Technology in Cancer Research & Treatment
Volume 21: 1-21

DOI: 10.1177/15330338221109798
journals.sagepub.com/home/tct
SAGE

Effect of *miR-196a2* rs11614913 Polymorphism on Cancer Susceptibility: Evidence From an Updated Meta-Analysis

Md. Abdul Aziz, MPharm[1], Tahmina Akter, MPharm[2,3], and Mohammad Safiqul Islam, PhD[2,3]

Abstract

Background: *MiR-196a2* rs11614913 polymorphism has been studied in a wide range of cancers throughout the years. Despite a large number of epidemiological studies performed in almost all ethnic populations, the contribution of this polymorphism to cancer risk is still inconclusive. Therefore, this updated meta-analysis was performed to estimate a meticulous correlation between *miR-196a2* rs11614913 variant and cancer susceptibility. **Methods:** A systematic study search was carried out using PubMed, ScienceDirect, CNKI, EMBASE, Scopus, and Google Scholar databases following PRISMA guidelines to find necessary literature up to December 15, 2021. Pooled odds ratios with corresponding 95% confidence intervals were estimated using RevMan 5.4 based on ethnicities, cancer types, control sources, and genotyping methods. **Results:** A total of 152 studies, including 120 135 subjects (53 818 patients and 66 317 controls; 140 studies, after removing studies that deviated from HWE: 51 459 cases and 62 588 controls), were included in this meta-analysis. Quantitative synthesis suggests that the *miR-196a2* rs11614913 genetic variant is significantly correlated with the reduced risk of overall cancer in CDM2, CDM3, RM, and AM (odds ratio < 1 and $P < .05$). It is also observed from ethnicity-based subgroup analysis that rs11614913 polymorphism is significantly ($P < .05$) linked with cancer in the Asian (in CDM2, CDM3, RM, AM) and the African population (in CDM1, CDM3, ODM). Stratified analysis based on the cancer types demonstrated a significantly decreased correlation for breast, hepatocellular, lung, and gynecological cancer and an increased association for oral and renal cell cancer. Again, the control population-based subgroup analysis reported a strongly reduced correlation for HB population in CDM2, RM, and AM. A substantially decreased risk was also observed for other genotyping methods in multiple genetic models. **Conclusions:** *MiR-196a2* rs11614913 variant is significantly correlated with overall cancer susceptibility. Besides, rs11614913 is correlated with cancer in Asians and Africans. It is also correlated with breast, gynecological, hepatocellular, lung, oral, and renal cell cancer.

Keywords

miRNAs, *MiR-196a2*, cancer, polymorphism, meta-analysis

Abbreviations

AM, allele model; ARMS, amplification refractory mutation system; CDM1, codominant model 1; CDM2, codominant model 2; CDM3, codominant model 3; CI, confidence interval; DM, dominant model; FE, fixed-effects; HB, hospital-based; HOX, homeobox; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; ODM, over-dominant model; OR, odds ratio; PB, population-based; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; RE, random-effects; RM, recessive model

Received: February 17, 2022; Revised: May 21, 2022; Accepted: June 8, 2022.

[1] Department of Pharmacy, Faculty of Pharmacy and Health Sciences, State University of Bangladesh, Dhaka, Bangladesh
[2] Department of Pharmacy, Faculty of Science, Noakhali Science and Technology University, Noakhali, Bangladesh
[3] Laboratory of Pharmacogenomics and Molecular Biology, Department of Pharmacy, Noakhali Science and Technology University, Noakhali, Bangladesh

Corresponding Author:
Mohammad Safiqul Islam, Department of Pharmacy, Noakhali Science and Technology University, Noakhali-3814, Bangladesh.
Emails: research_safiq@nstu.edu.bd; research_safiq@yahoo.com

Introduction

Cancer is one of the top global public health burdens, which ranks first or second in terms of deaths in many countries.[1,2] The latest statistics on worldwide cancer suggest that the ratio of cancer incidence and death is almost 1:5 and 1:6, respectively.[3] It is projected that there will be approximately 28.4 million new cancer incidences in 2040, which is an almost 47% rise over that of 2020 (19.3 million).[4] It has been alarmingly increasing in both developing and developed regions of the world, following a nonuniform pattern due to the complex interaction of multiple risk factors.[2] In addition, interactions between genetic and environmental components enhance the probability of different cancers.[5] Despite many efforts, there is still a long way to go in revealing the exact mechanism of cancer.

Recent advances in cancer research have demonstrated the significant link between noncoding RNAs and cancer progression. The microRNAs or miRNAs are relatively small noncoding RNAs that are described to be key players in the pathogenesis of cancer.[6,7] They have a significant role in post-transcriptional modification and possess both oncogenic and tumor-suppressive activities.[8] Aberrant expression of miRNAs has been studied for the etiopathology and development of various human cancers. Line of evidence reported that an individual miRNA could affect almost 200 genes. Surprisingly, greater than 50% of the microRNA genes are reported in cancer-susceptible areas of the human genome, and mature miRNAs have been found to control around 20% of human genes.[9–11]

MiR-196a2 is an important member of the miRNA-196 precursor family found in the homeobox (HOX) clusters region of the human genome.[12] An extensively studied *miR-196a2* variant is rs11614913 (C > T), which is investigated in a plethora of cancers, including breast cancer,[13–17] gastric cancer,[18–22] hepatocellular carcinoma,[23–25] colorectal cancer,[26–29] lung cancer,[30–32] gynecological cancer,[33–38] prostate cancer,[39–41] and so on. Despite a large number of studies performed in almost all ethnic populations, the contribution of rs11614913 polymorphism to cancer risk is still inconclusive. Therefore, this updated meta-analysis was performed to estimate a meticulous correlation between *miR-196a2* rs11614913 variant and cancer susceptibility based on the published case–control studies in different ethnicities.

Material and Methods

This updated meta-analysis was completed following the latest recommendations for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) by Page *et al*[42] and registered with INPLASY (https://inplasy.com/). The INPLASY registration number is INPLASY202250027.

Search Strategy of Literature

An organized online article search was carried out using PubMed, ScienceDirect, EMBASE, Scopus, CNKI, and Google Scholar databases to find all relevant literature using the following terms: *miR-196a2*, *microRNA-196a2*, *miRNA-196-a2*, *miR-196a*, 196a, rs11614913, polymorphism, single nucleotide polymorphism, SNP, variant, carcinoma, cancer, neoplasm, tumor, malignancy, either solely or in combination. For retrieving all possible publications, the reference list of the identified literature was also screened carefully. We did not implement any language restrictions in the literature search process. The search was limited to December 15, 2021.

Eligibility Criteria of Literature

Literature meeting the below criteria was incorporated in this meta-analysis: (a) analyzed the correlation between *miR-196a2* rs11614913 and cancer susceptibility, (b) designed as a case–control study (c) contained full-text, and (d) contained sufficient genotype frequencies for calculating odds ratio (OR) and 95% confidence interval (95% CI). On the other hand, literature with the below criteria was excluded: (a) systematic or narrative reviews, case reports, editorials, conference papers, and comments, (b) without a case–control design, (c) articles on animals or cell lines, and (d) without detailed genotype frequencies.

Data Extraction Procedure

All relevant data were collected from the selected studies utilizing a predesigned data extraction form and then cross-checked to confirm the consistency. The below-listed data was collected from each study: name of the main author, time of publication, country, type of malignancy, method of genotyping, source/type of controls, amount of cases and controls, amount of total participants, the frequency distribution of genotypes, and Hardy-Weinberg equilibrium (HWE) *P* value of controls.

For analytical purposes, we have categorized all information as follows: (a) ethnicities into Asian, Caucasian, and African, (b) cancers into the breast, gastric, gynecological (cervical, endometrial, ovarian), blood and bone marrow (acute leukemia, acute lymphocytic leukemia, multiple myeloma, chronic lymphocytic leukemia), glioma, hepatocellular carcinoma, colorectal, oral, prostate, esophageal, head and neck (head and neck squamous cell carcinoma, nasopharyngeal carcinoma, head and neck cancer), bladder, lung, and renal cell cancer, (c) sources of controls into hospital-based (HB) and population-based (PB), and methods of genotyping into the TaqMan, polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP), and others (ARMS (amplification refractory mutation system), Sequencing, MassARRAY).

Statistical Analysis

The review manager (RevMan) 5.4 for windows (The Cochrane Collaboration) was applied to perform the present meta-analysis. The significance of the correlation between rs11614913 variant and cancer susceptibility was evaluated via calculating ORs corresponding to 95% CIs. The ORs with 95% CIs have been

obtained assuming different genotypic and allelic comparisons, including codominant model 1 (CDM1-TC/CC), codominant model 2 (CDM2-TT/CC), codominant model 3 (CDM3-TT/TC), dominant model (DM-TT + TC/CC), recessive model (RM-TT/TC + CC), over-dominant model (ODM-TC/TT + CC), and allele model (AM-T/C). All of the above comparisons were implied for overall, ethnicity-based, cancer subtypes-based, control population-based, and genotyping methods-based analyses.

The variation in the outcomes of the study was measured through heterogeneity analysis applying the χ^2-based Q-test and analyzed through I^2. In terms of statistically significant heterogeneity ($P < .05$, or $I^2 \geq 50\%$), the random-effects (RE) model was applied (the DerSimonian and Laird technique).[43] In nonsignificant cases, the fixed-effects (FE) model was used (the Mantel-Haenszel technique).[44]

The consistency in the outcomes of the study and the influence of individual studies were measured through one-way sensitivity analysis. In this process, each study was deleted at a time and the values of ORs with corresponding 95% CIs were checked to determine any deviation. Any potential publication bias in the present meta-analysis was estimated using Egger's linear regression test via constructing funnel plots[45] and Begg-Mazumdar's rank correlation test.[46]

HWE P values for control sources were quantified utilizing the χ^2 test. The HWE P values were adjusted (corrected) by Benjamini and Hochberg's false discovery rate,[47] and all P values in this meta-analysis were regarded statistically significant if found to be <.05.

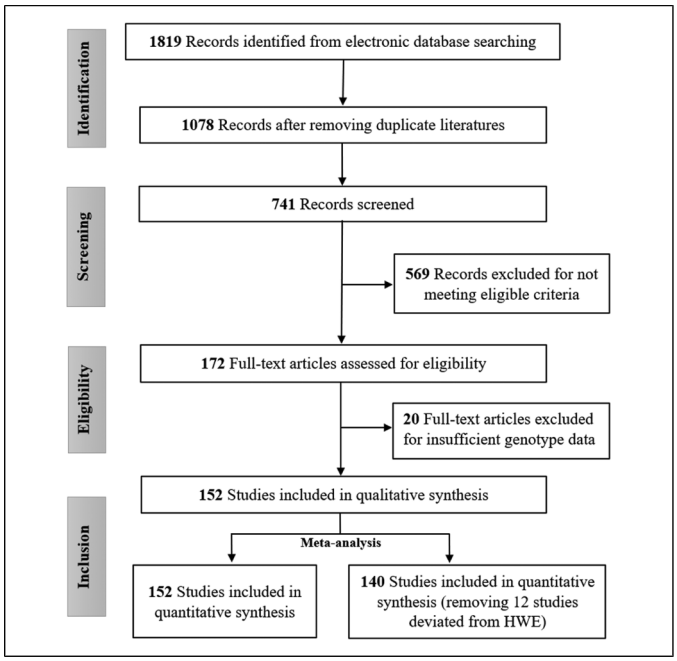

Figure 1. Study selection process according to PRISMA guidelines.

Results

Study Identification

From the initial search in online databases, we identified a total of 1819 initial records for *miR-196a2* rs11614913 polymorphism, from which 152 articles[13–41,48–163] were finally selected for the current meta-analysis, following the eligibility criteria mentioned above. The selection process of these studies based on the updated PRISMA guidelines is depicted in Figure 1. Overall, 120 135 subjects, including 53 818 patients with different cancers and 66 317 controls, are included in the analysis. After the adjustment of the HWE P values, 12 studies[13,48,66,83,96,103,105,114,124,128,129,161] were removed from the quantitative analysis, and all subgroup analyses were performed based on the remaining 140 studies. Table 1 represents the extracted characteristics or features of the incorporated literature.

In total, there were 107 studies from Asian ancestry, 24 studies from Caucasian ancestry, 6 studies from African ancestry, and 3 from other populations. Among the cancer types, there were 24 studies on hepatocellular cancer, 22 on breast carcinoma, 15 on colorectal carcinoma, 14 on gastric cancer, 12 on lung cancer, 11 on gynecological cancer (cervical-5, endometrial-1, ovarian-5), 7 on esophageal cancer, 6 on blood and bone marrow–related cancer, 5 on prostate cancer, 5 on oral cancer, 4 on glioma, 3 on bladder cancer, 3 on head and neck cancer, 3 on renal cell cancer, and 2 on non-Hodgkin lymphoma.

Stratification based on the control population sources showed that 79 studies contained HB controls and 59 studies contained PB controls. Most of the included studies used the PCR-RFLP for genotyping (n = 61), while 42 studies used TaqMan and 37 studies used other genotyping methods (ARMS + Sequencing + MassARRAY).

Quantitative Data Synthesis

Results from the pooled data analysis of overall 152 studies (Table 2 and Supplementary Figure S1) showed that human *miR-196a2* rs11614913 variant substantially reduced the susceptibility of overall cancer in the CDM2, CDM3, RM, and AM genetic models (OR = 0.89, $P = .006$, 95% CI = 0.83-0.97; OR = 0.93, $P = .014$, 95% CI = 0.87-0.99; OR = 0.91, $P = .003$, 95% CI = 0.86-0.97; and OR = 0.95, $P = .017$, 95% CI = 0.92-0.99, respectively). After excluding 12 studies deviating from HWE, the overall analysis of 140 studies showed that the similar genetic models (CDM2, CDM3, RM, and AM) were significantly associated with a reduced risk of cancer (OR = 0.89, $P = .003$, 95% CI = 0.82-0.96; OR = 0.92, $P = .008$, 95% CI = 0.87-0.98; OR = 0.91, $P = .001$, 95% CI = 0.86-0.96; and OR = 0.95, $P = .010$, 95% CI = 0.92-0.99, respectively). Additionally, ethnicity-based subgroup analysis (Table 2 and Figure 2) revealed a substantially reduced link of rs11614913 with cancer susceptibility among Asian population in the CDM2, CDM3, RM, and AM genetic models (OR = 0.89, $P = .005$, 95% CI = 0.82-0.96; OR = 0.91, $P = .009$, 95% CI = 0.86-0.98; OR = 0.90, $P = .002$, 95% CI = 0.85-0.96, and OR = 0.95, $P = .011$, 95% CI = 0.91-0.99,

Table 1. Characteristics of the selected studies for detecting the connection of *miR-196a2* rs11614913 polymorphism with cancer.

