asian         64         0.895 (0.820-1.256)         0.894           Caucasian         17         1.015 (0.820-1.256)         0.894           BRC         14         0.943 (0.815-1.091)         0.429           CRC         10         1.066 (0.823-1.381)         0.628           CRC         10         1.066 (0.823-1.381)         0.489           FSCC         6         0.813 (0.610-1.085)         0.160           HCC         19         0.910 (0.678-0.944)         0.489           HNC         5         1.205 (0.799-1.817)         0.375	0.025	0.000	75.80	0.974 ((	0.901-1.052)	0.498	0.000	
PCR         57         0.880 (0.800-0.9690)         0.009         0.000         73.20         0.949 (0.842-1.165)         0.386         0.000         82           Taqman         16         1.000 (0.858-1.166)         0.996         0.000         71.90         1.063 (0.969-1.165)         0.195         0.005         34           Ethnicity         64         0.895 (0.824-0.972)         0.008         0.000         75.30         0.972 (0.836-1.129)         0.493         0.000         72           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.956 (0.766-1.219)         0.772         0.000         73           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.956 (0.766-1.219)         0.772         0.000         73           Caucasian         17         1.015 (0.820-1.266)         0.894         0.000         75.30         0.956 (0.766-1.219)         0.772         0.000         73           Caucer type         14         0.943 (0.810-1.085)         0.443         0.000         73         0.763         0.764         0.772         0.000         75           CRC         10         1.066 (0.822-1.189)         0.160         <	PCR         57         0.880 (0.800-0.9690)         0.009           Taqman         16         1.000 (0.858-1.166)         0.996           Ethnicity         64         0.895 (0.824-0.972)         0.008           Asian         64         0.895 (0.820-1.256)         0.394           Caucastan         17         1.015 (0.820-1.256)         0.894           BRC         14         0.943 (0.815-1.091)         0.429           CRC         10         1.066 (0.823-1.381)         0.628           BRC         10         1.066 (0.823-1.381)         0.429           CRC         10         0.943 (0.610-1.085)         0.160           HCC         19         0.910 (0.678-0.944)         0.489           HNC         5         1.205 (0.799-1.817)         0.375					(			
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           Ethnicity         64         0.895 (0.824-0.972)         0.000         75.30         0.972 (0.8396-1:065)         0.193         0.000         72           Asian         64         0.895 (0.824-0.972)         0.000         75.30         0.972 (0.8396-1:065)         0.493         0.000         72           Asian         64         0.895 (0.824-0.972)         0.000         75.30         0.975 (0.8396-1:065)         0.493         0.000         72           Caucasian         17         1.015 (0.820-1:256)         0.884         0.000         75.30         0.966 (0.766-1:219)         0.772         0.000         73           Caucasian         17         1.015 (0.820-1:266)         0.429         0.000         75.30         0.966 (0.766-1:219)         0.772         0.000         73           CRC         10         1.066 (0.823-1:381)         0.623         0.366         0.366         0.772         0.000         73           CRC         10         10.010 (6.76-1:189)         0.489         0.000         73.30         0.766 (0.766-1:1219)         0.772         0.000	Taqman         16         1.000 (0.858–1.166)         0.996           Ethnicity         64         0.895 (0.824–0.972)         0.008           Asian         64         0.895 (0.820–1.256)         0.394           Caucastan         17         1.015 (0.820–1.256)         0.394           BRC         14         0.943 (0.815–1.091)         0.429           CRC         14         0.943 (0.823–1.381)         0.628           BRC         100         1.066 (0.823–1.381)         0.429           CRC         10         0.943 (0.610–1.085)         0.160           FSCC         6         0.813 (0.610–1.085)         0.160           HCC         14         0.201 (0.657–1.189)         0.160           HNC         5         1.205 (0.799–1.817)         0.375	0.009	0.000	73.20	0.949 (	0.842-1.069)	0.386	0.000	
Ethnicity         Ethnicity           Asian         64         0.895 (0.824-0.972)         0.008         76.50         0.972 (0.8396-1.005)         0.493         0.000         72           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.966 (0.766-1.219)         0.772         0.000         73           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.966 (0.766-1.219)         0.7772         0.000         73           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.966 (0.766-1.219)         0.7772         0.000         73           Caucasian         14         0.943 (0.815-1.081)         0.429         0.000         79.00         1.130 (0.826-1.246)         0.444         0.000         73           CRC         10         1.066 (0.823-1.381)         0.628         0.000         81.30         1.0010 (0.822-1.216)         0.444         0.000         66           FCC         14         0.8010 (0.678-0.944)         0.000         81.30         0.776-1.089)         0.194         0.000         66           HCC         14         0.800 (0.678-0.944)         0.000	Ethnicity         64         0.895 (0.824-0.972)         0.008           Asian         64         0.895 (0.820-1.256)         0.394           Caucasian         17         1.015 (0.820-1.256)         0.394           ERC         14         0.943 (0.815-1.091)         0.429           BRC         10         1.066 (0.823-1.381)         0.628           CRC         10         1.066 (0.823-1.381)         0.628           ESCC         6         0.813 (0.610-1.085)         0.160           HCC         19         0.910 (0.657-1.189)         0.489           HNC         5         1.205 (0.799-1.817)         0.375	0.996	0.000	71.90	1.063 (	0.969–1.165)	0.195	0.095	
Asian         64         0.895 (0.824-0.972)         0.008         0.000         75.30         0.972 (0.839-1.065)         0.493         0.000         72           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.966 (0.766-1.219)         0.772         0.000         73           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.966 (0.766-1.219)         0.772         0.000         73           Caucasian         17         1.015 (0.820-1.256)         0.894         0.000         75.30         0.966 (0.766-1.219)         0.772         0.000         73           Caucer type         10         1.066 (0.823-1.381)         0.429         0.000         79.00         1.130 (0.266-1.246)         0.444         0.000         73           CRC         6         0.813 (0.610-1.083)         0.489         0.000         83.30         0.367.146)         0.444         0.000         66           FCC         14         0.800 (0.678-0.944)         0.603         63.300         0.763 (0.507-1.148)         0.144         0.000         66           HNC         5         1.205 (0.799-1.817)         0.375         0.000         67.40 <t< td=""><td>Asian         64         0.895 (0.824-0.972)         0.008           Caucasian         17         1.015 (0.820-1.256)         0.894           Cancer type         1.015 (0.820-1.256)         0.894           BRC         14         0.943 (0.815-1.091)         0.429           CRC         10         1.066 (0.823-1.381)         0.628           ESCC         6         0.813 (0.610-1.085)         0.160           GC         10         0.910 (0.657-1.189)         0.489           HCC         14         0.800 (0.678-0.944)         0.008           HNC         5         1.205 (0.799-1.817)         0.375</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></t<>	Asian         64         0.895 (0.824-0.972)         0.008           Caucasian         17         1.015 (0.820-1.256)         0.894           Cancer type         1.015 (0.820-1.256)         0.894           BRC         14         0.943 (0.815-1.091)         0.429           CRC         10         1.066 (0.823-1.381)         0.628           ESCC         6         0.813 (0.610-1.085)         0.160           GC         10         0.910 (0.657-1.189)         0.489           HCC         14         0.800 (0.678-0.944)         0.008           HNC         5         1.205 (0.799-1.817)         0.375								
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           Cancer type         14         0.943 (0.815-1.091)         0.429         0.001         64.40         0.966 (0.766-1.219)         0.144         0.000         73           Cancer type         10         1.066 (0.823-1.381)         0.628         0.000         64.40         0.967 (0.830-1.126)         0.663         0.000         73           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           ESCC         6         0.813 (0.610-1.085)         0.160         0.000         81.30         1.130 (0.826-1.148)         0.000         92           CRC         14         0.9910 (0.657-0.944)         0.000         83.390         0.761-1.089)         0.332         0.000         92           HNC         5         1.205 (0.779-0.1817)         0.3375         0.000         83.390         0.776-1.089)         0.3178         0.019         65           HNC         5         1.205 (0.779-0.1817)         0.3575 (0.950-1.148)         0.746         0.0000         65	Caucasian         17         1.015         (0.820-1.256)         0.894           Cancer type         0.943         (0.815-1.091)         0.429           BRC         19         0.943         (0.815-1.091)         0.429           CRC         10         1.066         (0.823-1.381)         0.628           ESCC         6         0.813         (0.610-1.085)         0.160           GC         10         0.910         (0.678-0.944)         0.489           HCC         14         0.800         (0.678-0.944)         0.008           HNC         5         1.205         (0.799-1.817)         0.375	0.008	0.000	76.50	0.972 (i	0.8396-1.005)	0.493	0.000	
