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MiRNA-146a rs2910164 Confers a Susceptibility to Digestive System Cancer: A Meta-Analysis Involving 59,098 Subjects

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ABSTRACT

Background: *MicroRNA* (*miR*)*-146a* might participate in the occurrence of malignant tumor. The aim of the current investigation was to evaluate the relationship of *microRNA-146a* (*miR-146a*) rs2910164 C > G locus to the development of digestive system cancer (DSC).

Methods: We retrieved publications from PubMed, China Biology Medicine and EMBASE databases up to August 29, 2019. Finally, 56 independent case-control studies with 59,098 participants were included. The strength of the relationship between rs2910164 locus and a risk of DSC was assessed. The power value was also calculated in this study.

Results: We identified a correlation of rs2910164 locus in *miR-146a* with DSC development in dominant model (P = .035; power value = 0.994). *MiR-146a* rs2910164 locus was also identified to be correlated with a risk of DSC in Asians (GG/CG vs. CC: P = .033; power value = 0.989). Sensitivity analysis revealed that any individual study could not alter the final decision. In our study, no significant bias was found among these included studies (P > .1). The results of heterogeneity analysis suggested that small sample size (<1000 subjects), colorectal carcinoma, Asians, gastric carcinoma, esophageal squamous cell carcinoma, hepatocellular cancer, hospital-based study and high-quality score (≥7.0) subgroups contributed the heterogeneity to our findings. Galbraith radial plot determined that eleven outliers contributed to the main heterogeneity.

Conclusion: In summary, this meta-analysis highlights that rs2910164 locus might be implicated in the risk of DSC. More studies are, therefore, needed to confirm our results.

KEYWORDS
Meta-analysis; microRNA; polymorphism; cancer; digestive system

Introduction

Nowadays, malignant neoplasm of digestive system is a common burden on society which has seriously influenced individual's survival and fitness worldwide. Digestive system cancer (DSC) included colorectal carcinoma (CRC), oral carcinoma (OC), hepatocellular cancer (HCC), esophageal carcinoma (EC), gastric carcinoma (GC),

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gallbladder cancer (GBC), pancreatic cancer (PC), etc. The incidence of most subtypes of DSC was occurred frequently, such as EC, GC, HCC and CRC (Bray et al. 2018). Although the development of carcinoma has not been fully understood, accumulating evidences indicate that cancer is a result of complex interaction between multiple environmental factors and individual's genes.

In eukaryotes, microRNAs (miRs) are about 22 single-strand nucleotide acid which regulates related gene expression. Many investigations have suggested that miRs are important for controlling various functions of body. An abnormal expression of miR might be implicated in various human diseases. Accumulating evidences have indicated that miRs are implicated in growth and migration, inflammatory response, infection, immune response and cellular metabolism (Chen et al. 2019; Yang et al. 2019; Zhang et al. 2019a). *MiR-146a* is one of the common *miRs* which are of great importance for the roles of posttranscriptional regulatory. Investigations have suggested that *miR-146a* is important for process of innate immune response and inflammation, in which it acts as a vital negative regulator. In human infectious disease, pathogens must be recognized firstly, which is the necessary condition for activating the immune response (Saba et al. 2014). It is reported that several target loci of 3′-untranslated regions in toll-like receptors (TLRs) mRNAs are found (O'Neill et al. 2011). Interestingly, by using bioinformatics, a recent study has identified a potential interaction of *miR-146a* with TLR4 (Li and Shi 2013; Yang et al. 2011). *MiR-146a* is also implicated in cancer. It was reported that *miR-146a* facilitated oncogenesis of colorectal cancer and affected the microenvironment in tumor tissue (Cheng et al. 2019).

Single nucleotide polymorphisms (SNPs) in miRs could affect the stability and biological function of miR, and then influence the regulation of target gene. Rs2910164 C > G locus in *miR-146a* could influence the survival of CRC by regulating the cell apoptosis and the expression of cyclooxygenase-2 (Zhang et al. 2019b). A growing number of investigations have shown that *miR-146a* rs2910164 may confer the susceptibility to malignancy. Recently, many publications have explored the relationship of rs2910164 variants with DSC risk. Rs2910164 in *miR-146a* and its importance to the initiate of DSC have been widely explored. Some meta-analyses showed that G allele in rs2910164 polymorphism might not influence the initiate of DSC (Chen et al. 2014; Wang et al. 2012; Wu et al. 2013). Other published meta-analyses identified that rs2910164 variants could be implicated in the risk of DSC in Asian population (Li et al. 2014; Xie et al. 2015; Xu et al. 2014). As well, a meta-analysis reported that rs2910164 polymorphism conferred a risk of DSC in both Asians and Caucasians (Xie and Wang 2017). However, a more recent meta-analysis failed to confirm any relationship between rs2910164 and DSC risk (Xiong et al. 2017). Thus, the correlation of this locus with the development of DSC is more controversial. Nowadays, more studies have investigated the relationship of rs2910164 locus with DSC risk. By using a meta-analysis, pooling all eligible data might reduce the random error and increase the power of study. Finally, we could get a precise evaluation for the potential inherited correlation of rs2910164 polymorphism with DSC risk.