										Cases			Controls			HWE	
Study ID	Year	Country	Ethnicity	Cancer type	Genotyping method	Control type	Cases	Controls	Total	TT	TC	CC	TT	TC	CC	*P* value	*P* value (Adjusted)
Abd El Hassib *et al*	2021	Egypt	African	ALL	PCR-RFLP	PB	98	56	154	44	0	54	22	0	34	0	**0**
Abdal-zahra *et al*	2019	Iraq	Asian	CRC	Sequencing	PB	55	30	85	10	19	26	2	7	21	.227	.530
Abdel-Hamid *et al*	2018	Egypt	African	HCC	PCR-RFLP	PB	50	50	100	3	26	21	6	20	24	.567	.868
Afsharzadeh *et al*	2017	Iran	Asian	BC	ARMS-PCR	PB	100	150	250	14	52	34	19	93	38	.001	**.021**
Ahmad *et al*	2020	Pakistan	Asian	BC	Sequencing	PB	300	230	530	7	178	115	17	73	140	.092	.360
Ahn *et al*	2013	Korea	Asian	GC	PCR-RFLP	PB	461	447	908	119	242	100	128	232	87	.322	.653
Akkiz *et al*	2011	Turkey	Caucasian	HCC	PCR-RFLP	HB	185	185	370	22	86	77	40	87	58	.492	.788
Alshatwi *et al*	2012	Saudi Arabia	Asian	BC	TaqMan	PB	100	100	200	2	63	35	4	50	46	.032	.225
Ayadilord *et al*	2020	Iran	Asian	CRC	PCR-RFLP	HB	52	120	172	5	19	28	10	40	70	.224	.530
Bansal *et al*	2014	India	Asian	BC	PCR-RFLP	PB	121	165	286	12	41	68	21	59	85	.042	.228
Bodal *et al*	2017	India	Asian	BC	PCR-RFLP	HB	95	99	194	0	47	48	0	35	64	.033	.225
Catucci *et al*[a]	2010	Italy	Caucasian	BC	TaqMan	PB	751	1243	1994	87	330	334	161	550	532	.315	.647
Catucci *et al*[b]	2010	Germany	Caucasian	BC	TaqMan	PB	1101	1496	2597	157	512	432	216	696	584	.711	.923
Chayeb *et al*	2018	Tunisia	African	CRC	PCR-RFLP	HB	152	161	313	31	82	39	29	85	47	.380	.700
Chen *et al*[b]	2020	Taiwan	Asian	ALL	PCR-RFLP	PB	266	266	532	90	127	49	83	132	51	.908	.979
Chen *et al*[a]	2012	China	Asian	CRC	PCR-LDR	HB	126	407	533	35	64	27	107	206	94	.788	.965
Chen *et al*[c]	2020	China	Asian	CC	TaqMan	HB	288	440	728	105	125	58	140	220	80	.691	.917
Christensen *et al*	2010	USA	Caucasian	HNC	TaqMan	PB	484	555	1039	78	224	182	88	279	188	.357	.677
Chu *et al*[a]	2012	China	Asian	OC	PCR-RFLP	HB	470	425	895	136	277	57	132	206	87	.686	.917
Chu *et al*[b]	2014	Taiwan	Asian	HCC	PCR-RFLP	HB	188	337	525	66	81	41	100	167	70	.986	.990
Dai *et al*	2016	China	Asian	BC	MassARRAY	HB	560	583	1143	98	265	197	144	284	155	.540	.846
Damodaran *et al*	2020	India	Asian	PC	PCR-RFLP	HB	100	100	200	17	51	32	17	36	47	.037	.228
Deng *et al*	2015	China	Asian	UBC	PCR-RFLP	PB	159	298	457	52	66	41	76	166	56	.040	.228
Dikaiakos *et al*	2015	Greece	Caucasian	CRC	PCR-RFLP	PB	157	299	456	69	69	19	117	149	33	.156	.439
Dikeakos *et al*	2014	Greece	Caucasian	GC	PCR-RFLP	HB	163	480	643	15	46	102	172	229	79	.850	.969
Dou *et al*	2010	China	Asian	Glioma	PCR-LDR	HB	643	656	1299	189	343	111	208	305	143	.119	.392
Doulah *et al*	2018	Iran	Asian	BC	ARMS-PCR	HB	98	100	198	14	51	33	13	62	25	.010	.106
Du *et al*	2014	China	Asian	RCC	TaqMan	PB	1000	1022	2022	337	514	149	314	497	211	.578	.868
Eslami-S *et al*	2018	Iran	Asian	BC	PCR-RFLP	PB	100	100	200	5	42	53	6	38	56	.894	.971
Farokhizadeh *et al*	2019	Iran	Asian	HCC	PCR-RFLP	PB	100	120	220	17	57	26	20	59	41	.875	.971
Gawish *et al*	2020	Egypt	African	HCC	PCR-RFLP	HB	80	60	140	17	42	21	28	25	7	.697	.917
George *et al*	2011	Italy	Caucasian	PC	PCR-RFLP	PB	159	230	389	3	101	55	10	114	106	.002	**.033**
Gu *et al*	2016	China	Asian	GC	PCR-RFLP	HB	186	186	372	51	96	39	31	98	57	.308	.646
Haerian	2018	Iran	Asian	CRC	TaqMan	HB	907	1243	2150	262	196	449	187	551	505	.070	.324
Han *et al*	2013	China	Asian	HCC	TaqMan	PB	1017	1009	2026	305	505	207	304	485	220	.310	.646
Hao *et al*	2014	China	Asian	HCC	PCR-RFLP	HB	235	282	517	32	126	77	55	160	67	.022	.182
Hashemi *et al*	2016	Iran	Asian	PC	PCR-RFLP	PB	169	182	351	17	88	64	12	93	77	.021	.182
He *et al*[a]	2015	China	Asian	BC	MassARRAY	HB	450	450	900	136	233	81	134	223	93	.990	.990
He *et al*[b]	2018	China	Asian	NB	TaqMan	HB	393	812	1205	107	192	94	230	399	183	.691	.917
Hezova *et al*	2012	Czech	Caucasian	CRC	TaqMan	PB	197	212	409	26	89	82	22	103	87	.291	.632
Hoffman *et al*	2009	USA	Caucasian	BC	MassARRAY	HB	426	466	892	36	209	181	71	229	166	.583	.868
Hong *et al*	2011	Korea	Asian	LC	TaqMan	HB	406	428	834	96	224	86	134	198	96	.163	.443
Horikawa *et al*	2008	USA	Caucasian	RCC	SNPlex	PB	276	277	553	45	126	105	59	117	101	.024	.194

(continued)

Table 1. (continued)

Study ID	Year	Country	Ethnicity	Cancer type	Genotyping method	Control type	Cases	Controls	Total	Cases			Controls			HWE	
										TT	TC	CC	TT	TC	CC	*P* value	*P* value (Adjusted)
Hu *et al*[a]	2013	China	Asian	Glioma	Sequencing	HB	680	690	1370	181	314	185	210	342	138	.954	.986
Hu *et al*[b]	2008	China	Asian	LC	PCR-RFLP	PB	556	107	663	152	264	140	32	52	23	.827	.969
Hu *et al*[c]	2009	China	Asian	BC	PCR-RFLP	PB	1009	1093	2102	287	483	239	358	517	218	.207	.527
Huang *et al*	2017	China	Asian	HCC	PCR-RFLP	PB	165	284	449	62	81	22	111	134	39	.886	.971
Jedlinski *et al*	2011	Australia	Caucasian	BC	PCR-RFLP	PB	187	171	358	33	86	68	31	82	58	.830	.969
Jiang *et al*	2016	China	Asian	GC	MassARRAY	HB	889	975	1864	300	423	166	290	487	198	.804	.969
Kim *et al*[a]	2010	Korea	Asian	LC	PCR-RFLP	HB	654	640	1294	162	305	187	185	300	155	.126	.392
Kim *et al*[b]	2012	Korea	Asian	HCC	PCR-RFLP	PB	159	201	360	41	84	34	49	107	45	.356	.677
Kirik *et al*	2020	Turkey	Caucasian	MM	PCR-RFLP	HB	200	200	400	30	91	79	26	106	68	.124	.392
Kou *et al*	2014	China	Asian	HCC	PCR-RFLP	HB	271	532	803	37	150	84	103	304	125	.001	**.014**
Kupcinskas *et al*[a]	2014	Germany	Caucasian	GC	TaqMan	HB	363	350	713	35	184	144	46	145	159	.161	.443
Kupcinskas *et al*[b]	2014	Lithuania + Latvia	Caucasian	CRC	TaqMan	HB	193	427	620	27	87	79	54	174	199	.104	.366
Li *et al*[a]	2015	China	Asian	HCC	PCR-RFLP	HB	266	266	532	51	131	84	30	123	113	.689	.917
Li *et al*[b]	2014	China	Asian	NPC	TaqMan	PB	1020	1006	2026	322	489	209	270	518	218	.301	.645
Li *et al*[c]	2010	China	Asian	HCC	PCR-RFLP	HB	310	222	532	82	150	78	78	102	42	.402	.700
Li *et al*[d]	2012	China	Asian	HCC	AS-PCR	PB	560	560	1120	218	194	148	216	246	98	.057	.277
Li *et al*[e]	2016	China	Asian	HCC	Sequencing	NM	109	105	214	20	64	25	35	52	18	.861	.969
Li *et al*[f]	2016	China	Asian	GC	MassARRAY	HB	182	182	364	75	83	24	92	79	11	.265	.588
Li *et al*[g]	2015	China	Asian	NHL	PCR-RFLP	PB	318	320	638	111	146	61	144	134	42	.225	.530
Lim *et al*	2018	Korea	Asian	Glioma	PCR-RFLP	PB	79	183	262	22	44	13	46	92	45	.941	.979
Linhares *et al*	2012	Brazil	Mixed	BC	TaqMan	HB	388	388	776	117	177	94	96	165	127	.005	.054
Liu *et al*[a]	2015	China	Asian	EC	PCR-RFLP	HB	141	100	241	36	86	19	28	49	23	.861	.969
Liu *et al*[b]	2015	China	Asian	OVC	PCR-RFLP	HB	75	100	175	22	47	6	28	49	23	.861	.969
Liu *et al*[c]	2013	Taiwan	Asian	OC	PCR-RFLP	NM	315	92	407	104	147	64	30	36	26	.038	.228
Liu *et al*[d]	2010	USA	Caucasian	OC	PCR-RFLP	HB	1109	1130	2239	194	565	350	202	545	383	.737	.933
Lukács *et al*	2019	Hungary	Caucasian	OVC	TaqMan	PB	75	75	150	9	31	35	14	33	28	.445	.750
Lv *et al*	2013	China	Asian	CRC	PCR-RFLP	PB	347	531	878	114	223	10	91	331	109	.000	**0**
Ma *et al*	2013	China	Asian	BC	MassARRAY	HB	190	187	377	54	92	44	59	79	49	.037	.228
Martin-Guerrero *et al*	2015	Spain	Caucasian	CLL	TaqMan	PB	104	345	449	29	40	35	49	159	137	.793	.965
Mashayekhi *et al*	2018	Iran	Asian	BC	ARMS-PCR	PB	353	353	706	42	169	142	46	158	149	.686	.917
Miao *et al*	2016	China	Asian	HNSCC	Array	HB	576	1550	2126	162	284	130	503	755	292	.770	.960
Min *et al*	2012	Korea	Asian	CRC	PCR-RFLP	PB	446	502	948	125	201	120	148	254	100	.633	.908
Minh *et al*	2018	Vietnam	Asian	BC	HRMA	HB	113	127	240	30	35	48	32	64	31	.929	.979
Mirtalebi *et al*	2014	Iran	Asian	CRC	PCR-RFLP	HB	149	146	295	61	73	15	52	59	35	.029	.220
Mittal *et al*	2011	India	Asian	UBC	PCR-RFLP	HB	212	250	462	5	131	76	14	127	109	.003	**.038**
Morales *et al*	2016	Chile	Mixed	BC	TaqMan	HB	440	807	1247	57	191	192	114	351	342	.121	.392
Nejati-Azar *et al*	2018	Iran	Asian	BC	PCR-RFLP	PB	200	200	400	36	128	36	14	160	26	.000	**0**
Ni *et al*	2016	China	Asian	OVC	PCR-RFLP	HB	155	342	497	41	82	32	100	176	66	.465	.768
Nikolić *et al*	2015	Serbia	Caucasian	PC	HRMA	PB	351	309	660	40	161	150	41	147	121	.728	.929
Nouri *et al*	2019	Iran	Asian	PC	PCR-RFLP	PB	150	150	300	48	73	29	48	80	22	.222	.530
Okubo *et al*	2010	Japan	Asian	GC	PCR-RFLP	HB	552	697	1249	166	281	105	124	350	223	.510	.807
Omrani *et al*	2014	Iran	Asian	BC	ARMS-PCR	PB	236	203	439	0	18	218	0	25	178	.350	.677
Parlayan *et al*[a]	2014	Japan	Asian	CRC	TaqMan	HB	116	524	640	34	59	23	146	270	108	.410	.700

(continued)

Table 1. (continued)