Cancer type         Cancer type         0.943 (0.815-1.091)         0.429         0.001         64.40         0.967 (0.830-1.126)         0.6663         0.000         73           BRC         10         1.066 (0.823-1.381)         0.6228         0.000         79.00         1.130 (0.826-1.546)         0.444         0.000         84           CRC         10         1.066 (0.823-1.381)         0.6228         0.000         79.00         1.130 (0.826-1.546)         0.444         0.000         84           ESCC         6         0.813 (0.610-1.085)         0.160         0.000         81.30         1.000 (0.822-1.216)         0.997         0.000         92           GC         10         0.910 (0.678-0.944)         0.000         81.30         0.763 (0.507-1.148)         0.194         0.000         92           HCC         14         0.800 (0.678-0.944)         0.000         81.30         0.176-0.089)         0.194         0.000         66           HNC         5         1.205 (0.799-1.817)         0.3375         0.000         921 (0.814-1.191)         0.919 (0.776-1.089)         0.194         0.011         69           HNC         5         1.205 (0.799-1.817)         0.332         0.0100         1.156 (0.956-1.406)         0	Cancer type         14         0.943 (0.815–1.091)         0.429           BRC         10         1.066 (0.823–1.381)         0.628           CRC         10         1.066 (0.823–1.381)         0.628           ESCC         6         0.813 (0.610–1.085)         0.160           FSCC         10         0.910 (0.697–1.189)         0.489           HCC         14         0.800 (0.678–0.944)         0.008           HNC         5         1.205 (0.799–1.817)         0.375	0.894	0.000	75.30	0.966 (i	0.766-1.219)	0.772	0.000	
BRC         14         0.943 (0.815-1.091)         0.429         0.001         64.40         0.957 (0.830-1.126)         0.663         0.000         73           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           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           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           CC         10         0.910 (0.697-1.189)         0.489         0.000         81.30         0.763 (0.507-1.148)         0.194         0.000         92           HNC         5         1.205 (0.799-1.817)         0.375         0.000         67.40         0.997 (0.834-1.191)         0.973         0.011         69           HNC         5         1.205 (0.771-0.955)         0.005         0.156         0.324 (0.834-1.191)         0.973         0.019         56           Design         42         0.924 (0.826-1.034)         0.170         0.156         0.997 (0.834-1.191)         0.	BRC         14         0.943 (0.815-1.091)         0.429           CRC         10         1.066 (0.823-1.381)         0.628           ESCC         6         0.813 (0.610-1.085)         0.160           GC         10         0.910 (0.697-1.189)         0.489           HCC         14         0.800 (0.678-0.944)         0.008           HNC         5         1.205 (0.799-1.817)         0.375								
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           ESCC         6         0.813 (0.610-1.085)         0.160         0.000         81.30         1.000 (0.822-1.216)         0.997         0.000         84           FSCC         6         0.813 (0.610-1.085)         0.160         0.000         81.30         1.000 (0.822-1.216)         0.997         0.008         67           GC         10         0.910 (0.677-1.189)         0.489         0.000         83.390         0.763 (0.507-1.148)         0.194         0.000         92           HNC         5         1.205 (0.799-1.817)         0.375         0.000         87.40         0.919 (0.776-1.089)         0.332         0.001         66           HNC         5         1.205 (0.799-1.817)         0.375         0.000         97.10         0.1156         0.997 (0.834-1.191)         0.973         0.011         69           LC         9         0.858 (0.771-0.955)         0.005         0.156         0.997 (0.834-1.191)         0.973         0.019         56           Design         42         0.924 (0.826-1.034)         0.170         0.0900         73.90	CRC         10         1.066 (0.823-1.381)         0.628           ESCC         6         0.813 (0.610-1.085)         0.160           GC         10         0.910 (0.697-1.189)         0.489           HCC         14         0.800 (0.678-0.944)         0.008           HNC         5         1.205 (0.799-1.817)         0.375	0.429	0.001	64.40	0.967 (	0.830-1.126)	0.663	0.000	
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           GC         10         0.910 (0.697-1.189)         0.489         0.000         83.390         0.763 (0.507-1.148)         0.194         0.000         92           HCC         14         0.800 (0.678-0.944) <b>0.008</b> 0.000         67.40         0.919 (0.776-1.089)         0.332         0.000         92           HNC         5         1.205 (0.799-1.817)         0.375         0.000         67.40         0.919 (0.776-1.089)         0.332         0.001         66           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           LC         9         0.858 (0.771-0.955) <b>0.005</b> 0.158         32.50         0.997 (0.834-1.191)         0.973         0.019         56           Design         42         0.912 (0.822-1.010)         0.078         0.000         73         0.997 (0.834-1.191)         0.973         0.019         56           Persign         42         0.912 (0.822-1.010)         0.078         0.0000         73.90	ESCC         6         0.813 (0.610-1.085)         0.160           GC         10         0.910 (0.697-1.189)         0.489           HCC         14         0.800 (0.678-0.944)         0.008           HNC         5         1.205 (0.799-1.817)         0.375	0.628	0.000	79.00	1.130 (	0.826-1.546)	0.444	0.000	
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         HCC       14       0.800 (0.678-0.944) <b>0.008</b> 0.000       67.40       0.919 (0.776-1.089)       0.332       0.000       66         HNC       5       1.205 (0.799-1.817)       0.375       0.000       67.40       0.919 (0.776-1.089)       0.332       0.001       69         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         LC       9       0.858 (0.771-0.955) <b>0.005</b> 0.158       32.50       0.997 (0.834-1.191)       0.973       0.019       56         Design       42       0.924 (0.825-1.034)       0.170       0.000       73       0.019       0.55 (0.897-1.087)       0.2000       82         HB       42       0.912 (0.823-1.1010)       0.078       0.000       73.90       0.955 (0.843-1.081)       0.465       0.000       82	GC 10 0.910 (0.697–1.189) 0.489 HCC 14 0.800 (0.678–0.944) <b>0.008</b> HNC 5 1.205 (0.799–1.817) 0.375	0.160	0.000	81.30	000.1	0.822-1.216)	0.997	0.008	
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         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         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         Design       42       0.924 (0.826–1.034)       0.170       0.000       78.10       0.988 (0.897–1.087)       0.300       0.019       56         Pesign       42       0.912 (0.823–1.010)       0.078       0.000       73.90       0.955 (0.843–1.191)       0.465       0.000       82         Maxee borden date and date an	HCC 14 0.800 (0.678–0.944) <b>0.008</b> HNC 5 1.205 (0.799–1.817) 0.375	0.489	0.000	83.90	0.763 (	0.507-I.I48)	0.194	0.000	
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         LC       9       0.858 (0.771-0.955) <b>0.005</b> 0.158       32.50       0.997 (0.834-1.191)       0.973       0.019       56         Design       42       0.924 (0.826-1.034)       0.170       0.000       78.10       0.988 (0.897-1.087)       0.800       0.000       72         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         Most heat heat and	HNC 5 1.205 (0.799–1.817) 0.375	0.008	0.000	67.40	0.919 (	0.776-1.089)	0.332	0.000	
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         Design       42       0.924 (0.825–1.034)       0.170       0.000       78.10       0.988 (0.897–1.087)       0.800       0.000       72         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         Month Data Landon and when Data Landon and when Data Landon and the contract of the Antonian food different model we used 40.975% on hearmonian 250% in the hearmonean 250% in thearmonean 250% in the hearmonean 250% in thearmonean 250		0.375	0.000	90.10	1.156 (	0.950-1.406)	0.148	0.011	
Design         Design         42         0.924 (0.826-1.034)         0.170         0.000         73.10         0.988 (0.897-1.087)         0.800         0.000         72           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           Anome Devide and the formation of 0 and for the homomonic set (P-1) is 0.000         73.90         0.955 (0.843-1.081)         0.465         0.000         82	LC 9 0.858 (0.771–0.955) 0.005	0.005	0.158	32.50	0.997 (	0.834-1.191)	0.973	0.019	
PB         42         0.924 (0.826-1.034)         0.170         0.000         72           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           More a Partine Marce Instrument of Date for Instrument of Date Instrument of Date Instrument of Da	Design								
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           Monor Product Mark Mark Mark Mark Mark Mark Mark Mark	PB 42 0.924 (0.826–1.034) 0.170	0.170	0.000	78.10	0.988 (	0.897–1.087)	0.800	0.000	
Netro Briden Metric model use used when Durlin of O test for heteroconsist sets (D-II) is CONE, etherwise fixed affect model use used (P. 0%-55% on heteroconsister) 55%, figh heteroconsister >55%, high heteroconsister >55%, high heteroconsister = 200, high heteroconsiste	HB 42 0.912 (0.823–1.010) 0.078	0.078	0.000	73.90	0.955 (	0.843-1.081)	0.465	0.000	
	<b>Notes:</b> Random-effects model was used when P-value of 0-test for heterogeneity test (P–H) is <0.03; c	heity test (P–H) is $< 0.0$	5: otherwise. fi	xed-effect model was	used. P: 0%–25%.	no heterogeneit	v: 25%–50%. modest heteroge	eneity: ≥50%. his	gh heterog