Materials and methods

Study researching

Using PubMed, China Biology Medicine and EMBASE databases, we searched the related studies (up to August 29, 2019). The following researching strategy was used: (microRNA-146a2 OR *miR-146a2* OR rs2910164) AND (cancer OR carcinoma) AND (SNP OR polymorphism). To retrieve more related publications, the references in reviews and the original studies were also searched. In this study, there was no language restriction. According to the Table S1 PRISMA Checklist, this study was reported.

Data extraction

Two authors (L. Lv and Z. Chen) conducted data extraction independently. The eligible publication met the major included criteria: (a) assessing an association of rs2910164 with DSC risk; (b) designed as a case-control study; and (c) data could be obtained. Otherwise, the publications were excluded. The following exclusion criteria were used: (a) not case-control study; (b) only considering the prognosis of DSC; (c) review or meta-analysis; and (d) comments. If the extracted data were conflicting, another author (W. Tang) was invited to discuss until a consensus opinion was reached. The following information was extracted: source of controls, year of publication, first author, cancer type, Hardy–Weinberg equilibrium (HWE), country, ethnicity, the number of participants and genotypes.

Quality assessment

By using the Newcastle–Ottawa Quality Assessment Scale, we evaluated the quality score of the included studies. A high-quality study was defined as scores ≥ 7 stars (Wang et al. 2015).

Statistical methods

The correlation between this SNP and DSC risk was assessed by using odds ratios (ORs) and the corresponding 95% confidence intervals (CIs). The results were summarized in the corresponding models: homozygote comparison (GG vs. CC), recessive model (GG vs. CC/CG), dominant model (GG/CG vs. CC) and allelic model (G vs. C). I^2 test and Q test were used to assess the heterogeneity. And $P < .1$ and/or $I^2 \geq 50\%$ were considered as the level of significance. When significant heterogeneity was observed, DerSimonian and Laird method (a random-effects model) was conducted to evaluate the association of rs2910164 with DSC (DerSimonian and Laird 1986; Higgins et al. 2003). Otherwise, a fixed-effects model (Mantel–Haenszel) was used to get a evaluation of rs2910164 variants with DSC risk (Mantel and Haenszel 1959). We also conducted subgroup analyses according to ethnicity, type of cancer, source of control, sample size (≥1000/<1000) and quality scores (≥7.0/<7). Galbraith radial plot was harnessed to further determine the source the heterogeneity. We carried out a sensitivity analysis to determine whether a single study could influence the final decision. Bgger's funnel plots and the Egger's test were done to assess the bias of publication. A $P < .1$ was considered as statistically significant for bias. All the *P*-values are two-sided. Stata12.0 software was used to conduct statistical analysis. In this study, the power value was also calculated by a Power-SampleSize software ($\alpha = 0.05$) (Tang et al. 2013).

Results

Study characteristics

First, we retrieved 505 publications from PubMed, China Biology Medicine and EMBASE databases. After a primary filtrate, 210 duplicated articles were excluded. Figure 1 shows the process of the meta-analysis. Finally, 52 papers (56 independent case-control studies) involving 24,161 DSC patients and 34,937 cancer-free controls were included. Of these investigations, year of publication ranged between 2008 and 2018 and the number of participants in the eligible studies ranged from 128 to 3,585. In summary, there were 17 GC studies (Ahn et al. 2013; Chen et al. 2018; Dikeakos