Study ID	Year	Country	Ethnicity	Cancer type	Genotyping method	Control type	Cases	Controls	Total	Cases			Controls			HWE	
										TT	TC	CC	TT	TC	CC	*P* value	*P* value (Adjusted)
Parlayan *et al*[b]	2014	Japan	Asian	PC	TaqMan	HB	89	524	613	24	48	17	146	270	108	.410	.700
Parlayan *et al*[c]	2014	Japan	Asian	AL	TaqMan	HB	72	524	596	20	31	21	146	270	108	.410	.700
Parlayan *et al*[d]	2014	Japan	Asian	GC	TaqMan	HB	160	524	684	44	72	44	146	270	108	.410	.700
Parlayan *et al*[e]	2014	Japan	Asian	LC	TaqMan	HB	148	524	672	29	81	38	146	270	108	.410	.700
Pavlakis *et al*	2013	Greece	Caucasian	PNC	PCR-RFLP	PB	93	122	215	48	33	12	50	58	14	.647	.917
Peckham-Gregory *et al*	2016	USA	Caucasian	NHL	ASPCR	PB	179	529	708	19	88	72	76	257	196	.575	.868
Peng *et al*	2010	China	Asian	GC	PCR-RFLP	HB	213	213	426	43	94	76	50	107	56	.936	.979
Poltronieri-Oliveira *et al*	2017	Brazil	Hispanic	GC	PCR-RFLP	PB	149	246	395	28	57	64	21	120	105	.102	.366
Pu *et al*	2014	China	Asian	GC	PCR-RFLP	HB	159	511	670	25	95	39	86	324	101	.000	**0**
Qi *et al*[a]	2015	China	Asian	BC	TaqMan	PB	321	290	611	168	119	34	185	88	17	.141	.412
Qi *et al*[b]	2014	China	Asian	HCC	HRMA	PB	314	406	720	60	209	45	121	214	71	.156	.439
Qi *et al*[c]	2010	China	Asian	HCC	PCR-LDR	HB	361	391	752	100	179	82	102	197	92	.869	.971
Qiu *et al*	2021	China	Asian	LC	SNPscan	HB	1184	1053	2237	392	572	220	293	544	216	.208	.527
Qu *et al*	2014	China	Asian	ESCC	PCR-RFLP	PB	381	426	807	48	207	126	82	211	133	.918	.979
Rakmanee *et al*	2017	Thailand	Asian	ALL	PCR-RFLP	HB	104	180	284	13	43	48	53	78	49	.075	.334
Rogoveanu *et al*	2017	Romania	Caucasian	GC	TaqMan	HB	142	288	430	18	63	61	39	128	121	.579	.868
Roy *et al*	2014	China	Asian	OC	TaqMan	HB	451	448	899	46	187	218	38	168	242	.255	.578
Shang *et al*	2016	China	Asian	LC	PCR-RFLP	PB	32	84	116	7	17	8	48	26	10	.042	.228
Shen *et al*	2016	China	Asian	ESCC	SNaPshot	PB	1400	2185	3585	407	698	295	672	1121	392	.043	.228
Sodhi *et al*	2015	India	Asian	LC	PCR-RFLP	PB	250	255	505	19	161	70	8	146	101	.000	**0**
Soltanian *et al*	2021	Iran	Asian	CRC	PCR-RFLP	HB	194	286	480	29	91	74	48	138	100	.973	.986
Song *et al*	2016	China	Asian	OVC	PCR-RFLP	PB	479	431	910	111	247	121	142	203	86	.385	.700
Srivastava *et al*[a]	2010	India	Asian	GBC	PCR-RFLP	PB	230	230	460	16	95	119	19	75	136	.068	.324
Srivastava *et al*[b]	2017	India	Asian	CC	PCR-RFLP	HB	184	164	348	71	93	20	62	81	21	.492	.788
Su *et al*	2016	China	Asian	GC	PCR-RFLP	HB	245	315	560	34	128	83	38	158	119	.188	.501
Sun *et al*	2016	China	Asian	OVC	PCR-RFLP	HB	134	227	361	39	66	29	77	116	34	.366	.686
Sushma *et al*	2015	India	Asian	OSCC	PCR-RFLP	PB	100	102	202	68	10	22	81	15	6	.000	**.006**
Thakur *et al*	2019	India	Asian	CC	PCR-RFLP	PB	150	150	300	17	58	75	57	51	42	.000	**.002**
Tian *et al*	2009	China	Asian	LC	PCR-RFLP	PB	1058	1035	2093	293	512	253	307	519	209	.700	.917
Tong *et al*	2014	China	Asian	ALL	TaqMan	PB	570	673	1243	159	308	103	237	307	129	.099	.366
Toraih *et al*[a]	2016	Egypt	African	Mixed cancer	TaqMan	HB	209	100	309	84	93	32	55	35	10	.222	.530
Toraih *et al*[b]	2016	Egypt	African	HCC	TaqMan	PB	60	150	210	3	32	25	17	53	80	.082	.337
Toraih *et al*[c]	2016	Egypt	African	RCC	TaqMan	PB	65	150	215	11	31	23	17	53	80	.082	.337
Umar *et al*	2013	India	Asian	ESCC	PCR-RFLP	PB	289	309	598	22	121	146	16	122	171	.332	.656
Vinci *et al*[a]	2013	Italy	Caucasian	CRC	HRMA	HB	160	178	338	12	86	62	11	84	83	.087	.346
Vinci *et al*[b]	2011	Italy	Caucasian	LC	TaqMan	PB	101	129	230	12	54	35	10	61	58	.267	.588
Wang *et al*[a]	2019	China	Asian	CC	TaqMan	HB	929	1322	2251	271	464	194	424	629	269	.201	.527
Wang *et al*[b]	2016	China	Asian	UBC	MassARRAY	PB	283	283	566	52	158	73	94	124	65	.054	.275
Wang *et al*[c]	2013	China	Asian	GC	TaqMan	HB	1689	1946	3635	519	851	319	524	940	482	.140	.412
Wang *et al*[d]	2010	China	Asian	ESCC	SNaPshot	HB	458	489	947	48	262	148	111	250	128	.600	.879
Wang *et al*[e]	2014	China	Asian	ESCC	PCR-LDR	PB	597	597	1194	162	307	128	154	298	145	.972	.986
Wei *et al*	2013	China	Asian	ESCC	MassARRAY	HB	367	370	737	106	196	65	113	170	87	.141	.412
Xu *et al*[a]	2016	China	Asian	HCC	PCR-RFLP	HB	251	543	794	56	127	68	163	267	113	.849	.969

(continued)

Table 1. (continued)

Study ID	Year	Country	Ethnicity	Cancer type	Genotyping method	Control type	Cases	Controls	Total	Cases			Controls			HWE	
										TT	TC	CC	TT	TC	CC	*P* value	*P* value (Adjusted)
Xu *et al*[b]	2010	China	Asian	HCC	PCR-RFLP	HB	492	495	987	130	247	115	144	251	100	.621	.899
Yan *et al*[a]	2019	China	Asian	CC	TaqMan	HB	547	567	1114	117	277	153	153	282	132	.926	.979
Yan *et al*[b]	2015	China	Asian	HCC	PCR-RFLP	HB	274	328	602	81	147	46	136	165	27	.018	.176
Yang *et al*[a]	2013	China	Asian	GC	TaqMan	PB	232	250	482	21	109	102	42	136	72	.100	.366
Yang *et al*[b]	2008	USA	Caucasian	UBC	SNPlex	PB	736	731	1467	133	348	255	132	342	257	.329	.656
Yang *et al*[c]	2020	China	Asian	Glioma	Sequenom	HB	605	1300	1905	192	274	139	349	656	295	.692	.917
Ye *et al*	2008	USA	Caucasian	ESCC	SNPlex	HB	307	338	645	83	138	86	59	170	109	.601	.879
Yin *et al*[a]	2017	China	Asian	LC	TaqMan	HB	1003	1003	2006	196	555	252	286	496	221	.830	.969
Yin *et al*[b]	2016	China	Asian	LC	TaqMan	HB	575	608	1183	149	298	128	178	297	133	.664	.917
Yin *et al*[c]	2015	China	Asian	LC	TaqMan	HB	258	310	568	67	141	50	97	150	63	.719	.926
Yoon *et al*	2012	Korea	Asian	LC	TaqMan	PB	386	71	457	99	186	101	24	32	15	.480	.784
Zhan *et al*	2011	China	Asian	CRC	PCR-RFLP	HB	252	543	795	56	128	68	163	267	113	.849	.969
Zhang *et al*[a]	2017	China	Asian	OSCC	TaqMan	HB	340	340	680	100	169	71	97	155	88	.106	.367
Zhang *et al*[b]	2012	China	Asian	BC	PCR-RFLP	PB	248	243	491	148	89	11	133	93	17	.893	.971
Zhang *et al*[c]	2013	China	Asian	HCC	Sequenom	HB	996	995	1991	294	488	214	328	502	165	.245	.564
Zhang *et al*[d]	2016	China	Asian	HCC	PCR-RFLP	PB	175	302	477	65	85	25	122	138	42	.766	.960
Zhang *et al*[e]	2020	China	Asian	HCC	TaqMan	HB	575	921	1496	181	281	113	289	474	158	.125	.392
Zhang *et al*[f]	2011	China	Asian	HCC	PIRA-PCR	HB	934	837	1771	277	449	208	239	417	181	.972	.986
Zhao *et al*	2016	China	Asian	BC	Sequencing	HB	114	114	228	33	50	31	25	61	28	.449	.750
Zhou *et al*[a]	2014	China	Asian	HCC	Sequenom	HB	266	281	547	34	139	93	55	160	66	.019	.176
Zhou *et al*[b]	2019	China	Asian	NB	TaqMan	HB	313	762	1075	226	68	19	542	161	59	.000	**0**
Zhou *et al*[c]	2011	China	Asian	CC	PCR-RFLP	PB	226	309	535	57	123	46	82	169	58	.077	.336
Zhu *et al*	2012	China	Asian	CRC	TaqMan	HB	573	588	1161	130	303	140	172	295	121	.790	.965
Total							53 818	66 317	120 135	13 365	26 009	14 444	17 206	31 860	17 251		

Bold values indicate statistically significant. The alphabets a,b,c,d,e,f,g indicates that the last name of the authors are the same but the first names are different.

Abbreviations: AL, acute leukemia; ALL, acute lymphocytic leukemia; BC, breast cancer; BCC, basal cell carcinoma; CC, cervical cancer; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CRC, colorectal cancer; EC, endometrial cancer; ESCC, esophageal cancer; GC, gastric cancer; GBC, gallbladder cancer; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; LC, lung cancer; MM, multiple myeloma; NB, neuroblastoma; NHL, non-Hodgkin lymphoma; NPC, nasopharyngeal carcinoma; OC, oral cancer; OSCC, oral squamous cell carcinoma; OVC, ovarian cancer; PC, prostate cancer; PCN, pancreatic cancer; RCC, renal cell cancer; UBC, bladder cancer; NM, not mentioned.

Table 2. Meta-analysis for detecting the connection of *miR-196a2* rs11614913 polymorphism with overall cancer and ethnicity.

		Test of association			Test of heterogeneity				Test of association			Test of heterogeneity		
Genetic model	No. of studies	OR	95% CI	*P* value	Model	*P* value	I^2 (%)	No. of studies	OR	95% CI	*P* value	Model	*P* value	I^2 (%)
	Overall							**Caucasians**						
CDM1		0.98	0.93-1.05	.595	RE	<.0001	73.32		0.91	0.79-1.05	.188	RE	<.0001	74.71
CDM2		0.89	0.83-0.97	**.006**	RE	<.0001	77.66		0.86	0.69-1.08	.194	RE	<.0001	80.35
CDM3		0.93	0.87-0.99	**.014**	RE	<.0001	71.15		0.97	0.85-1.12	.687	RE	.001	53.17
DM	**152**	0.96	0.91-1.02	.186	RE	<.0001	76.21	**24**	0.90	0.77-1.05	.191	RE	<.0001	82.91
RM		0.91	0.86-0.97	**.003**	RE	<.0001	74.30		0.93	0.79-1.10	.399	RE	.007	72.21
ODM		1.03	0.99-1.08	.145	RE	<.0001	66.50		0.96	0.88-1.04	.323	RE	<.0001	46.18
AM		0.95	0.92-0.99	**.017**	RE	<.0001	79.08		0.94	0.83-1.06	.283	RE	<.0001	85.34
Overall (excluding 12 studies that deviate from HWE)								**Africans**						
CDM1		0.98	0.92-1.04	.453	RE	<.0001	71.56		1.33	1.01-1.77	**.044**	FE	.179	34.32
CDM2		0.89	0.82-0.96	**.003**	RE	<.0001	75.33		0.71	0.35-1.43	.334	RE	.007	68.64
CDM3		0.92	0.87-0.98	**.008**	RE	<.0001	70.01		0.66	0.48-0.89	**.007**	FE	.115	43.49
DM	**140**	0.96	0.90-1.01	.125	RE	<.0001	74.28	**6**	1.10	0.70-1.72	.680	RE	.021	62.27
RM		0.91	0.86-0.96	**.001**	RE	<.0001	72.36		0.67	0.39-1.13	.129	RE	.018	63.42
ODM		1.03	0.99-1.08	.147	RE	<.0001	66.47		1.46	1.16-1.85	**.001**	FE	.580	0
AM		0.95	0.92-0.99	**.010**	RE	<.0001	77.04		0.92	0.63-1.34	.665	RE	.0003	78.22
	Asian							**Other population (Hispanic + mixed)**						
CDM1		0.98	0.92-1.05	.617	RE	<.0001	72.01		1.05	0.76-1.45	.787	RE	.062	64.12
CDM2		0.89	0.82-0.96	**.005**	RE	<.0001	74.36		1.41	0.84-2.38	.190	RE	.017	75.43
CDM3		0.91	0.86-0.98	**.009**	RE	<.0001	72.72		1.33	0.79-2.24	.277	RE	.013	77.11
DM	**107**	0.96	0.90-1.02	.184	RE	<.0001	72.2	**3**	1.12	0.83-1.53	.457	RE	.054	65.82
RM		0.90	0.85-0.96	**.002**	RE	<.0001	72.67		1.35	0.84-2.17	.214	RE	.015	76.15
ODM		1.04	0.99-1.10	.098	RE	<.0001	69.87		0.94	0.72-1.23	.651	RE	.092	58.19
AM		0.95	0.91-0.99	**.011**	RE	<.0001	74.31		1.15	0.91-1.44	.245	RE	.035	70.18

Bold values indicate statistically significant.

Abbreviations: CDM1, Codominant 1 (TC vs CC); CDM2, Codominant 2 (TT vs CC); CDM3, Codominant 3 (TT vs TC); DM, Dominant model (TT + TC vs CC); RM, recessive model (TT vs TC + CC); ODM, over-dominant model (TC vs TT + CC); AM, allele model (T vs C); FE, fixed-effects; RE, random-effects.

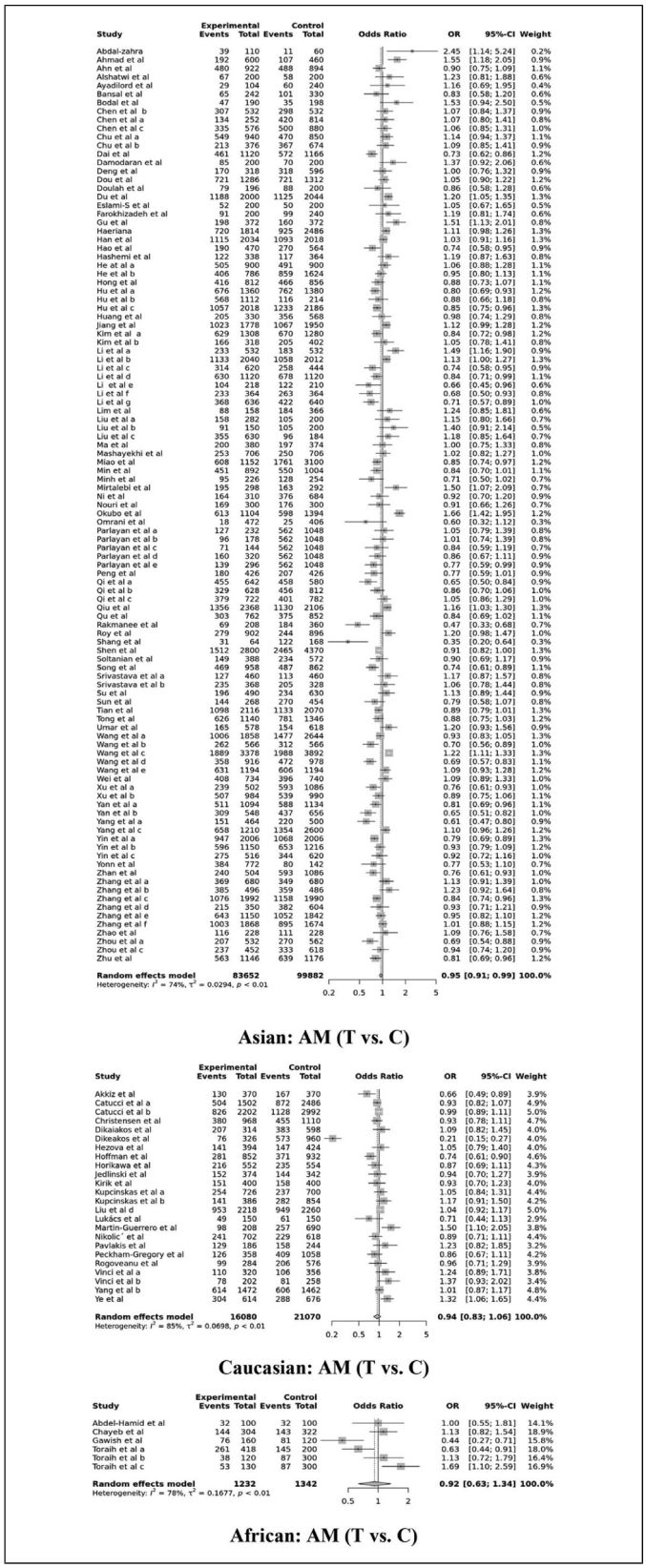

Figure 2. Ethnicity-based forest plot indicating the connection of *miR-196a2* rs11614913 polymorphism with overall cancer susceptibility in the allele model (AM).

respectively). Among African population, CDM1 and ODM genetic models showed significantly enhanced association with cancer (OR = 1.33, $P = .044$, 95% CI = 1.01-1.77; OR = 1.46, $P = .001$, 95% CI = 1.16-1.85, respectively) but CDM3 genetic model showed reduced association (OR = 0.66, $P = .007$, 95% CI = 0.48-0.89). No strong association was observed between rs11614913 genetic variant and susceptibility of cancer among Caucasian and other population (Hispanic and mixed) ($P > .05$).