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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<sup>101</sup> found that the C allele had the effect of increasing cancer risk in gastric cancer, and Ma et al<sup>102</sup> found that TT could decrease the risk of colorectal cancer. Moreover, Wang et al<sup>103</sup> and Zhang et al<sup>104</sup> 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;<sup>105</sup> 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,<sup>106,107</sup> which is identified as a key factor in oncogenesis, and contributes to regulate the translation or degradation of messenger RNA (mRNA).<sup>23</sup> Hoffman et al<sup>5</sup> 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<sup>7</sup> and CRC<sup>42</sup> tissues. Xu et al<sup>108</sup> have shown that miR-196a2 rs11614913 CC is associated with significantly increased expression of mature miR-196a

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 <sup>7</sup>	*	*	*	*	**	*	*	NA
Hu et al <sup>35</sup>	*	*	NA	*	**	*	*	NA
Tian et al <sup>3</sup>	*	*	NA	*	*	*	*	NA
Hoffman et al⁵	*	*	*	*	*	*	*	NA
Catucci et al <sup>36</sup>	*	*	NA	*	**	NA	*	NA
Wang et al <sup>38</sup>	*	*	NA	*	**	*	*	NA
Okubo et al <sup>83</sup>	*	*	*	*	**	*	*	NA
Peng et al⁴	*	*	NA	*	**	NA	*	NA
Srivastava et al <sup>10</sup>	*	*	NA	*	**	*	*	NA
Dou et al <sup>6</sup>	*	*	NA	NA	*	NA	*	NA
Li et al <sup>9</sup>	*	*	*	*	**	NA	*	NA
Akkiz et al <sup>8</sup>	*	*	NA	*	**	NA	*	NA
Liu et al <sup>11</sup>	*	*	NA	*	*	*	*	NA
Kim et al <sup>110</sup>	*	*	NA	NA	*	*	*	NA
Catucci et al <sup>36</sup>	*	*	*	*	**	*	*	NA
Christensen et al <sup>37</sup>	*	*	NA	*	**	*	*	NA
Mittal et al41	*	*	NA	*	**	*	*	NA
Jedlinski et al40	*	*	*	*	**	NA	*	NA
Zhan et al42	*	*	NA	*	*	NA	*	NA
Zhou et al43	*	*	NA	*	**	NA	*	NA
Vinci et al <sup>111</sup>	*	*	NA	*	**	*	*	NA
Hong et al <sup>2</sup>	*	*	NA	*	*	*	*	NA
George et al <sup>39</sup>	*	*	NA	*	**	*	*	NA
Linhares et al45	*	*	NA	*	**	*	*	NA
Chen et al44	*	*	NA	*	**	NA	*	NA
Min et al <sup>24</sup>	*	*	NA	*	**	*	*	NA
Zhu et al47	*	*	NA	*	**	*	*	NA
Hezova et al <sup>25</sup>	*	*	NA	*	**	NA	*	NA