Stratified analysis based on the cancer types (shown in Table 3 and Figure 3) demonstrated that there were significantly reduced correlation of rs11614913 with hepatocellular cancer from 24 studies (CDM2—OR = 0.76, $P = .001$, 95% CI = 0.64-0.89; CDM3—OR = 0.87, $P = .021$, 95% CI = 0.77-0.98; DM—OR = 0.86, $P = .024$, 95% CI = 0.76-0.98; RM—OR = 0.83, $P = .003$, 95% CI = 0.74-0.94; and AM—OR = 0.89, $P = .003$, 95% CI = 0.82-0.96), lung cancer from 12 studies (CDM2—OR = 0.79, $P = .022$, 95% CI = 0.65-0.97; CDM3—OR = 0.80, $P = .020$, 95% CI = 0.66-0.97; DM—OR = 0.91, $P = .045$, 95% CI = 0.84-1.00; RM—OR = 0.79, $P = .014$, 95% CI = 0.66-0.95; and AM—OR = 0.88, $P = .025$, 95% CI = 0.79-0.99), gynecological cancer from 11 studies (CDM3—OR = 0.87, $P = .010$, 95% CI = 0.78-0.97; RM—OR = 0.86, $P = .003$, 95% CI = 0.77-0.95), and breast cancer from 22 studies (CDM2—OR = 0.84, $P = .041$, 95% CI = 0.72-0.99; RM—OR = 0.88, $P = .039$, 95% CI = 0.77-0.99). On the other hand, rs11614913 showed significantly increased association with oral cancer from 5 studies (CDM1—OR = 1.38, $P = .003$, 95% CI = 1.11-1.70; CDM2—OR = 1.22, $P = .018$, 95% CI = 1.04-1.45; DM—OR = 1.26, $P = .0002$, 95% CI = 1.11-1.43; ODM—OR = 1.21, $P = .0007$, 95% CI = 1.09-1.36; and AM—OR = 1.10, $P = .019$, 95% CI = 1.02-1.19), and renal cell cancer from 6 studies (CDM1—OR = 1.37, $P = .001$, 95% CI = 1.13-1.67). The correlation of rs11614913 with bladder (3 studies), colorectal (15 studies), esophageal (7 studies), gastric (14 studies), head and neck (3 studies), prostate (5 studies), blood and bone marrow related cancer (6 studies), and glioma (4 studies) was not statistically significant ($P > .05$). No statistically significant correlation was observed for non-Hodgkin lymphoma from 2 studies (Table 4).

Again, control population-based subgroup analysis (Table 4) reported a strongly reduced correlation between rs11614913 and cancer susceptibility for the HB population from 79 studies in the CDM2, RM, and AM genetic models (OR = 0.88, $P = .028$, 95% CI = 0.79-0.99; OR = 0.91, $P = .020$, 95% CI = 0.84-0.99; OR = 0.94, $P = .027$, 95% CI = 0.89-0.99, respectively) but no association was found for PB-based controls from 59 studies. Although no significant association was observed for PCR-RFLP (61 studies) and TaqMan (42 studies) genotyping methods during subgroup analysis, a substantially decreased risk was observed for other genotyping methods (ARMS + Sequencing + MassARRAY) from 37 studies in the CDM2, CDM3, RM, and AM genetic

Table 3. Meta-analysis for detecting the connection of *miR-196a2* rs11614913 polymorphism with different cancer subtypes.

		Test of association			Test of heterogeneity				Test of association			Test of heterogeneity				Test of association			Test of heterogeneity		
Genetic model	No. of studies	OR	95% CI	*P* value	Model	*P* value	I^2 (%)	No. of studies	OR	95% CI	*P* value	Model	*P* value	I^2 (%)	No. of studies	OR	95% CI	*P* value	Model	*P* value	I^2 (%)
BC											**GC**					**Gynecological cancer (CC-5 + EC-1 + OVC-5)**					
CDM1		1.01	0.87-1.18	.876	RE	<.0001	72.53		0.85	0.64-1.13	.260	RE	<.0001	89.66		0.97	0.80-1.15	.697	RE	.076	40.86
CDM2		0.84	0.72-0.99	**.041**	RE	.0015	55.37		0.86	0.57-1.30	.477	RE	<.0001	92.24		0.84	0.69-1.04	.110	RE	.042	47.11
CDM3		0.89	0.78-1.01	.075	RE	.0116	46.73		1.04	0.86-1.25	.691	RE	.0001	69.45		0.87	0.78-0.97	**.010**	FE	.334	11.58
DM	**22**	0.98	0.85-1.14	.805	RE	<.0001	73.53	**14**	0.85	0.61-1.18	.321	RE	<.0001	93.09	**11**	0.92	0.77-1.10	.343	RE	.047	45.95
RM		0.88	0.77-0.99	**.039**	RE	.0085	48.31		0.96	0.75-1.24	.771	RE	<.0001	86.04		0.86	0.77-0.95	**.003**	FE	.204	25.22
ODM		1.06	0.94-1.20	.371	RE	<.0001	68.82		0.92	0.81-1.05	.209	RE	.0004	65.21		1.06	0.97-1.17	.207	FE	.317	13.32
AM		0.96	0.88-1.05	.377	RE	<.0001	68.49		0.91	0.74-1.13	.413	RE	<.0001	93.73		0.91	0.83-1.01	.066	RE	.074	41.26
Blood and bone marrow related cancer (AL + ALL + CLL + MM)											**Glioma**							**HCC**			
CDM1		0.86	0.66-1.13	.274	RE	.062	52.38		1.04	.71-1.52	.848	RE	.001	81.65		0.90	0.79-1.02	.104	RE	.0004	56.34
CDM2		0.88	0.54-1.41	.589	RE	.0003	78.62		1.03	0.72-1.48	.876	RE	.007	75.50		0.76	0.64-0.89	**.001**	RE	<.0001	66.19
CDM3		1.04	0.68-1.58	.864	RE	.0003	78.77		1.00	0.79-1.29	.973	RE	.034	65.48		0.87	0.77-0.98	**.021**	RE	.0003	57.11
DM	**6**	0.85	0.63-1.14	.280	RE	.0141	64.92	**4**	1.04	0.73-1.48	.843	RE	.001	81.14	**24**	0.86	0.76-0.98	**.024**	RE	<.0001	62.74
RM		0.97	0.63-1.47	.873	RE	.0001	78.46		1.00	0.80-1.26	.984	RE	.040	63.89		0.83	0.74-0.94	**.003**	RE	<.0001	62.63
ODM		0.91	0.70-1.19	.487	RE	.011	66.42		1.01	0.78-1.30	.950	RE	.006	76.02		1.03	0.94-1.13	.499	RE	.005	47.98
AM		0.91	0.71-1.16	.437	RE	.0002	79.83		1.01	0.85-1.20	.941	RE	.009	74.27		0.89	0.82-0.96	**.003**	RE	<.0001	66.94
CRC											**OC**							**PC**			
CDM1		0.99	0.76-1.28	.934	RE	<.0001	82.32		1.38	1.11-1.70	**.003**	RE	.077	52.56		1.04	0.84-1.28	.721	FE	.109	47.1
CDM2		1.09	0.85-1.40	.488	RE	<.0001	68.88		1.22	1.04-1.45	**.018**	FE	.506	0		0.99	0.74-1.34	.971	FE	.397	1.67
CDM3		1.14	0.81-1.60	.445	RE	<.0001	87.3		0.90	0.78-1.04	.144	FE	.757	0		0.98	0.75-1.27	.870	FE	.713	0
DM	**15**	1.01	0.841.20	.954	RE	.0002	65.96	**5**	1.26	1.11-1.43	**.0002**	FE	.134	43.13	**5**	1.03	0.84-1.26	.755	FE	.116	46.01
RM		1.12	0.87-1.43	.387	RE	<.0001	79.56		0.99	0.86-1.14	.929	FE	.848	0		0.99	0.77-1.27	.921	FE	.750	0
ODM		0.97	0.751.24	.787	RE	<.0001	86.93		1.21	1.09-1.36	**.0007**	FE	.382	4.44		1.03	0.86-1.24	.723	FE	.243	26.85
AM		1.03	0.93-1.15	.537	RE	.0013	60.45		1.10	1.02-1.19	**.019**	FE	.766	0		1.01	0.88-1.16	.870	FE	.292	19.33
ESCC											**HNC (HNC-1 + HNSCC-1 + NPC-1)**							**RCC**			
CDM1		1.04	0.89-1.22	.603	RE	.069	48.73		0.89	0.78-1.03	.117	FE	.550	0		1.37	1.13-1.67	**.001**	FE	.141	49.04
CDM2		0.95	0.66-1.36	.772	RE	<.0001	84.63		0.94	0.67-1.30	.734	RE	.015	76.09		1.28	0.72-2.29	.402	RE	.015	76.18
CDM3		0.88	0.66-1.19	.409	RE	<.0001	82.30		1.06	0.82-1.38	.662	RE	.041	68.78		0.98	0.82-1.18	.854	FE	.318	12.71
DM	**7**	1.02	0.86-1.23	.790	RE	.008	65.75	**3**	0.91	0.80-1.04	.177	FE	.147	47.81	**3**	1.36	0.92-2.03	.126	RE	.030	71.63
RM		0.91	0.67-1.22	.523	RE	<.0001	84.69		1.02	0.76-1.36	.911	RE	.012	77.61		1.03	0.71-1.50	.864	RE	.097	57.20
ODM		1.08	0.95-1.23	.236	RE	.075	47.63		0.92	0.82-1.03	.134	FE	.365	0.74		1.15	0.99-1.34	.063	FE	.443	0
AM		0.99	0.85-1.15	.875	RE	<.0001	80.45		.97	0.81-1.16	.700	RE	.009	78.81		1.16	0.87-1.55	.319	RE	.014	76.42
UBC											**LC**					**Other cancers**					
CDM1		0.89	0.62-1.30	.553	RE	.048	67.1		0.97	0.88-1.06	.490	FE	.530	0		1.19	0.86-1.65	.300	FE	.182	41.4
CDM2		0.79	0.50-1.24	.304	RE	.038	69.47		0.79	0.65-0.97	**.022**	RE	.0005	66.66		0.80	0.51-1.25	.323	FE	.288	19.78
CDM3		0.90	0.45-1.81	.771	RE	<.0001	90.14		0.80	0.66-0.97	**.020**	RE	<.0001	72.78		0.87	0.43-1.74	.687	RE	.019	74.86
DM	**3**	0.93	0.78-1.10	.399	FE	.228	32.31	**12**	.91	0.84-1.00	**.045**	FE	.133	32.16	**3**	1.11	0.82-1.52	.488	FE	.153	46.81
RM		0.86	0.47-1.57	.630	RE	.0002	88.26		0.79	0.66-0.95	**.014**	RE	<.0001	75.88		0.88	0.47-1.68	.704	RE	.021	74.02
ODM		0.99	0.60-1.63	.961	RE	.0003	87.76		1.11	0.99-1.25	.081	RE	.019	51.86		1.12	0.66-1.91	.667	RE	.023	73.46
AM		0.90	0.71-1.13	.367	RE	.029	71.87		0.88	0.79-0.99	**.025**	RE	.0001	71.9		0.97	0.64-1.47	.889	RE	.017	75.37

Bold values indicate statistically significant.

Abbreviations: CDM1, Codominant 1 (TC vs CC); CDM2, Codominant 2 (TT vs CC); CDM3, Codominant 3 (TT vs TC); DM, Dominant model (TT + TC vs CC); RM, recessive model (TT vs TC + CC); ODM, over-dominant model (TC vs TT + CC); AM, allele model (T vs C); FE, fixed-effects; RE, random-effects; AL, acute leukemia; ALL, acute lymphocytic leukemia; BC, breast cancer; BCC, basal cell carcinoma; CC, cervical cancer; CLL, chronic lymphocytic leukemia; CML, chronic myeloid leukemia; CRC, colorectal cancer; EC, endometrial cancer; ESCC, esophageal cancer; GC, gastric cancer; HCC, hepatocellular carcinoma; HNC, head and neck cancer; HNSCC, head and neck squamous cell carcinoma; LC, lung cancer; MM, multiple myeloma; NPC, nasopharyngeal carcinoma; OC, oral cancer; OVC, ovarian cancer; PC, prostate cancer; RCC, renal cell cancer; UBC, bladder cancer.

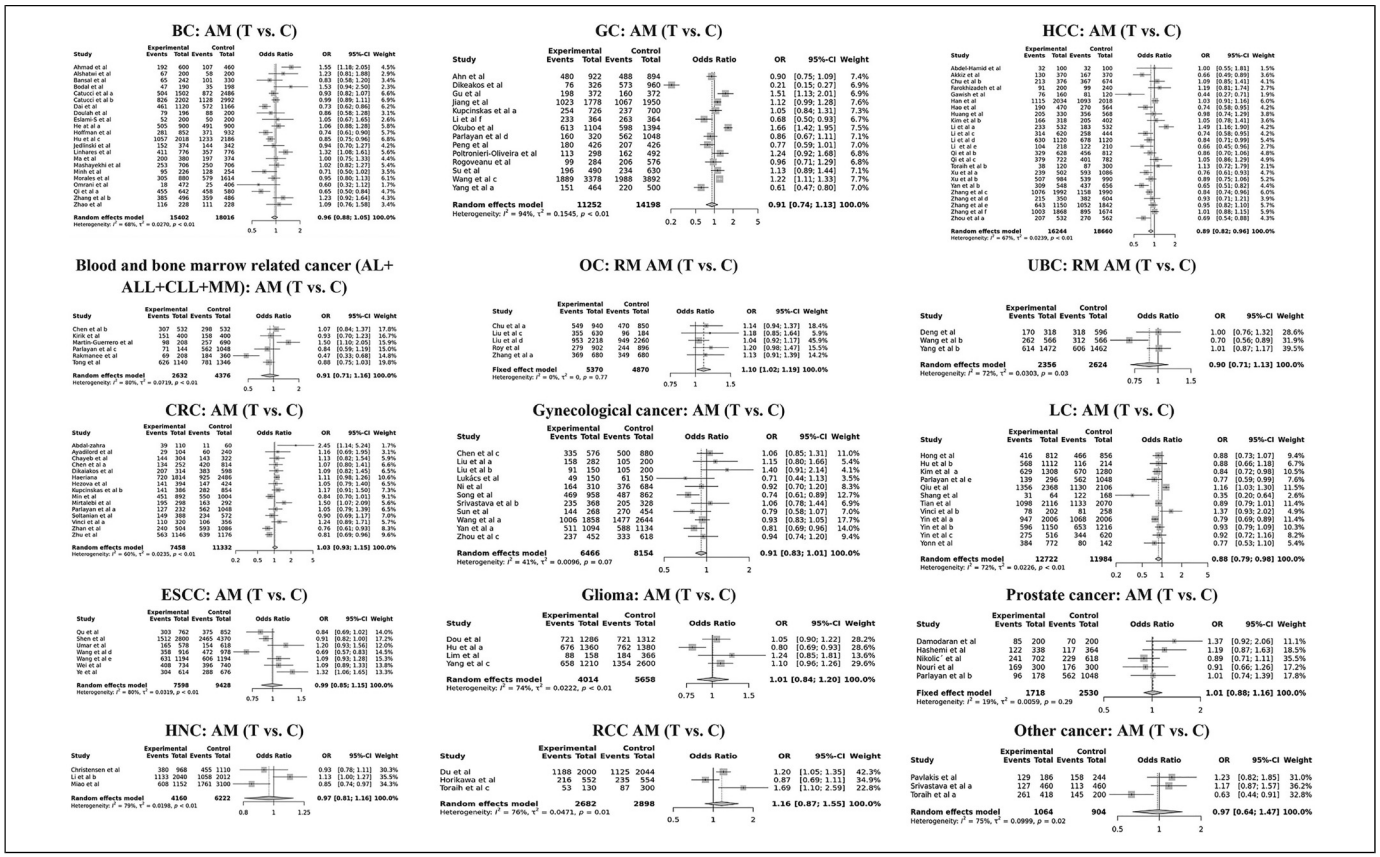

Figure 3. Forest plot in allele model (AM) indicating the connection of *miR-196a2* rs11614913 polymorphism with cancer types.

models (OR = 0.84, $P = .007$, 95% CI = 0.74-0.95; OR = 0.89, $P = .037$, 95% CI = 0.80-0.99; OR = 0.88, $P = .011$, 95% CI = 0.79-0.97; and OR = 0.94, $P = .037$, 95% CI = 0.88-1.00, respectively) as shown in Table 4.

Test of Heterogeneity

Heterogeneity analysis was performed for all applied genetic models in overall analysis (Table 2) and subgroup analyses based on ethnicity (Table 2), cancer types (Table 3), control sources, and genotyping methods (Table 4). We have observed significant heterogeneity in the overall analysis and all subgroup analyses ($P < .05$ or $I^2 > 50\%$) in our meta-analysis, and we have applied RE models consequently.

Publication Bias

Table 5 and Figure 4 present publication bias to detect the connection of *miR-196a2* rs11614913 genetic variant with overall cancer in all genetic models. However, no statistically substantial bias was reported in any genetic models that were confirmed by Egger's symmetric funnel plots and *P* values of Begg-Mazumdar's assessment (*P* values were found to be greater than .05 in every comparison).

Sensitivity Analysis

One-way sensitivity analysis was implemented in all genetic models to measure the robustness in the outcomes of the study and the influence of individual studies by deleting each study at a time. Our estimation showed that the values of ORs and 95% CIs were consistent in all genotypic and allele models, which demonstrates the reliability and robustness of the meta-analysis, as shown in Figure 5.

Discussion

The potential impact of miRNAs on the susceptibility of cancer, especially *miR-196a2*, has drawn the attention of the scientists that led to the production of hundreds of studies, including genetic epidemiological studies and systemic reviews and meta-analyses. The inconsistencies of these studies have influenced to perform an updated meta-analysis for estimating a meticulous correlation between human *miR-196a2* rs11614913 genetic variant and a wide range of malignancies. The outcomes of the current meta-analysis confirm that the rs11614913 variant is linked with the overall cancer susceptibility.

Accumulating studies have explicated that single nucleotide polymorphisms in the miRNA-encoding genes might modulate the binding and processing capacity of microRNAs by

Table 4. Meta-analysis for detecting the connection of *miR-196a2* rs11614913 polymorphism with cancer based on the cancer subtype (NHL), control sources, and genotyping methods.

		Test of association			Test of heterogeneity		
Genetic model	No. of studies	OR	95% CI	*P* value	Model	*P* value	I^2 (%)
			NHL				
CDM1		0.86	0.65-1.14	.288	Fixed	.466	0
CDM2		0.59	0.41-0.84	.004	Fixed	.508	0
CDM3		0.71	0.53-0.96	.023	Fixed	.925	0
DM	**2**	0.77	0.59-1.01	.059	Fixed	.258	21.79
RM		0.67	0.51-0.88	.004	Fixed	.808	0
ODM		1.10	0.88-1.39	.398	Fixed	.550	0
AM		0.77	0.66-0.92	.003	Fixed	.258	21.8
			PB				
CDM1		1.00	0.93-1.08	.960	RE	<.0001	58.49
CDM2		0.89	0.81-0.99	.023	RE	<.0001	55.81
CDM3		0.92	0.85-1.01	.065	RE	<.0001	59.59
DM	**59**	0.98	0.91-1.06	.567	RE	<.0001	59.78
RM		0.92	0.85-0.99	.033	RE	<.0001	60.23
ODM		1.05	0.98-1.13	.140	RE	<.0001	61.6
AM		0.96	0.92-1.01	.150	RE	<.0001	62.52
			HB				
CDM1		0.95	0.88-1.04	.287	RE	<.0001	77.38
CDM2		0.88	0.79-0.99	**.028**	RE	<.0001	81.64
CDM3		0.93	0.86-1.01	.079	RE	<.0001	75.19
DM	**79**	0.93	0.86-1.02	.118	RE	<.0001	80.1
RM		0.91	0.84-0.99	**.020**	RE	<.0001	77.75
ODM		1.02	0.96-1.08	0.614	RE	<.0001	69.94
AM		0.94	0.89-0.99	**.027**	RE	<.0001	82.48
			PCR-RFLP				
CDM1		0.97	0.87-1.08	.562	RE	<.0001	70.65
CDM2		0.89	0.76-1.03	.110	RE	<.0001	78.9
CDM3		0.93	0.85-1.01	.073	RE	<.0001	49.83
DM	**61**	0.94	0.84-1.06	.332	RE	<.0001	79.04
RM		0.91	0.82-1.00	.054	RE	<.0001	68.41
ODM		1.03	0.97-1.09	.410	RE	.0013	38.96
AM		0.94	0.87-1.02	.127	RE	<.0001	81.63
			TaqMan				
CDM1		1.01	0.91-1.11	.868	RE	<.0001	73.99
CDM2		0.95	0.85-1.07	.378	RE	<.0001	70.25
CDM3		0.95	0.84-1.07	.365	RE	<.0001	80.83
DM	**42**	1.00	0.92-1.08	0.946	RE	<.0001	65.58
RM		0.94	0.85-1.05	.263	RE	<.0001	76.89
ODM		1.05	0.96-1.15	.330	RE	<.0001	78.69
AM		0.98	.93-1.03	.415	RE	<.0001	70.19
			Other genotyping methods (ARMS + Sequencing + MassARRAY)				
CDM1		0.96	0.87-1.07	.437	RE	<.0001	70.98
CDM2		0.84	0.74-.95	**.007**	RE	<.0001	71.55
CDM3		0.89	0.80-0.99	**.037**	RE	<.0001	71.65
DM		0.94	0.85-1.03	.188	RE	<.0001	71.92
RM	**37**	0.88	0.79-.97	**.011**	RE	<.0001	72.31
ODM		1.03	0.95-1.12	.484	RE	<.0001	70.79
AM		0.94	0.88-1.00	**.037**	RE	<.0001	72.75

Bold values indicate statistically significant.

Abbreviations: CDM1, Codominant 1 (TC vs CC); CDM2, Codominant 2 (TT vs CC); CDM3, Codominant 3 (TT vs TC); DM, dominant model (TT + TC vs CC); RM, recessive model (TT vs TC + CC); ODM, over-dominant model (TC vs TT + CC); AM, allele model (T vs C); NHL, non-Hodgkin lymphoma; FE, fixed-effects; RE, random-effects.

attenuating the secondary structures of their progenitors. This results in biological dysfunctions and abnormal expression of miRNA target genes that ultimately lead to cancer development.[164–166] More than 150 genetic association studies have been performed until now to analyze the role of the human *miR-196a2* rs11614913 variant with the

susceptibility to a variety of cancer; however, these concluded in contradictory findings. As a result, multiple meta-analyses were performed both on overall cancer and individual cancer risk to verify the contribution of rs11614913 polymorphism.[7,167–170] Notably, these meta-analyses also lacked some potential and updated studies that must be taken into consideration to reveal the absolute correlation between this variant and cancer susceptibility. Therefore, we performed this meta-analysis, including the largest possible number of association studies conducted in different cohorts or ethnicities to provide a cement outcome.

Our quantitative data synthesis from 152 studies (before adjusting the HWE *P* value) showed that rs11614913 in human *miR-196a2* is significantly correlated with the reduced risk of overall cancer in the CDM2, CDM3, RM, and AM genetic models (OR = 0.89, 0.93, 0.91, and 0.95, respectively). Again, analysis from the overall 140 studies (after adjusting the HWE *P* value) revealed that rs11614913 is also associated with the decreased risk of cancer in the same genetic models (OR = 0.89, 0.92, 0.91, and 0.95, respectively). Additionally, an ethnicity-based stratified analysis of 107 studies of Asian ancestry revealed a substantially decreased link of rs11614913 with cancer in the CDM2, CDM3, RM, and AM models (OR = 0.89, 0.91, 0.90, and 0.95, respectively) and of 6 studies from African ancestry showed a significantly increased correlation with cancer in the CDM1 and ODM genetic models (OR = 1.33 and 1.46) and decreased correlation in the CDM3 genetic model (OR = 0.66). A total of 24 studies of Caucasian ancestry were analyzed, but no significant association was observed for rs11614913 with cancer susceptibility ($P > .05$). Although our findings are comparable to the past studies,[7,167–170] there are discrepancies because of the small number of literature incorporated in these analyses.

Stratified analyses based on the cancer types, control population sources, and genotyping methods were also performed. A significantly reduced correlation of rs11614913 was observed with hepatocellular carcinoma, lung cancer, gynecological cancer, and breast cancer. In terms of the association of rs11614913 with oral cancer and renal cell cancer, a significantly increased association was reported. No significant correlation was reported for rs11614913 with bladder, colorectal, esophageal, gastric, head and neck, prostate, blood and bone marrow related cancer, non-Hodgkin's lymphoma, and glioma ($P > .05$). Again, the control population-based subgroup analysis reported a strongly reduced correlation between rs11614913 and cancer susceptibility for the HB population, but no association was found for PB-based controls. Although no significant association was observed for PCR-RFLP and TaqMan genotyping methods during subgroup analysis, a substantially reduced risk was observed for other genotyping methods (ARMS + Sequencing + MassARRAY). However, while some previous meta-analyses are consistent with

Table 5. Publication bias for the meta-analysis to detect the connection of *miR-196a2* rs11614913 polymorphism with overall cancer.

Genetic models	Egger's test *P* value	Begg-Mazumdar's test *P* value
CDM1	.553	.519
CDM2	.155	.761
CDM3	.056	.514
DM	.982	.514
RM	.054	.823
ODM	.092	.227
AM	.391	.434

Abbreviations: CDM1, Codominant 1 (TC vs CC); CDM2, Codominant 2 (TT vs CC); CDM3, Codominant 3 (TT vs TC); DM, dominant model (TT + TC vs CC); RM, recessive model (TT vs TC + CC); ODM, over-dominant model (TC vs TT + CC); AM, allele model (T vs C).

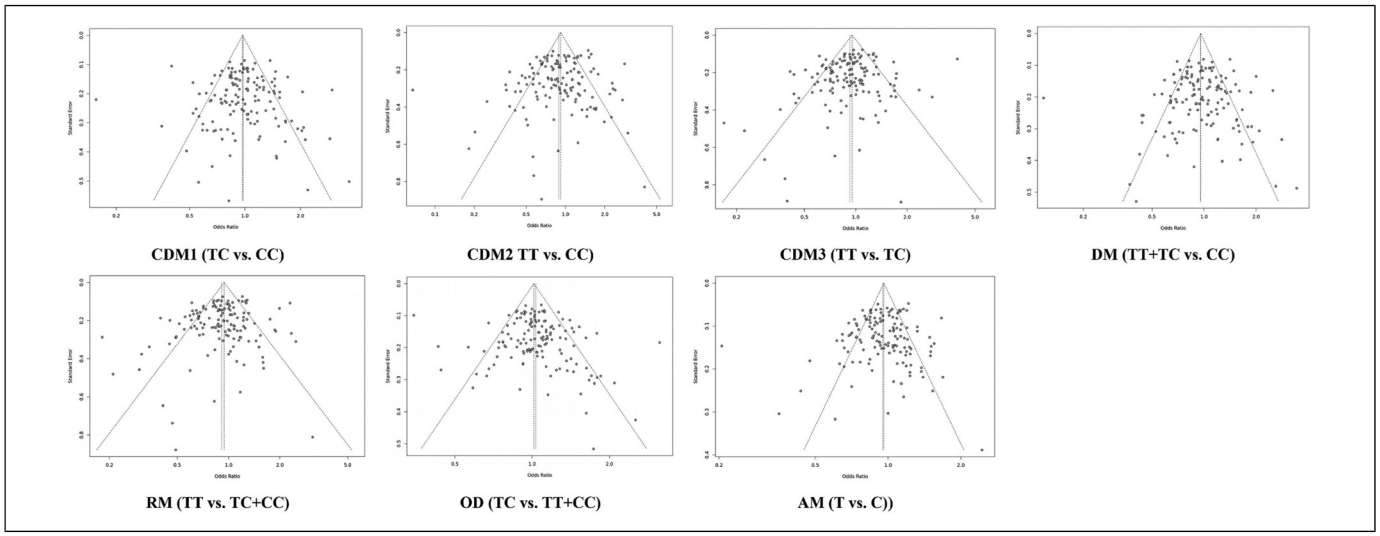

Figure 4. Funnel plots indicating the publication bias for detecting the connection of *miR-196a2* rs11614913 polymorphism with overall cancer susceptibility.