(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 <sup>100</sup>	*	*	*	*	**	*	*	NA
Ahn et al <sup>48</sup>	*	*	NA	*	**	*	*	NA
Yoon et al <sup>46</sup>	*	*	NA	*	**	*	*	NA
Zhang et al <sup>104</sup>	*	*	*	*	**	NA	*	NA
Chu et al <sup>87</sup>	*	*	ΝΔ	*	**		*	NIΔ
	*	*	*	*	**		*	
Vinci et al	*	*	*	*	**		*	
Limar of all <sup>12</sup>	*	*	ΝΙΑ	ΝΙΑ	**	*	*	
	*	*		*	**	*	*	
Torreib at al <sup>98</sup>	*	*		*	**	*	*	
Mang at al <sup>53</sup>	*	*		*	**		*	
	*	*			**		*	
Znang et also	*	*	INA *	INA *	**	INA *	*	
Han et al"	*	*	*	*	**	*	* *	INA NA
I ong et al <sup>65</sup>	т *	*	NA	*	non deste	* *	<b></b>	
Pavlakis et al <sup>73</sup>	*	*	NA	*	**	*	<b>个</b>	NA
Pu et al®*	*	*	*	*	**	NA	*	NA
Bansal et al <sup>36</sup>	*	*	NA	*	**	*	*	NA
Kupcinskas et al <sup>62</sup>	*	*	*	*	**	*	*	NA
Qu et al <sup>64</sup>	*	*	NA	NA	**	*	*	NA
Wang et al <sup>66</sup>	*	*	NA	*	**	*	*	NA
Dikeakos et al <sup>58</sup>	*	*	NA	*	**	*	*	NA
Qi et al <sup>86</sup>	*	*	NA	*	**	NA	*	NA
Chu et al <sup>57</sup>	*	*	*	*	*	*	*	NA
Parlayan et al <sup>115</sup>	*	*	*	*	**	*	*	NA
Li et al <sup>63</sup>	*	*	NA	*	**	*	*	NA
Du et al <sup>59,60</sup>	*	*	NA	*	*	NA	*	NA
Omrani et al <sup>85</sup>	*	*	NA	*	**	*	*	NA
Kou et al <sup>91</sup>	*	*	*	*	**	*	*	NA
Roy et al <sup>94</sup>	*	*	NA	*	**	*	*	NA
Li et al <sup>63</sup>	*	*	NA	*	**	NA	*	NA
Deng et al <sup>67</sup>	*	*	*	*	**	NA	*	NA
Qi et al <sup>72</sup>	*	*	NA	*	**	NA	*	NA
Dikaiakos et al <sup>68</sup>	*	*	*	*	*	*	*	NA
Li et alº <sup>7</sup>	*	*	NA	NA	**	*	*	NA
Li et al <sup>o</sup>	*	*	INA *	INA *	**	*	*	
NIKOIIC et al	*	*	NIA	NIA	**		*	
Sushma et al <sup>97</sup>	*	*		*	**	*	*	NA
Sodhi et al <sup>95</sup>	*	*	*	*	**	*	*	NA
liang et al <sup>26</sup>	*	*	NA	*	**	*	*	NA
Dai et al <sup>74</sup>	*	*	NA	*	**	NA	*	NA
Zhao et al <sup>82</sup>	*	*	NA	*	**	*	*	NA
Song et al <sup>79</sup>	*	*	*	*	*	NA	*	NA
Shen et al <sup>78</sup>	*	*	NA	*	**	*	*	NA
Li et al <sup>75</sup>	*	*	NA	*	**	NA	*	NA
Li et al <sup>76</sup>	*	*	NA	*	*	*	*	NA
Xu et al <sup>80</sup>	*	*	NA	NA	*	*	*	NA
Qiu and Liu <sup>17</sup>	*	*	*	*	*	*	*	NA
Jiang et al <sup>20</sup>	* *	т *	Υ ΝΙΑ	~ *	*	т *	т *	
I IN ET al"	*	*	INA *	*	**		*	
Linding et al?	*	*	*	*	*	*	*	
Toraih et al <sup>98</sup>	*	*	NA	*	**		*	NA
Morales et al <sup>92</sup>	*	*	NA	*	**	*	*	NA
Gu and Tu <sup>88</sup>	*	*	NA	*	*	*	*	NA
Hashemi et al <sup>89</sup>	*	*	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.