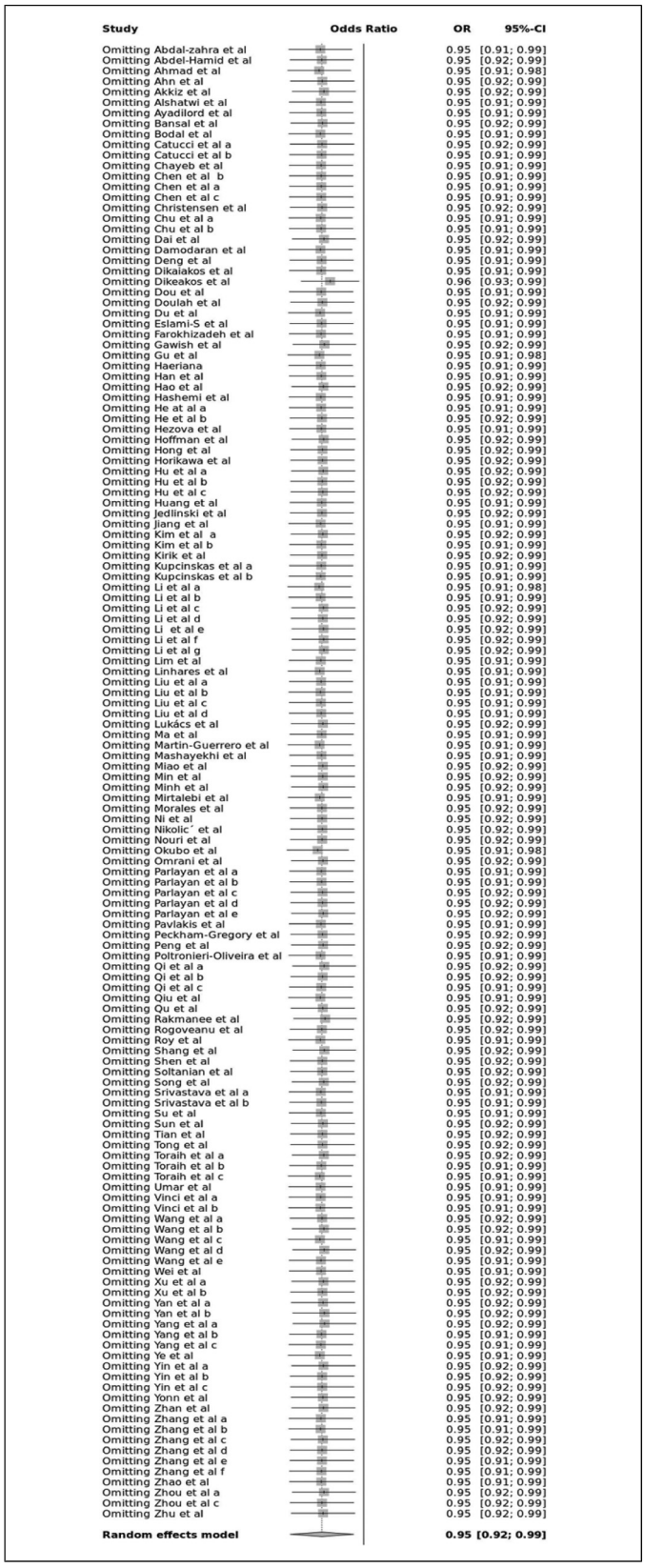

Figure 5. Sensitivity plot in allele model (AM) for detecting the connection of *miR-196a2* rs11614913 polymorphism and overall cancer.

our findings for hepatocellular carcinoma,[171,172] some others found no correlation between HCC and rs11614913 polymorphism.[173] Ren *et al*[174] reported the association of rs11614913 with lung cancer in a meta-analysis with 5 studies, which is consistent with our findings. Other meta-analyses with individual cancer susceptibility also produced conflicting outcomes, such as in breast cancer,[175] gastric cancer,[176,177] colorectal cancer,[178,179] esophageal cancer,[180] and prostate cancer.[181]

Moreover, we have performed heterogeneity analysis for all applied genetic models in the overall analysis and stratified analyses based on the cancer types, ethnicity, control sources, and genotyping methods. Even though we have conducted stratification based on the multiple parameters, we have observed significant heterogeneity in the case of the overall analysis and all stratified analyses in which RE models were applied. Notably, we did not observe any statistically significant publication bias in any genetic models, as depicted by Egger's funnel plots and Begg-Mazumdar's *P* values. Again, sensitivity analysis was implemented in all genetic models to measure the robustness of the outcomes of the study by omitting each study at a time. Our estimation showed that the values of ORs and 95% CIs were consistent in all genotypic and allele models, which demonstrates the reliability of our meta-analysis.

As far as we are aware, this is the most comprehensive and updated meta-analysis regarding the correlation between the human *miR-196a2* rs11614913 variant and cancer susceptibility. Also, ours is the first meta-analysis of *miR-196a2* rs11614913 which performed quantitative synthesis based on the ethnicity, cancer types, control sources, and genotyping methods at a time under 7 genetic models. Nevertheless, a few drawbacks of our study should be addressed. First, there is significant heterogeneity in most of the genetic models. Second, we may miss some potential studies due to the unresponsiveness of the authors who were contacted for full-text articles or detailed genotype data. Thirdly, there are relatively fewer studies on the African population, which might affect the statistical power of the current meta-analysis.

Conclusions

To summarize, the findings of the current meta-analysis confirm that the human *miR-196a2* rs11614913 genetic variant is correlated with cancer susceptibility in the overall population, especially in Asians and Africans. It is also correlated with breast cancer, lung cancer, hepatocellular carcinoma, gynecological malignancy, renal cell cancer, blood and bone marrow-related cancer, NHL, and oral cancer.

Authors' Note

Systematic review registration: INPLASY registration number: INPLASY202250027. Mohammad Safiqul Islam: conceptualized the meta-analysis. Md. Abdul Aziz: searched studies, extracted information, wrote the primary draft. Tahmina Akter: searched studies, extracted information, wrote the primary draft. Mohammad Safiqul

Islam: carried out the statistical analyses. Mohammad Safiqul Islam: critically reviewed and revised the manuscript. Before submission, all authors read and approved the final version of the manuscript. All data generated or analyzed during the present meta-analysis are available from the corresponding author on reasonable request.

Acknowledgments

The scientific contribution of this study is dedicated to the freedom fighters of Bangladesh who sacrificed their lives in the 1971 liberation war on the 50th anniversary of Bangladesh.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Mohammad Safiqul Islam https://orcid.org/0000-0003-4924-5319

Supplemental Material

Supplemental material for this article is available online.

References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics 2021. *CA Cancer J Clin*. 2021;71(3):7-33.
2. Cao W, Chen HD, Yu YW, Li N, Chen WQ. Changing profiles of cancer burden worldwide and in China: a secondary analysis of the global cancer statistics 2020. *Chin Med J (Engl)*. 2021;134(7):783-791.
3. Hong S, Won YJ, Lee JJ, et al. Cancer statistics in Korea: incidence mortality survival and prevalence in 2018. *Cancer Res Treat*. 2021;53(2):301-315.
4. Sung H, Ferlay J, Siegel RL, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin*. 2021;71(3):209-249.
5. Aziz MA, Jafrin S, Islam MS. Human TERT promoter polymorphism rs2853669 is associated with cancers: an updated meta-analysis. *Hum Cell*. 2021;34(4):1066-1081.
6. Feng L, Chen X, Zhang S, Chen Y, Yu Y. Role of miR-139-5p in ectopic endometrial stromal cells and the underlying molecular mechanism. *Exp Ther Med*. 2021;22(5):1251.
7. Choupani J, Nariman-Saleh-Fam Z, Saadatian Z, Ouladsahebmadarek E, Masotti A, Bastami M. Association of mir-196a-2 rs11614913 and mir-149 rs2292832 polymorphisms with risk of cancer: an updated meta-analysis. *Front Genet*. 2019;10:186.
8. Nazneen F, Millat MS, Barek MA, et al. Genetic polymorphism of miR-218-2 (rs11134527) in cervical cancer: a case-control study in the Bangladeshi women. *MicroRNA*. 2021;10(3):219-224.
9. Yan W, Gao X, Zhang S. Association of miR-196a2 rs11614913 and miR-499 rs3746444 polymorphisms with cancer risk: a meta-analysis. *Oncotarget*. 2017;8(69):114344-114359.
10. Li M, Marin-Muller C, Bharadwaj U, Chow KH, Yao Q, Chen C. MicroRNAs: control and loss of control in human physiology and disease. *World J Surg*. 2009;33(4):667-684.
11. Zhang B, Pan X, Cobb GP, Anderson TA. microRNAs as oncogenes and tumor suppressors. *Dev Biol*. 2007;302(1):1-12.
12. Mahmoud D, El-Sisi O, Sheta M, et al. Association of miR-196a2 and miR-149 single-nucleotide polymorphisms with atherosclerotic ischemic stroke susceptibility. *Egypt J Neurol Psychiatry Neurosurg*. 2020;56:87.
13. Afsharzadeh SM, Mohaddes Ardebili SM, Seyedi SM, Karimian Fathi N, Mojarrad M. Association between rs11614913 rs3746444 rs2910164 and occurrence of breast cancer in Iranian population. *Meta Gene*. 2017;11:20-25.
14. Ahmad M, Shah AA. Predictive role of single nucleotide polymorphism (rs11614913) in the development of breast cancer in Pakistani population. *Per Med*. 2020;17(3):213-227.
15. Bodal VK, Sangwan S, Bal MS, Kaur M, Sharma S, Kaur B. Association between Microrna 146a and Microrna 196a2 genes polymorphism and breast cancer risk in North Indian women. *Asian Pac J Cancer Prev*. 2017;18(9):2345-2348.
16. Dai ZM, Kang HF, Zhang WG, et al. The associations of single nucleotide polymorphisms in miR196a2 miR-499 and miR-608 with breast cancer susceptibility: a STROBE-compliant observational study. *Medicine (Baltimore)*. 2016;95(7):e2826.
17. Minh TTH, Thanh NTN, Van Thiep T, Hue NT. Association between single nucleotide polymorphism Rs11614913 (C > T) on Mir-196a2 and breast cancer in Vietnamese population in *IFMBE Proceedings* (ed. T. Vo Van T. Nguyen Le T. Nguyen Duc) 2018;63:381-386.
18. Ahn DH, Rah H, Choi YK, et al. Association of the miR-146aC>G miR-149T>C miR-196a2T>C and miR-499A>G polymorphisms with gastric cancer risk and survival in the Korean population. *Mol Carcinog*. 52(Suppl 1): E39-E51.
19. Gu JY, Tu L. Investigating the role of polymorphisms in miR-146a, -149, and -196a2 in the development of gastric cancer. *Genet Mol Res*. 2016;15(2):1-7.
20. Li M, Li RJ, Bai H, Association between the pre-miR-196a2 rs11614913 polymorphism and gastric cancer susceptibility in a Chinese population. *Genet Mol Res*. 2016;15(2):15027516.
21. Poltronieri-Oliveira AB, Madeira FF, Nunes DBSM, et al. Polymorphisms of miR-196a2 (rs11614913) and miR-605 (rs2043556) confer susceptibility to gastric cancer. *Gene Rep*. 2017;7:154-163.
22. Yang QY, Jie ZG, Wang J, Zhang SZ. Association between miR-196a rs11614913 C/T polymorphisms and gastric cancer susceptibility. *Acad J Guangzhou Med Coll*. 2013;41(3):13-17
23. Abdel-Hamid M, Elshaer S, Darwish A. Association of MicroRNA related single nucleotide polymorphisms 196A-2 and 499 with the risk of hepatocellular carcinoma in Egyptian patients. *Meta Gene*. 2018;16:139-142.
24. Gawish EA, Abu-Raia GY, Osheba I, et al. Association between miR-196a2 polymorphism and the development of

hepatocellular carcinoma in the Egyptian population. *Egypt Liver J*. 2020;10:16.
25. Huang Y, Sheng S, Chen B, Lin R, Yang J, Hao B. MiR-146a genetic polymorphism contributes to the susceptibility to hepatocellular carcinoma in a Chinese population. *Int J Clin Exp Pathol*. 2017;10:1833-1839.
26. Abdal-zahra N, Hamza SJ, Shamran HA, Al-Mayah QS. The significant of miR-196a2 C > T single nucleotide polymorphism and serum levels of Interleukin-1β (IL-1β) and Intrleukin-6 (IL-6) in colorectal cancer. *J Pharm Sci Res*. 2019;11(4):1652-1656.
27. Ayadilord M, Tavakoli T, Fakharian T, Soltaninejad E, Naseri M. Relationship analysis of the miR-196a2 polymorphism (rs11614913) with colorectal cancer risk in southern Khorasan eastern Iran. *Meta Gene*. 2020;26:100813.
28. Chayeb V, Mahjoub S, Zitouni H, et al. Contribution of microRNA-149 microRNA-146a and microRNA-196a2 SNPs in colorectal cancer risk and clinicopathological features in Tunisia. *Gene*. 2018;666:100-107.
29. Soltanian AR, Hosseini B, Mahjub H, Bahreini F, Mojarad EN, Ghaffari ME. Association between rs11614913 polymorphism of the MiR-196-a2 gene and colorectal cancer in the presence of departure from Hardy-Weinberg equilibrium. *Cell J*. 2021;23(3):313-318.
30. Hong YS, Kang HJ, Kwak JY, et al. Association between MicroRNA196a2 rs11614913 genotypes and the risk of non-small cell lung cancer in Korean population. *J Prevent Med Public Health*. 2011;44(3):125-130.
31. Shang W, Pang M, Liu Y. High resolution melting analysis of the correlation of the miRNA-196a2 gene polymorphism and lung cancer. *BMU J*. 2016;2:85-88.
32. Yin Z, Cui Z, Ren Y, Xia L, Li H, Zhou B. MiR-196a2 and lung cancer in Chinese non-smoking females: a genetic association study and expression analysis. *Oncotarget*. 2017;8(41):70890
33. Chen G, Zhang M, Zhu J, et al. Common genetic variants in pre-microRNAs are associated with cervical cancer susceptibility in southern Chinese women. *J Cancer*. 2020;11(8):2133
34. Liu X, Xu B, Li S, et al. Association of SNPs in miR-146a miR-196a2 and miR-499 with the risk of endometrial/ovarian cancer. *Acta Biochim Biophys Sin (Shanghai)*. 2015;47(7):564-566.
35. Lukács J, Soltész B, Penyige A, Nagy B, Póka R. Identification of miR-146a and miR-196a-2 single nucleotide polymorphisms at patients with high-grade serous ovarian cancer. *J Biotechnol*. 2019;297:54-57.
36. Srivastava S, Singh S, Fatima N, Mittal B, Srivastava AN. Pre-microrna gene polymorphisms and risk of cervical squamous cell carcinoma. *J Clin Diagn Res*. 2017;11(9):GC01-GC04.
37. Song ZS, Wu Y, Zhao HG, et al. Association between the rs11614913 variant of miRNA-196a-2 and the risk of epithelial ovarian cancer. *Oncol Lett*. 2016;11(1):194-200.
38. Yan Z, Zhou Z, Li C, et al. Polymorphisms in miRNA genes play roles in the initiation and development of cervical cancer. *J Cancer*. 2019;10(20):4747-4753.
39. Damodaran M, Paul SFD, Venkatesan V. Genetic polymorphisms in miR-146a miR-196a2 and miR-125a genes and its association in prostate cancer. *Pathol Oncol Res*. 2020;26(1):193-200.
40. Hashemi M, Moradi N, Ziaee SA, et al. Association between single nucleotide polymorphism in miR-499 miR-196a2 miR-146a and miR-149 and prostate cancer risk in a sample of Iranian population. *J Adv Res*. 2016;7(3):491-498.
41. Nouri R, Ghorbian S. Association of single nucleotide polymorphism in hsa-miR-499 and hsa-miR-196a2 with the risk of prostate cancer. *Int Urol Nephrol*. 2019;51(5):811-816.
42. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Br Med J*. 2021;372:n71.
43. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
44. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst*. 1959;22(4):719-748.
45. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple graphical test. *Br Med J*. 1997;315(7109):629-634.
46. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics*. 1994;50(4):1088-1101.
47. Benjamini Y, Hochberg Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. *J R Stat Soc Ser B Methodol*. 1995;57:(1)289-300.
48. Abd El Hassib DM, Abdulhafeez NA, Atef OM, Ameen SG. The role of miRNA-196a2 genotypes in the susceptibility of acute lymphoblastic leukemia in Egyptian children. *Gene Rep*. 2021;24:101237.
49. Akkiz H, Bayram S, Bekar A, Akgöllü E, Ülger Y. A functional polymorphism in pre-microRNA-196a-2 contributes to the susceptibility of hepatocellular carcinoma in a Turkish population: a case-control study. *J Viral Hepat*. 2011;18(7):e399-e407.
50. Alshatwi AA, Shafi G, Hasan TN, et al. Differential expression profile and genetic variants of microRNAs sequences in breast cancer patients. *PLoS One*. 2012;7(2):e30049.
51. Bansal C, Sharma KL, Misra S, Srivastava AN, Mittal B, Singh US. Common genetic variants in pre-microRNAs and risk of breast cancer in the north Indian population. *Ecancermedicalscience*. 2014;8:473
52. Catucci I, Yang R, Verderio P, et al. Evaluation of SNPs in miR-146a miR196a2 and miR-499 as low-penetrance alleles in German and Italian familial breast cancer cases. *Hum Mutat*. 2010;31(1):E1052-E1057.
53. Chen CC, Hsu PC, Shih LC, et al. MiR-196a-2 genotypes determine the susceptibility and early onset of childhood acute lymphoblastic leukemia. *Anticancer Res*. 2020;40(8):4465-4469.
54. Chen H, Sun L, Chen LL Y, Zheng HQ, Zhang QF. A variant in microRNA-196a2 is not associated with susceptibility to and progression of colorectal cancer in Chinese. *Intern Med J*. 2012;42(6):e115-e119
55. Christensen BC, Avissar-Whiting M, Ouellet LG, et al. Mature microRNA sequence polymorphism in MIR196A2 is associated with risk and prognosis of head and neck cancer. *Clin Cancer Res*. 2010;16(14):3713-3720.
56. Chu YH, Tzeng SL, Lin CW, Chien MH, Chen MK, Yang SF. Impacts of microRNA gene polymorphisms on the susceptibility