### Table 3 (Continued)

Study ID	OR (95% CI)	% weight
LC Hu et al <sup>7</sup> Tian et al <sup>9</sup> Kim (2010) Vinci (2011) Hong et al <sup>40</sup> Parlayan (2014) Sodhi et al <sup>40</sup> Parlayan (2014) Sodhi et al <sup>40</sup> Subtotal (l <sup>2</sup> =48.1%, p=0.052)	0.78 (0.44–1.40) 0.79 (0.62–1.01) 0.73 (0.54–0.98) 1.99 (0.78–5.08) 0.80 (0.54–1.18) 0.61 (0.30–1.24) 0.97 (0.56–1.67) 3.43 (1.42–8.27) 0.87 (0.63–1.20) 0.88 (0.72–1.09)	1.11 1.59 1.52 0.70 1.39 0.95 1.17 0.76 1.49 <b>10.69</b>
Hu et al <sup>55</sup> Hoffman et al <sup>56</sup> Catucci et al <sup>56</sup> Catucci et al <sup>56</sup> Linhares et al <sup>56</sup> Dai et al <sup>72</sup> He et al <sup>60</sup> Dai et al <sup>72</sup> He et al <sup>60</sup> Omrani et al <sup>56</sup> Subtotal ( <i>l</i> = <i>1</i> 2.8%, <i>p</i> =0.000) Esc.C	0.73 (0.57-0.93) 2.15 (1.37-3.38) 0.93 (0.77-1.12) 1.02 (0.80-1.29) 0.91 (0.50-1.66) 1.56 (1.13-2.41) 0.58 (0.26-1.29) 0.71 (0.33-1.55) 0.45 (0.24-0.84) 0.86 (0.59-1.26) 0.54 (0.38-0.75) 1.19 (0.58-2.47) 0.69 (0.62-1.28) (Excluded) 0.81 (0.74-1.11)	1.60 1.30 1.66 1.09 1.41 0.85 0.87 1.06 1.41 1.48 0.92 1.43 0.00 <b>16.66</b>
Last         Image: Algebra and Al	0.37 (0.25–0.57) 1.61 (0.82–3.18) 1.26 (0.83–1.90) 0.62 (0.40–0.95) 1.19 (0.86–1.65) 0.80 (0.66–0.98) 0.85 (0.60–1.22)	1.36 0.98 1.35 1.33 1.49 1.65 <b>8.16</b>
GC Okubo et al <sup>43</sup> Peng et al <sup>4</sup> Ahm (2012) Wang et al <sup>54</sup> Pu et al <sup>54</sup> Jiang et al <sup>56</sup> Jiang et al <sup>56</sup> Gu and Tu <sup>58</sup> Hashemi et al <sup>169</sup> Subtotal ( <i>P=</i> 91.5%, <i>p=</i> 0.000)	0.92 (0.68–1.23) 0.63 (0.37–1.08) 0.81 (0.55–1.18) 1.41 (1.07–1.86) 0.75 (0.42–1.34) 0.07 (0.04–0.12) 1.23 (0.95–1.60) 0.37 (0.17–0.81) 2.40 (1.31–4.40) 1.70 (0.76–3.83) 0.77 (0.48–1.23)	1.53 1.18 1.41 1.55 1.12 1.08 1.57 0.87 1.08 0.83 <b>12.22</b>
Others       Srivastava et al <sup>10</sup> Dou et al <sup>8</sup> Mittal et al <sup>14</sup> Zhou et al <sup>19</sup> George et al <sup>190</sup> Torain et al <sup>10</sup> Dou et al <sup>10</sup> Dou et al <sup>10</sup> Dou et al <sup>10</sup> Dou et al <sup>10</sup> Sub et al <sup>10</sup> Deng et al <sup>10</sup> Deng et al <sup>10</sup> Sushma et al <sup>10</sup> Sun et al <sup>10</sup>	0.71 (0.35–1.45) 1.17 (0.85–1.61) 0.51 (0.18–1.48) 0.88 (0.52–1.47) 0.58 (0.15–2.19) 2.10 (0.95–4.60) 0.44 (0.61–1.17) - 1.24 (0.97–1.60) 1.91 (1.21–3.02) 0.93 (0.55–1.60) 0.53 (0.33–0.84) 0.79 (0.48–1.29) 0.23 (0.09–0.60) 0.56 (0.38–0.81) 0.56 (0.38–0.81) 0.59 (0.22–1.11)	0.95 1.50 0.60 1.21 0.44 0.85 1.48 0.77 1.59 1.30 1.18 1.28 1.28 1.24 0.69 1.42 1.05
Subtotal (P=68.3%, p=0.000) HCC Li et al <sup>®</sup> Akkz (2010) Zhang et al <sup>®6</sup> Gli et al <sup>®6</sup> Li et al <sup>®6</sup> Li et al <sup>®6</sup> Qi et al <sup>®7</sup> Xu et al <sup>®6</sup> Qi and Liu <sup>77</sup> Jiang et al <sup>®6</sup> Zhang et al <sup>®6</sup> Subtotal (P=70.5%, p=0.000)	0.86 (0.68-1.08) 0.57 (0.35-0.92) 0.41 (0.22-0.77) 0.69 (0.53-0.89) 1.07 (0.83-1.37) 0.78 (0.48-1.27) 1.13 (0.69-1.85) 0.53 (0.34-0.85) 2.29 (134-3.89) 0.41 (0.18-0.33) 0.57 (0.37-0.88) 0.59 (0.35-0.98) 0.84 (0.61-1.17) 0.90 (0.50-1.60) 2.25 (0.93-5.47) 0.79 (0.63-0.99)	17.54 1.25 1.06 1.58 1.59 1.25 1.24 1.28 1.34 1.34 1.32 1.34 1.22 1.34 1.22 1.48 1.12 0.75 17.16
HNC Liu et al <sup>11</sup> Chu et al <sup>87</sup> Roy et al <sup>94</sup> Li et al <sup>95</sup> Christensen et al <sup>37</sup> Subtotal ( <i>l</i> <sup>2</sup> =2.5%, <i>p</i> =0.380)	- 1.05 (0.82–1.34) - 1.57 (1.04–2.37) 1.34 (0.84–2.14) 1.24 (0.97–1.60) (Excluded) 1.22 (1.04–1.42)	1.59 1.36 1.28 1.59 0.00 <b>5.82</b>
CRC Zhan et al <sup>42</sup> Chen et al <sup>44</sup> Min et al <sup>44</sup> Zhu et al <sup>47</sup> Zhan et al <sup>50</sup> Zhang et al <sup>50</sup> Zhang et al <sup>50</sup> Dikaiakos et al <sup>62</sup> Subtotal (l <sup>2</sup> =87.6%, p=0.000)	- 0.57 (0.37-0.88) 1.14 (0.64-2.02) 0.70 (0.49-1.01) 0.65 (0.47-0.91) 1.25 (0.66-2.38) 0.95 (0.66-1.38) 1.46 (0.60-3.53) 1.46 (0.60-3.53) 1.26 (0.74-2.74) 1.26 (0.74-2.14) 1.02 (0.54-1.94) 1.19 (0.77-1.86)	1.34 1.13 1.44 1.47 1.03 1.42 0.76 0.95 1.19 1.04 <b>11.76</b>
Uveraii (r <sup>i</sup> =78.8%, p=0.000) ♀	0.90 (0.81–1.00)	100
0.0362 1	27.6	

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.

Study ID	OR (95% CI)	% weight
LC Hu et al <sup>7</sup> Tian et al <sup>9</sup> Kim (2010) Vinci (2011) Hong et al <sup>9</sup> Parlayan (2014) Sodhi et al <sup>96</sup> Yin et al <sup>91</sup> Subtotal (l <sup>2</sup> =32.5%, p=0.158)	0.88 (0.56−1.39) 0.91 (0.75−1.10) 0.81 (0.63−1.04) 1.60 (0.66−3.88) 0.68 (0.50−0.92) 0.68 (0.59−1.35) 2.54 (1.09−5.91) 0.84 (0.65−1.09) 0.84 (0.65−1.09)	1.10 1.65 1.54 0.52 1.41 0.94 1.18 0.55 1.52 <b>10.43</b>
BRC Hu et al <sup>35</sup> Hoffman et al <sup>96</sup> Catucci et al <sup>96</sup> Catucci et al <sup>96</sup> Linhares et al <sup>96</sup> Judinski et al <sup>96</sup> Linhares et al <sup>96</sup> Zhang et al <sup>96</sup> Dai et al <sup>97</sup> He et al <sup>90</sup> Dai et al <sup>72</sup> He et al <sup>90</sup> Ormani et al <sup>86</sup> Subtotal ( <i>l</i> <sup>2</sup> =64.4%, <i>p</i> =0.001)	0.82 (0.68-0.98) 1.95 (1.27-2.98) 0.94 (0.79-1.12) 1.01 (0.81-1.27) 0.97 (0.56-1.66) 0.82 (0.57-1.16) 0.75 (0.36-1.60) 0.62 (0.45-0.86) 0.98 (0.74-1.30) 0.65 (0.48-0.86) 1.45 (0.80-2.64) 0.94 (0.81-1.09)	1.66 1.16 1.59 0.94 1.39 1.30 0.65 1.37 1.46 1.45 0.85 1.34 0.00 <b>16.85</b>
ESCC Wang et al <sup>36</sup> Umar (2013) Ou et al <sup>86</sup> Wang et al <sup>86</sup> Subtotal ( <i>i</i> <sup>2</sup> =81.3%, <i>p</i> =0.000)		1.28 0.76 1.39 1.24 1.52 1.72 <b>7.91</b>
GC Okubo et al <sup>143</sup> Peng et al <sup>4</sup> Ahn (2012) Wang et al <sup>25</sup> Pu et al <sup>24</sup> Jiang et al <sup>26</sup> Li et al <sup>16</sup> Gu and Tu <sup>88</sup> Subtotal ( <i>I</i> =83.9%, <i>p</i> =0.000)	0.93 (0.75-1.16) 0.82 (0.52-1.31) 0.87 (0.65-1.16) 1.24 (1.00-1.54) 0.92 (0.57-1.50) 0.18 (0.10-0.32) 1.20 (0.99-1.46) 0.69 (0.45-1.04) 1.88 (1.14-3.12) 1.88 (1.73-3.42) 0.91 (0.70-1.19)	1.59 1.09 1.44 1.60 1.04 0.91 1.64 1.18 1.01 0.63 <b>12.14</b>
Others         Srivatza et al <sup>10</sup> Dou et al <sup>4</sup> Mitta et al <sup>11</sup> Zhou et al <sup>43</sup> George et al <sup>10</sup> Torain et al <sup>40</sup> Torain et al <sup>40</sup> Pavlakis et al <sup>80</sup> Li et al <sup>40</sup> Du et al <sup>40</sup> Sushma et al <sup>80</sup> Sun et al <sup>80</sup> Subtotal (l <sup>2</sup> e67.1%, p=0.000)	0.92 (0.64-1.33) 0.90 (0.71-1.14) 0.41 (0.14-1.15) 0.93 (0.63-1.38) 0.42 (0.11-1.56) 1.63 (0.77-3.46) 0.71 (0.56-0.91) 1.54 (0.89-2.65) 1.26 (1.04-1.52) 1.26 (1.04-1.52) 1.21 (0.88-1.66) 0.66 (0.48-0.90) 0.65 (0.28-1.04) 0.65 (0.28-1.04) 0.61 (0.48-0.82) 0.80 (0.50-1.27) 0.80 (0.56-1.06)	1.29 1.56 0.41 1.23 0.28 0.65 1.55 0.94 1.65 1.40 1.17 1.39 1.40 0.79 1.44 1.09 1.09
HCC Liet al <sup>®</sup> Akkz (2010) Zhang et al <sup>®5</sup> Han et al <sup>®5</sup> Oi et al <sup>®6</sup> Chu et al <sup>®7</sup> Liet al <sup>®6</sup> Liet al <sup>®6</sup> Qiu et al <sup>®7</sup> Liet al <sup>®6</sup> Zhang et al <sup>®6</sup> Zhang et al <sup>®6</sup> Subtotal ( <i>P</i> =67.4%, <i>p</i> =0.000)	0.66 (0.46-0.96) 0.49 (0.28-0.86) 0.85 (0.70-1.03) 0.99 (0.82-1.20) 0.56 (0.39-0.79) 1.28 (0.88-1.87) 0.66 (0.44-0.99) 1.87 (1.15-3.04) 0.45 (0.24-0.85) 0.67 (0.47-0.94) 0.70 (0.47-1.04) 0.77 (0.56-0.91) 0.87 (0.59-1.28) 1.59 (0.70-3.62) 0.80 (0.68-0.94)	1.27 0.90 1.65 1.65 1.25 1.20 1.04 0.80 1.32 1.21 1.55 1.25 0.58 <b>16.99</b>
HNC Liu et al <sup>11</sup> Chu et al <sup>17</sup> Roy et al <sup>14</sup> Li et al <sup>16</sup> Christensen et al <sup>17</sup> Subtotal ( <i>P</i> =90.1%, <i>p</i> =0.000)	0.97 (0.78–1.21) 0.90 (0.68–1.20) 1.23 (0.78–1.92) 1.91 (1.59–2.29) (Excluded) 1.20 (0.80–1.82)	1.60 1.46 1.11 1.67 0.00 <b>5.83</b>
CRC Zhan et al <sup>42</sup> Chen et al <sup>44</sup> Min et al <sup>44</sup> Min et al <sup>44</sup> Zhang et al <sup>47</sup> Hezova et al <sup>45</sup> Zhang et al <sup>40</sup> Vinci (2013) Lv et al <sup>47</sup> Mupcinskas et al <sup>46</sup> Subtotal ( <i>l</i> =75.9%, <i>p</i> =0.000) Overall ( <i>l</i> =75.8%, <i>p</i> =0.000)	0.67 (0.47–0.94) 1.08 (0.69–1.69) 0.93 (0.70–1.23) 0.71 (0.54–0.92) 1.31 (0.72–2.40) 0.91 (0.70–1.19) 1.23 (0.55–2.87) 2.37 (1.72–3.25) 1.12 (0.68–1.85) 1.22 (0.82–1.80) 0.92 (0.85–0.99)	1.32 1.12 1.47 1.50 0.84 1.50 0.55 1.39 1.02 1.23 11.94 100
0.103	 9.67	