of environmental factors leading to carcinogenesis in oral cancer. *PLoS One*. 2012;7(6):39777.
57. Chu YH, et al. MicroRNA gene polymorphisms and environmental factors increase patient susceptibility to hepatocellular carcinoma. *PLoS One*. 2014;9:089930.
58. Deng S, Wang W, Li X, Zhang P. Common genetic polymorphisms in pre-microRNAs and risk of bladder cancer. *World J Surg Oncol*. 2015;13:297.
59. Dikaiakos P, Gazouli M, Rizos S, Zografos G, Theodoropoulos GE. Evaluation of genetic variants in miRNAs in patients with colorectal cancer. *Cancer Biomark*. 2015;15(2):163-168.
60. Dikeakos P, Theodoropoulos G, Rizos S, Tzanakis N, Zografos G, Gazouli M. Association of the miR-146aC>G miR-149T>C and miR-196a2T>C polymorphisms with gastric cancer risk and survival in the Greek population. *Mol Biol Rep*. 2014;41(2):1075-1080.
61. Dou T, Wu Q, Chen X, et al. A polymorphism of microRNA196a genome region was associated with decreased risk of glioma in Chinese population. *J Cancer Res Clin Oncol*. 2010;136(12):1853-1859.
62. Doulah A, Salehzadeh A, Mojarrad M. Association of single nucleotide polymorphisms in miR-499 and miR-196a with susceptibility to breast cancer. *Trop J Pharm Res*. 2018;17(2): 319-323.
63. Du W, Ma XL, Zhao C, et al. Associations of single nucleotide polymorphisms in mir-146a mir-196a mir-149 and mir-499 with colorectal cancer susceptibility. *Asian Pac J Cancer Prev*. 2014;15(2):1047-1055.
64. Eslami SZ, Tahmaseb M, Ghaderi A. The investigation of miR-196a2 rs11614913 with breast cancer susceptibility in south of IRAN. *Meta Gene*. 2018;17:43-47.
65. Farokhizadeh Z, Dehbidi S, Geramizadeh B, et al. Association of microRNA polymorphisms with hepatocellular carcinoma in an Iranian population. *Ann Lab Med*. 2019;39(1):58-66.
66. George GP, Gangwar R, Mandal RK, Sankhwar SN, Mittal RD. Genetic variation in microRNA genes and prostate cancer risk in north Indian population. *Mol Biol Rep*. 2011;38(3):1609-1615.
67. Haerian MS, Haerian BS, Molanaei S, et al. MIR196A2 Rs11614913 contributes to susceptibility to colorectal cancer in Iranian population: a multi-center case-control study and meta-analysis. *Gene*. 2018;669:82-90.
68. Han Y, Pu R, Han X, et al. Associations of pri-miR-34b/c and pre-miR-196a2 polymorphisms and their multiplicative interactions with hepatitis B virus mutations with hepatocellular carcinoma risk. *PLoS One*. 2013;8(3):e58564
69. Hao YX, Wang JP, Zhao LF. Associations between three common MicroRNA polymorphisms and hepatocellular carcinoma risk in Chinese. *Asian Pac J Cancer Prevent*. 2014;14(11): 6601-6604.
70. He B, et al. Associations of polymorphisms in microRNAs with female breast cancer risk in Chinese population. *Tumor Biol*. 2015;36(6):4575-4582.
71. He J, Zou Y, Liu X, et al. Association of common genetic variants in pre-microRNAs and neuroblastoma susceptibility: a two-center study in Chinese children. *Mol Ther Nucleic Acids*. 2018;11:1-8.
72. Hezova R, Kovarikova A, Bienertova-Vasku J, et al. Evaluation of SNPs in miR-196-a2 miR-27a and miR-146a as risk factors of colorectal cancer. *World J Gastroenterol*. 2012;18(22):2827-2831.
73. Hoffman AE, Zheng T, Yi C, et al. microRNA miR-196a-2 and breast cancer: a genetic and epigenetic association study and functional analysis. *Cancer Res*. 2009;69(14): 5970-5977.
74. Horikawa Y, Wood CG, Yang H, et al. Single nucleotide polymorphisms of microRNA machinery genes modify the risk of renal cell carcinoma. *Clin Cancer Res*. 2008;14:7956-7962.
75. Hu E, Wang D, Zhang X, et al. Four common polymorphisms in microRNAs and the risk of adult glioma in a Chinese case-control study. *J Mol Neurosci*. 2013;51(3):933-940.
76. Hu Z, Chen J, Tian T, et al. Genetic variants of miRNA sequences and non-small cell lung cancer survival. *J Clin Invest*. 2008;118(7):2600-2608.
77. Hu Z, Liang J, Wang Z, et al. Common genetic variants in pre-microRNAs were associated with increased risk of breast cancer in Chinese women. *Hum Mutat*. 2009;30(1):79-84.
78. Jedlinski DJ, Gabrovska PN, Weinstein SR, Smith RA, Griffiths LR. Single nucleotide polymorphism in hsa-mir-196a-2 and breast cancer risk: a case control study. *Twin Res Hum Genet*. 2011;14(5):417-421.
79. Jiang J, Jia ZF, Cao DH, Wu YH, Sun ZW, Cao XY. Association of the MIR-146a rs2910164 polymorphism with gastric cancer susceptibility and prognosis. *Futur Oncol*. 2016;12(19):2215-2226.
80. Kim MJ, Yoo SS, Choi YY, Park JY. A functional polymorphism in the pre-microRNA-196a2 and the risk of lung cancer in a Korean population. *Lung Cancer*. 2010;69:(1)127-129.
81. Kim WH, Min KT, Jeon YJ, et al. Association study of microRNA polymorphisms with hepatocellular carcinoma in Korean population. *Gene*. 2012;504(1):92-97.
82. Kirik MP, Pehlivan M, Nursal AF, Oyaci Y, Pehlivan S, Serin I. The miRNA 196a2 rs11614913 variant has prognostic impact on Turkish patients with multiple myeloma. *BMC Res Notes*. 2020;13(1):545.
83. Kou JT, Fan H, Han D, et al. Association between four common microRNA polymorphisms and the risk of hepatocellular carcinoma and HBV infection. *Oncol Lett*. 2014;8(3):1255-1260.
84. Kupcinskas J, Wex T, Link A, et al. Gene polymorphisms of micrornas in helicobacter pylori-induced high risk atrophic gastritis and gastric cancer. *PLoS One*. 2014b;9(1):e87467
85. Kupcinskas J, Bruzaite I, Juzenas S, et al. Lack of association between miR-27a, miR-146a, miR-196a-2, miR-492 and miR-608 gene polymorphisms and colorectal cancer. *Sci Rep*. 2014a;4:5993.
86. Li D, Peng JJ, Tan Y, et al. Genetic variations in microRNA genes and susceptibility to hepatocellular carcinoma. *Genet Mol Res*. 2015;14(1):1926-1931.
87. Li P, Yan H, Zhang H, et al. A functional polymorphism in MIR196A2 is associated with risk and progression of

nasopharyngeal carcinoma in the Chinese population. *Genet Test Mol Biomarkers*. 2014;18(3):149-155.
88. Li XD, Li ZG, Song XX, Liu CF. A variant in microRNA-196a2 is associated with susceptibility to hepatocellular carcinoma in Chinese patients with cirrhosis. *Pathology*. 2010;42(7):669-673.
89. Li Y. MicroRNA related SNPs and genetic susceptibility to hepatocellular carcinoma. Master thesis: Chinese PLA. *Military Med Sci Acad PLA*. 2012;735:1-87.
90. Li J, Cheng G, Wang S. A single-nucleotide polymorphism of miR-196a2T>C rs11614913 is associated with hepatocellular carcinoma in the Chinese population. *Genet Test Mol Biomarkers*. 2016;20(4):213-215.
91. Li T, Niu L, Wu L, et al. A functional polymorphism in microRNA-196a2 is associated with increased susceptibility to non-Hodgkin lymphoma. *Tumor Biol*. 2015;36(5):3279-3284.
92. Lim J, Kim JO, Park HS, et al. Associations of miR-146aC>G, miR-149C>T, miR-196a2C>T and miR-499A>G polymorphisms with brain tumors. *Oncol Rep*. 2018;40(3):1813-1823.
93. Linhares JJ, Azevedo M Jr, Siufi AA, et al. Evaluation of single nucleotide polymorphisms in microRNAs (hsa-miR-196a2 rs11614913 C/T) from Brazilian women with breast cancer. *BMC Med Genet*. 2012;13:119.
94. Liu CJ, Tsai MM, Tu HF, Lui MT, Cheng HW, Lin SC. MiR-196a overexpression and mir-196a2 gene polymorphism are prognostic predictors of oral carcinomas. *Ann Surg Oncol*. 2013;20(Suppl 3):S406-S414.
95. Liu Z, Li G, Wei S, et al. Genetic variants in selected pre-MicroRNA genes and the risk of squamous cell carcinoma of the head and neck. *Cancer*. 2010;116(20):4753-4760.
96. Lv M, Dong W, Li L, et al. Association between genetic variants in pre-miRNA and colorectal cancer risk in a Chinese population. *J Cancer Res Clin Oncol*. 2013;139(8):1405-1410.
97. Ma F, Zhang P, Lin D, et al. There is no association between microRNA gene polymorphisms and risk of triple negative breast cancer in a Chinese Han population. *PLoS One*. 2013;8(3):e60195.
98. Martin-Guerrero I, Gutierrez-Camino A, Lopez-Lopez E, et al. Genetic variants in miRNA processing genes and pre-MiRNAs are associated with the risk of chronic lymphocytic leukemia. *PLoS One*. 2015;10(3):0118905.
99. Mashayekhi S, Saeidi Saedi H, Salehi Z, Soltanipour S, Mirzajani E. Effects of miR-27a, miR-196a2 and miR-146a polymorphisms on the risk of breast cancer. *Br J Biomed Sci*. 2018;75(2):76-81.
100. Miao L, Wang L, Zhu L, et al. Association of microRNA polymorphisms with the risk of head and neck squamous cell carcinoma in a Chinese population: a case-control study. *Chin J Cancer*. 2016;35(1):77.
101. Min KT, Kim JW, Jeon YJ, et al. Association of the miR-146aC>G, 149C>T, 196a2C>T, and 499A>G polymorphisms with colorectal cancer in the Korean population. *Mol Carcinog*. 2012;51(Suppl 1):E65-E73.
102. Mirtalebi H, Heydari Nasrabadi M, Pourhoseingholi MA, Asadzadeh-Aghdaei H. Association of miR-196a2 (rs11614913) polymorphism with colorectal cancer in Tehran population. *Med Sci J Islamic Azad Univ*. 2014;23(4):11-15.
103. Mittal RD, Gangwar R, George GP, Mittal T, Kapoor R. Investigative role of pre-MicroRNAs in bladder cancer patients: a case-control study in north India. *DNA Cell Biol*. 2011;30(6):401-406.
104. Morales S, Gulppi F, Gonzalez-Hormazabal P, et al. Association of single nucleotide polymorphisms in pre-miR-27a, pre-miR-196a2, pre-miR-423, miR-608 and pre-miR-618 with breast cancer susceptibility in a south American population. *BMC Genet*. 2016;17(1):1-10.
105. Nejati-Azar A, Alivand MR. MiRNA 196a2(rs11614913) & 146a(rs2910164) polymorphisms & breast cancer risk for women in an Iranian population. *Per Med*. 2018;15(4):279-289.
106. Ni J, Huang Y. Role of polymorphisms in miR-146a, miR-149, miR-196a2 and miR-499 in the development of ovarian cancer in a Chinese population. *Int J Clin Exp Pathol*. 2016; 9:5706-5711.
107. Nikolić Z, Savić Pavićević D, Vučić N, et al. Assessment of association between genetic variants in microRNA genes hsa-miR-499, hsa-miR-196a2 and hsa-miR-27a and prostate cancer risk in Serbian population. *Exp Mol Pathol*. 2015;99(1):145-150.
108. Okubo M, Tahara T, Shibata T, et al. Association between common genetic variants in pre-microRNAs and gastric cancer risk in Japanese population. *Helicobacter*. 2010;15(6):524-531.
109. Omrani M, Hashemi M, Eskandari-Nasab E, et al. . Hsa-mir-499 rs3746444 gene polymorphism is associated with susceptibility to breast cancer in an Iranian population. *Biomark Med*. 2014;8(2):259-267.
110. Parlayan C, Ikeda S, Sato N, Sawabe M, Muramatsu M, Arai T. Association analysis of single nucleotide polymorphisms in miR-146a and miR-196a2 on the prevalence of cancer in elderly Japanese: a case-control study. *Asian Pac J Cancer Prev*. 2014;15(5):2101-2107.
111. Pavlakis E, Papaconstantinou I, Gazouli M, et al. MicroRNA gene polymorphisms in pancreatic cancer. *Pancreatology*. 2013;13(3):273-278.
112. Peckham-Gregory EC, Thapa DR, Martinson J, et al. MicroRNA-related polymorphisms and non-Hodgkin lymphoma susceptibility in the multicenter AIDS cohort study. *Cancer Epidemiol*. 2016;45:47-57.
113. Peng S, Kuang Z, Sheng C, Zhang Y, Xu H, Cheng Q. Association of MicroRNA-196a-2 gene polymorphism with gastric cancer risk in a Chinese population. *Digest Dis Sci*. 2010;55(8):2288-2293.
114. Pu JY, Dong W, Zhang L, Liang WB, Yang Y, Lv ML.et al. No association between single nucleotide polymorphisms in pre-mirnas and the risk of gastric cancer in Chinese population. *Iran J Basic Med Sci*. 2014;17(2):128-133.
115. Qi P, Wang L, Zhou B, et al. Associations of miRNA polymorphisms and expression levels with breast cancer risk in the Chinese population. *Genet Mol Res*. 2015;14(2):6289-6296.
116. Qi JH, Wang J, Chen J, et al. High-resolution melting analysis reveals genetic polymorphisms in MicroRNAs confer hepatocellular carcinoma risk in Chinese patients. *BMC Cancer*. 2014;14:643.
117. Qi P, Dou TH, Geng L, et al. Association of a variant in MIR 196A2 with susceptibility to hepatocellular carcinoma in male