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.<sup>104,109</sup> 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<sup>109</sup> 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.<sup>101–103,109</sup> 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 SI** 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% Con	f Interval)		Kou et al <sup>91</sup>	0.907
Companison	orday officied	Lotinate				Roy et al <sup>94</sup>	0.896
			Lower CI	Upper CI		Li et al <sup>63</sup>	0.896
TT vs CC	Hu et al <sup>7</sup>	0.902	0.814	0.999		Deng et al <sup>67</sup>	0.900
	Hu et al³⁵	0.904	0.815	1.002		Qi et al <sup>72</sup>	0.907
	Tian et al <sup>3</sup>	0.902	0.814	1.001		Dikaiakos et al <sup>68</sup>	0.899
	Hoffman et al⁵	0.890	0.805	0.985		Li et al <sup>69</sup>	0.890
	Catucci et al <sup>36</sup>	0.900	0.811	1.000		Li et al <sup>69</sup>	0.907
	Wang et al <sup>38</sup>	0.911	0.824	1.008		Nikolic et al <sup>71</sup>	0.902
	Okubo et al <sup>83</sup>	0.900	0.812	0.998		He et al <sup>90</sup>	0.901
	Peng et al⁴	0.904	0.816	1.002		Sushma et al <sup>97</sup>	0.909
	Srivastava et al <sup>10</sup>	0.903	0.815	1.000		Sodhi et al <sup>95</sup>	0.891
	Dou et al <sup>6</sup>	0.897	0.809	0.994		Jiang et al <sup>26</sup>	0.896
	Li et al <sup>9</sup>	0.906	0.818	1.003		Toraih et al <sup>98</sup>	0.894
	Akkiz et al <sup>8</sup>	0.908	0.820	1.005		Dai et al <sup>74</sup>	0.908
	Liu et al <sup>11</sup>	0.898	0.810	0.997		Zhao et al <sup>82</sup>	0.898
	Kim et al <sup>101</sup>	0.904	0.815	1.002		Song et al <sup>79</sup>	0.907
	Catucci et al <sup>36</sup>	0.899	0.810	0.997		Shen et al <sup>78</sup>	0.902
	Christensen et al <sup>37</sup>	0.900	0.813	0.997		Li et al <sup>75</sup>	0.907
	Mittal et al41	0.904	0.816	1.001		Li et al <sup>76</sup>	0.906
	Jedlinski et al40	0.900	0.813	0.998		Xu et al <sup>80</sup>	0.906
	Zhan et al⁴²	0.906	0.818	1.004		Qiu et al <sup>77</sup>	0.905
	Zhou et al <sup>43</sup>	0.901	0.813	0.998		liang et al <sup>26</sup>	0.901
	Vinci et al <sup>102</sup>	0.895	0.809	0.992		Yin et al <sup>81</sup>	0.901
	Hong et al <sup>2</sup>	0.902	0.814	1.000		Zhang et al <sup>99</sup>	0.901
	George et al <sup>39</sup>	0.902	0.815	0.999		Sun et al <sup>96</sup>	0.904
	Linhares et al45	0.893	0.806	0.988		Toraih et al <sup>98</sup>	0.894
	Chen et al44	0.898	0.811	0.995		Morales et al <sup>92</sup>	0.901
	Min et al <sup>24</sup>	0.904	0.815	1.002		Gu et al <sup>88</sup>	0.891
	Zhu et al47	0.905	0.816	1.003		Hashemi et al <sup>89</sup>	0.896
	Hezova et al <sup>25</sup>	0.897	0.810	0.994		Combined <sup>2–10,25,26,35–107</sup>	0.900
	Zhang et al <sup>100</sup>	0.900	0.812	0.998	TT vs TC+CC	Hu et al <sup>7</sup>	0.918
	Yoon et al <sup>46</sup>	0.904	0.816	1.001	11 13 10100	Hu et al <sup>35</sup>	0.920
	Zhang et al <sup>99</sup>	0.904	0.816	1.001		Tian et al <sup>3</sup>	0.918
	Chu et al <sup>87</sup>	0.894	0.807	0.990		Hoffman et al <sup>5</sup>	0.910
	Vinci et al <sup>105</sup>	0.897	0.810	0.994		Catucci et al <sup>36</sup>	0.917
	Ahn et al <sup>103</sup>	0.902	0.814	1 000		Wang at al <sup>38</sup>	0.919
	l v et al <sup>51</sup>	0.878	0.798	0.965		Okubo ot al <sup>83</sup>	0.720
	Umar et al <sup>104</sup>	0.895	0.808	0.992		Pong of al <sup>4</sup>	0.717
	Wei et al <sup>106</sup>	0.896	0.809	0.993			0.717
	Wang et al <sup>53</sup>	0.894	0.807	0.990		Dou ot al	0.910
	Zhang et al <sup>55</sup>	0.074	0.816	1.003		Li ot al <sup>9</sup>	0.710
	Han of al <sup>49</sup>	0.204	0.010	0.994			0.722
	Paylakis of al <sup>93</sup>	0.070	0.010	0.770		AKKIZ ET al	0.923
	Tong of al <sup>65</sup>	0.077	0.012	1,000		Liu et al <sup>10</sup>	0.717
	Pu of al <sup>84</sup>	0.201	0.015	1.000		Catucci et al <sup>36</sup>	0.920
	Bansal et al <sup>56</sup>	0.702	0.01-	1.000		Christensen et al <sup>37</sup>	0.918
	Kupcinskas at al <sup>62</sup>	0.702	0.015	0.994		Mittal et al <sup>41</sup>	0.921
		0.07/	0.007	1.002		Jedlinski et al <sup>40</sup>	0.917
	Vang at all	0.705	0.017	1.003		Zhan et al <sup>42</sup>	0.922
	Dileales 158	0.07/	0.007	0.774		Zhou et al <sup>43</sup>	0.918
		0.925	0.043	1.015		Vinci et al <sup>102</sup>	0.915
		0.902	0.014	0.005		Hong et al <sup>2</sup>	0.922
	Chu et al"	0.848	0.810	0.775		George et al <sup>39</sup>	0.920