Chinese patients with chronic hepatitis B virus infection. *Hum Immunol*. 2010;71(6):621-626.
118. Qiu H, Xie Z, Tang W, et al. Association between microRNA-146a, -499a, and -196a-2 SNPs and non-small cell lung cancer: a case–control study involving 2249 subjects. *Biosci Rep*. 2021;41(2):1-13.
119. Qu Y, Qu H, Luo M, et al. MicroRNAs related polymorphisms and genetic susceptibility to esophageal squamous cell carcinoma. *Mol Genet Genom*. 2014;289(6):1123-1130.
120. Rakmanee S, Pakakasama S, Hongeng S, Sanguansin S, Thongmee A, Pongstaporn W. Increased risk of Thai childhood acute lymphoblastic leukemia with the MiR196a2 T > C polymorphism. *Asian Pac J Cancer Prevent*. 2017;18(4):1117-1120.
121. Rogoveanu I, Burada F, Cucu MG, Vere CC, Ioana M, Cîmpeanu RA. Association of microRNA polymorphisms with the risk of gastric cancer in a Romanian population. *J Gastrointest Liver Dis*. 2017;26(3):231-238.
122. Roy R, De Sarkar N, Ghose S, et al. Genetic variations at microRNA and processing genes and risk of oral cancer. *Tumor Biol*. 2014;35(4):3409-3414.
123. Shen F, Chen J, Guo S, et al. Genetic variants in miR-196a2 and miR-499 are associated with susceptibility to esophageal squamous cell carcinoma in Chinese Han population. *Tumor Biol*. 2016;37(4):4777-4784.
124. Sodhi KK, Bahl C, Singh N, Behera D, Sharma S. Functional genetic variants in pre-MIR-146a and 196a2 genes are associated with risk of lung cancer in north Indians. *Future Oncol*. 2015;11(15):2159-2173.
125. Srivastava K, Srivastava A, Mittal B. Common genetic variants in pre-microRNAs and risk of gallbladder cancer in north Indian population. *J Hum Genet*. 2010;55(8):495-499.
126. Su R, Li W, Luo R. Association between miR-146a, miR-149, miR-196a2 and miR-499 gene polymorphisms and the susceptibility to gastric cancer in a Chinese population. *Int J Clin Exp Pathol*. 2016;9:2192-2199.
127. Sun XC, Zhang AC, Tong LL, et al. miR-146a and miR-196a2 polymorphisms in ovarian cancer risk. *Genet Mol Res*. 2016;15(3):10.4238/gmr.15038468.
128. Sushma PS, Jamil K, Kumar PU, Satyanarayana U, Ramakrishna M, Triveni B. Genetic variation in microRNAs and risk of oral squamous cell carcinoma in south Indian population. *Asian Pac J Cancer Prev*. 2015;16(17):7589-7594.
129. Thakur N, Singhal P, Mehrotra R, Bharadwaj M. Impacts of single nucleotide polymorphisms in three microRNAs (miR-146a, miR-196a2 and miR-499) on the susceptibility to cervical cancer among Indian women. *Biosci Rep*. 2019;39(4): BSR20180723.
130. Tian T, Shu Y, Chen J, et al. A functional genetic variant in microRNA-196a2 is associated with increased susceptibility of lung cancer in Chinese. *Cancer Epidemiol Biomarkers Prevent*. 2009;18(4):1183-1187.
131. Tong N, Xu B, Shi D, et al. Hsa-miR-196a2 polymorphism increases the risk of acute lymphoblastic leukemia in Chinese children. *Mutat Res*. 2014;759:16-21.
132. Toraih EA, Fawzy MS, Mohammed EA, Hussein MH, EL-Labban MM. MicroRNA-196a2 biomarker and targetome network analysis in solid tumors. *Mol Diagn Ther*. 2016;20(6): 559-577.
133. Toraih EA, Fawz MS, Elgazzaz MG, Hussein MH, Shehata RH, Daoud HG. Combined genotype analyses of precursor miRNA-196a2 and -499a variants with hepatic and renal cancer susceptibility a preliminary study. *Asian Pac J Cancer Prev*. 2016;17(7):3369-3375.
134. Umar M, Upadhyay R, Prakash G, Kumar S, Ghoshal UC, Mittal B. Evaluation of common genetic variants in pre-microRNA in susceptibility and prognosis of esophageal cancer. *Mol Carcinog*. 2013;52(Suppl 1):E10-E18.
135. Vinci S, Gelmini S, Mancini I, et al. Genetic and epigenetic factors in regulation of microRNA in colorectal cancers. *Methods*. 2013;59(1):138-146.
136. Vinci S, Gelmini S, Pratesi N, et al. Genetic variants in miR-146a, miR-149, miR-196a2, miR-499 and their influence on relative expression in lung cancers. *Clin Chem Lab Med* 2011;49(12):2073-2080.
137. Wang S, Zhu H, Ding B, et al. Genetic variants in microRNAs are associated with cervical cancer risk. *Mutagenesis*. 2019;34(2):127-133.
138. Wang J, Zhang Y, Zhang Y, Chen L. Correlation between miRNA-196a2 and miRNA-499 polymorphisms and bladder cancer. *Int J Clin Exp Med*. 2016;9:20484-20488.
139. Wang S, Tao G, Wu D, et al. A functional polymorphism in MIR196A2 is associated with risk and prognosis of gastric cancer. *Mol Carcinog*. 2013;52(Suppl 1):E87-E95.
140. Wang K, Guo H, Hu H, et al. A functional variation in pre-microRNA-196a is associated with susceptibility of esophageal squamous cell carcinoma risk in Chinese Han. *Biomarkers*. 2010;15(7):614-618.
141. Wang N, Li Y, Zhou RM, et al. Hsa-miR-196a2 functional SNP is associated with the risk of ESCC in individuals under 60 years old. *Biomarkers*. 2014;19(1):43-48.
142. Wei J, Zheng L, Liu S, et al. MiR-196a2 rs11614913 T > C polymorphism and risk of esophageal cancer in a Chinese population. *Hum Immunol*. 2013;74(9):1199-1205.
143. Xu X, Ling Q, Wang J, et al. Donor miR-196a-2 polymorphism is associated with hepatocellular carcinoma recurrence after liver transplantation in a Han Chinese population. *Int J Cancer*. 2016;138(3):620-629.
144. Xu Y. Association Study of Polymorphisms in MiRNAs Genes with the Susceptibility of Hepatocellular Carcinoma. *Nanjing Medical University*. 2010.
145. Yan P, et al. Predictive role of miR-146a rs2910164 (C > G), miR-149 rs2292832 (T > C), miR-196a2 rs11614913 (T > C) and miR-499 rs3746444 (T > C) in the development of hepatocellular carcinoma. *Int J Clin Exp Pathol*. 2015;8(11):15177-15183.
146. Yang H, Dinney CP, Ye Y, Zhu Y, Grossman HB, Wu X. et al. Evaluation of genetic variants in microRNA-related genes and risk of bladder cancer. *Cancer Res*. 2008;68(7):2530-2537.
147. Yang S, Zheng Y, Zhou L, et al. miR-499 rs3746444 and miR-196a-2 rs11614913 are associated with the risk of glioma, but not the prognosis. *Mol Ther Nucleic Acids*. 2020;22:340-351.

148. Ye Y, Wang KK, Gu J, et al. Genetic variations in microRNA-related genes are novel susceptibility loci for esophageal cancer risk. *Cancer Prev Res (Phila)*. 2008;1(6):460-469.
149. Yin Z, Cui Z, Ren Y, et al. Association between polymorphisms in pre-miRNA genes and risk of lung cancer in a Chinese nonsmoking female population. *Lung Cancer*. 2016;94:15-21.
150. Yin Z, Cui Z, Guan P, et al. Interaction between polymorphisms in pre-miRNA genes and cooking oil fume exposure on the risk of lung cancer in Chinese non-smoking female population. *PLoS One*. 2015;10(6):0128572.
151. Yoon KA, Yoon H, Park S, et al. The prognostic impact of microRNA sequence polymorphisms on the recurrence of patients with completely resected non-small cell lung cancer. *J Thorac Cardiovasc Surg*. 2012;144(4):794-807.
152. Zhan JF, Chen LH, Chen ZX, et al. A functional variant in MicroRNA-196a2 is associated with susceptibility of colorectal cancer in a Chinese population. *Arch Med Res*. 2011;42(2):144-148.
153. Zhang E, Xu Z, Duan W, Huang S, Lu L. Association between polymorphisms in premiRNA genes & risk of oral squamous cell cancer in a Chinese population. *PLoS One*. 2017;12(6):0176044.
154. Zhang M, Jin M, Yu Y, et al. Associations of miRNA polymorphisms and female physiological characteristics with breast cancer risk in Chinese population. *Eur J Cancer Care (Engl)*. 2012;21(2):274-280.
155. Zhang J, Wang R, Ma YY, et al. Association between single nucleotide polymorphisms in miRNA196a-2 and miRNA146a and susceptibility to hepatocellular carcinoma in a Chinese population. *Asian Pac J Cancer Prev*. 2013;14(11):6427-6431.
156. Zhang LH, Hao BB, Zhang CY, Dai XZ, Zhang F. Contributions of polymorphisms in mir146a, mir196a, and mir499 to the development of hepatocellular carcinoma. *Genet Mol Res*. 2016;15(3):10.4238/gmr.15038582.
157. Zhang S, Chen L, Wang Y, Tang W, Chen Y, Liu L. Investigation of the association of miRNA-499, miRNA-146a, miRNA-196a2 loci with hepatocellular carcinoma risk: a case-control study involving 1507 subjects. *DNA Cell Biol*. 2020;39(3):379-388.
158. Zhang XW, Pan SD, Feng YL, et al. Relationship between genetic polymorphism in microRNAs precursor and genetic predisposition of hepatocellular carcinoma. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2011;45(3):239-243.
159. Zhao H, Xu J, Zhao D, et al. Somatic mutation of the SNP rs11614913 and its association with increased MIR 196A2 expression in breast cancer. *DNA Cell Biol*. 2016;35(2):81-87.
160. Zhou B, Dong LP, Jing XY, et al. Association between miR-146aG>C and miR-196a2C>T polymorphisms and the risk of hepatocellular carcinoma in a Chinese population. *Tumor Biol*. 2014;35(8):7775-7780.
161. Zhou C, Tang Y, Zhu J, et al. Association of miR-146a, miR-149 and miR-196a2 polymorphisms with neuroblastoma risk in eastern Chinese population: a three-center case-control study. *Biosci Rep*. 2019;39(6):BSR20181907.
162. Zhou B, Wang K, Wang Y, et al. Common genetic polymorphisms in pre-microRNAs and risk of cervical squamous cell carcinoma. *Mol Carcinog*. 2011;50(7):499-505.
163. Zhu L, Chu H, Gu D, et al. A functional polymorphism in miRNA-196a2 is associated with colorectal cancer risk in a Chinese population. *DNA Cell Biol*. 2012;31(3):349-353.
164. Nariman-Saleh-Fam Z, Bastami M, Somi MH, et al. In silico dissection of miRNA targetome polymorphisms and their role in regulating miRNA-mediated gene expression in esophageal cancer. *Cell Biochem Biophys*. 2016;74(4):483-497.
165. Ghaedi H, Bastami M, Zare-Abdollahi D, et al. Bioinformatics prioritization of SNPs perturbing microRNA regulation of hematological malignancy-implicated genes. *Genomics*. 2015;106(6):360-366.
166. Ryan BM, Robles AI, Harris CC. Genetic variation in microRNA networks: the implications for cancer research. *Nat Rev Cancer*. 2010;10(6):389-402.
167. Liu Y, He A, Liu B, et al. Rs11614913 polymorphism in miRNA-196a2 and cancer risk: an updated meta-analysis. *Onco Targets Ther*. 2018;11:1121-1139.
168. Kang Z, Li Y, He X, et al. Quantitative assessment of the association between miR-196a2 rs11614913 polymorphism and cancer risk: evidence based on 45,816 subjects. *Tumor Biol*. 2014;35(7):6271-6282.
169. Zhang H, Su YL, Yu H, Qian BY. Meta-Analysis of the association between Mir-196a-2 polymorphism and cancer susceptibility. *Cancer Biol Med*. 2012;9(1):63-72.
170. Chu H, Wang M, Shi D, et al. Hsa-miR-196a2 Rs11614913 polymorphism contributes to cancer susceptibility: evidence from 15 case-control studies. *PLoS One*. 2011;6(3):e18108.
171. Zheng L, Zhuang C, Zhao J, Ming L. Functional miR-146a, miR-149, miR-196a2 and miR-499 polymorphisms and the susceptibility to hepatocellular carcinoma: an updated meta-analysis. *Clin Res Hepatol Gastroenterol*. 2017;41(6):664-676.
172. Yu JY, Hu F, Du W, Ma XL, Yuan K. Study of the association between five polymorphisms and risk of hepatocellular carcinoma: a meta-analysis. *J Chin Med Assoc*. 2017;80(4):191-203.
173. Peng Q, Li S, Lao X, et al. The association of common functional polymorphisms in mir-146a and mir-196a2 and hepatocellular carcinoma risk: evidence from a meta-analysis. *Medicine (Baltimore)*. 2014;93(29):e252.
174. Ren YG, Zhou XM, Cui ZG, Hou G. Effects of common polymorphisms in miR-146a and miR-196a2 on lung cancer susceptibility: a meta-analysis. *J Thorac Dis*. 2016;8(6):1297-1305.
175. Mu K, Wu ZZ, Yu JP, et al. Meta-analysis of the association between three microRNA polymorphisms and breast cancer susceptibility. *Oncotarget*. 2017;8(40):68809-68824.
176. Ni Q, Ji A, Yin J, Wang X, Liu X. Effects of two common polymorphisms rs2910164 in miR-146a and rs11614913 in miR-196a2 on gastric cancer susceptibility. *Gastroenterol Res Pract*. 2015; 2015:764163.
177. Zhang L, Gao J, Zhou D, Bao F. Lack of association of two common polymorphisms rs2910164 and rs11614913 with susceptibility to gastric cancer: a meta-analysis. *Turk J Gastroenterol*. 2015;26(5):378-385.
178. Wan D, Gu W, Xu G, et al. Effects of common polymorphisms rs2910164 in miR-146a and rs11614913 in miR-196a2 on susceptibility to colorectal cancer: a systematic review meta-analysis. *Clin Transl Oncol*. 2014;16(9):792-800.

179. Du W, Ma X, Kong W, et al. Association between rs11614913 polymorphism in miR-196a2 and colorectal cancer risk: a meta-analysis. *Cancer Biomark*. 2013;13(6):457-464.
180. Guo X, Zhao L, Shen Y, Shao Y, Wei W, Liu F. Polymorphism of miRNA and esophageal cancer risk: an updated systemic review and meta-analysis. *Onco Targets Ther*. 2019;12:3565-3580.
181. Mi Y, Ren K, Zou J, et al. The association between three genetic variants in MicroRNAs (Rs11614913, Rs2910164, Rs3746444) and prostate cancer risk. *Cell Physiol Biochem*. 2018;48(1):149-157.