0.900

0.896

0.892

0.900

Estimate (95% Conf Interval)

0.812

0.808

0.806

0.813

0.819

0.809

0.808

0.812

0.819

0.812

0.805

0.819

0.814

0.813

0.821

0.806

0.808

0.807

0.820

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0.805

0.809

0.813

0.851

0.852

0.850

0.844

0.849

0.862

0.850

0.852

0.850

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0.854

0.850 0.849

0.854

0.853

Lower CI Upper CI

0.997

0.993

0.987

0.997

1.004

0.993

0.993

0.997

1.005

0.996

0.985

1.004

1.000

0.999

1.006

0.986

0.993

0.990

1.005

0.995

1.004

1.002

1.005

1.004

1.004

1.003

1.000

0.999

0.998

1.002

0.990

0.999

0.986

0.992

0.997

0.991

0.993

0.991

0.980

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0.992 (Continued)

Table SI (Continued)

Comparison Study omitted

Parlayan et al<sup>107</sup>

Omrani et al<sup>85</sup>

Li et al<sup>63</sup>

Du et al<sup>59</sup>

#### Table SI (Continued)

Comparison	Study omitted	Estimate	(95% Conf Interval)				
			Lower CI Upper Cl				
	Linhares et al <sup>45</sup>	0.913	0.847	0.985			
	Chen et al <sup>44</sup>	0.916	0.849	0.988			
	Min et al <sup>24</sup>	0.918	0.850	0.990			
	Zhu et al <sup>47</sup>	0.921	0.854	0.994			
	Hezova et al <sup>20</sup>	0.915	0.848	0.987			
	Yoon et al <sup>46</sup>	0.910	0.853	0.993			
	Zhang et al <sup>99</sup>	0.919	0.852	0.992			
	Chu et al <sup>87</sup>	0.918	0.851	0.991			
	Vinci et al <sup>105</sup>	0.919	0.851	0.991			
	Ahn et al <sup>103</sup>	0.916	0.850	0.988			
	Lv et al <sup>51</sup>	0.905	0.842	0.974			
	Umar et al <sup>104</sup>	0.914	0.848	0.986			
	Wei et al <sup>106</sup>	0.918	0.850	0.990			
	Vvang et al <sup>55</sup> Zhang et al <sup>55</sup>	0.913	0.846	0.985			
	Han et al <sup>49</sup>	0.917	0.849	0.992			
	Pavlakis et al <sup>93</sup>	0.921	0.854	0.994			
	Tong et al <sup>65</sup>	0.913	0.847	0.985			
	Pu et al <sup>84</sup>	0.918	0.851	0.990			
	Bansal et al <sup>56</sup>	0.919	0.852	0.991			
	Kupcinskas et al <sup>62</sup>	0.916	0.849	0.988			
	Qu et al <sup>64</sup>	0.923	0.855	0.995			
	Wang et al <sup>66</sup>	0.916	0.848	0.988			
	Dikeakos et al <sup>58</sup>	0.931	0.866	1.001			
	Qi et al <sup>57</sup>	0.924	0.857	0.996			
	Parlavan et al <sup>107</sup>	0.918	0.851	0.980			
	lietal <sup>63</sup>	0.913	0.846	0.985			
	Du et al <sup>59</sup>	0.914	0.847	0.986			
	Omrani et al <sup>85</sup>	0.918	0.851	0.989			
	Kou et al <sup>91</sup>	0.921	0.854	0.994			
	Roy et al <sup>94</sup>	0.915	0.848	0.987			
	Li et al <sup>63</sup>	0.906	0.845	0.971			
	Deng et al <sup>67</sup>	0.913	0.847	0.985			
	Qi et al <sup>2</sup>	0.923	0.856	0.995			
	Li et al <sup>69</sup>	0.714	0.040	0.767			
	Lietal <sup>69</sup>	0.922	0.855	0.995			
	Nikolic et al <sup>71</sup>	0.919	0.852	0.991			
	He et al <sup>90</sup>	0.917	0.850	0.990			
	Sushma et al <sup>97</sup>	0.921	0.855	0.994			
	Sodhi et al <sup>95</sup>	0.913	0.847	0.984			
	Jiang et al <sup>26</sup>	0.914	0.847	0.986			
	Toraih et al <sup>98</sup>	0.914	0.848	0.986			
	Dai et al <sup>74</sup>	0.922	0.855	0.995			
	Zhao et al <sup>82</sup>	0.914	0.848	0.986			
	Song et al <sup>79</sup>	0.923	0.856	0.995			
	Shen et al <sup>78</sup>	0.918	0.849	0.992			
	Li et al <sup>75</sup>	0.921	0.854	0.993			
	Li et al <sup>76</sup>	0.923	0.856	0.995			
	Xu et al <sup>80</sup>	0.922	0.854	0.994			
	Qiu et al <sup>77</sup>	0.921	0.854	0.993			
	Jiang et al <sup>26</sup>	0.921	0.854	0.994			
	Yin et al <sup>81</sup>	0.919	0.851	0.992			
	Zhang et al <sup>99</sup>	0.918	0.851	0.991			
	Sun et al%	0.919	0.852	0.992			
	Toraih et al <sup>98</sup>	0.915	0.848	0.986			
	Morales et al <sup>92</sup>	0.918	0.851	0.991			
	Gu et al <sup>88</sup>	0.911	0.845	0.982			
	Hashemi et al <sup>89</sup>	0.915	0.848	0.986			
	Combined <sup>2-10,25,26,35-107</sup>	0.918	0.851	0.989			

Table S2 P-values of Begg's and Egger	's test for th	e 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
		НВ	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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