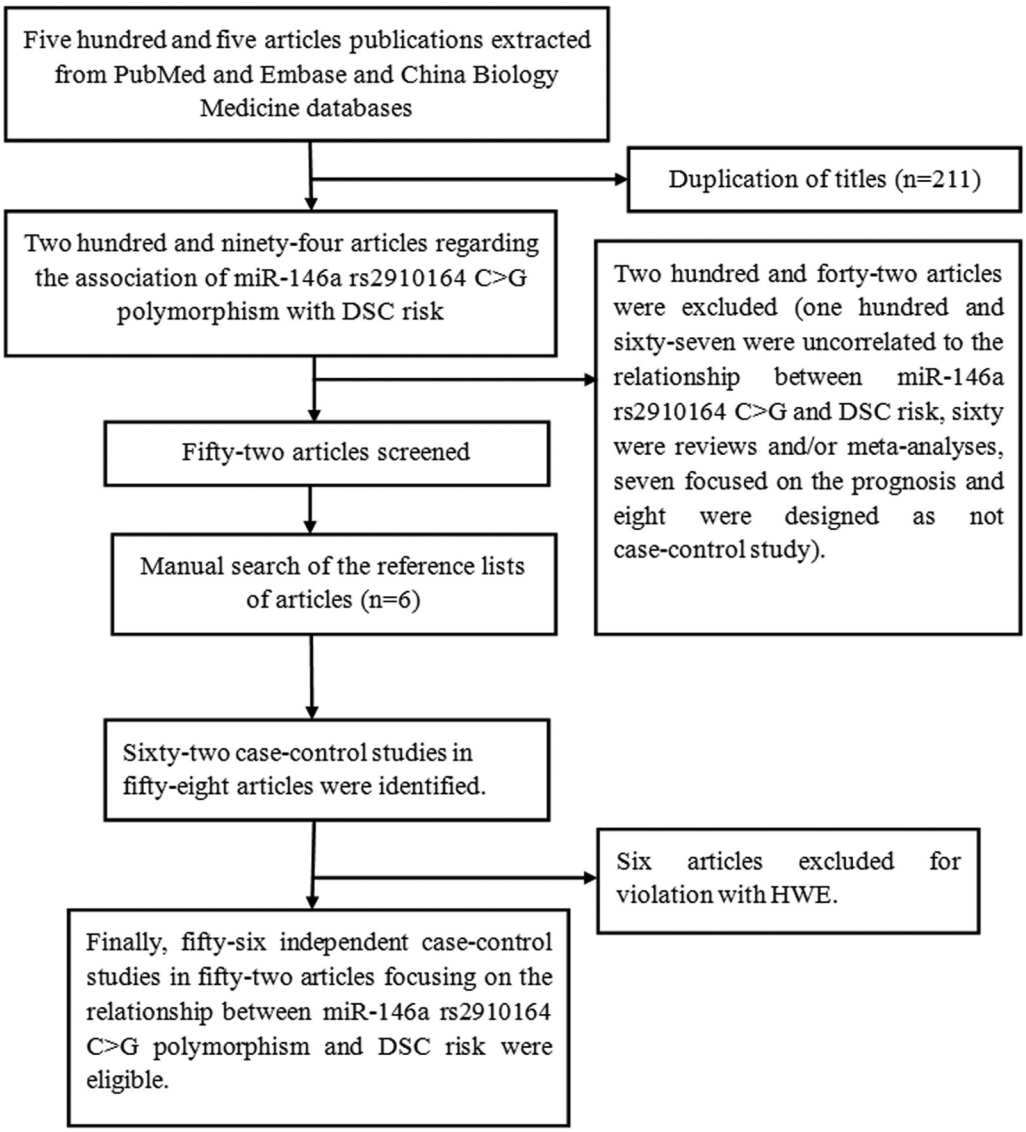

Figure 1. Flow diagram of the meta–analysis.

et al. 2014; Hishida et al. 2011; Jiang et al. 2016; Lin et al. 2019; Kupcinskas et al. 2014b; Ma 2012; Okubo et al. 2010; Parlayan et al. 2014; Pu et al. 2014; Rogoveanu et al. 2017; Soleimani et al. 2016; Xia et al. 2016; Yadegari et al. 2016; Zeng et al. 2010; Zhou et al. 2012a), 16 CRC studies (Chae et al. 2013; Chayeb et al. 2018; Dikaiakos et al. 2015; Gao et al. 2018; Hai-feng et al. 2016; Hezova et al. 2012; Kupcinskas et al. 2014a; Lv et al. 2013; Ma et al. 2013; Mao et al. 2014; Min et al. 2012; Ying et al. 2016), 15 HCC studies (Akkiz et al. 2011; Chu et al. 2014; Cong et al. 2014; Duan Lei 2017; Huang et al. 2013; Li et al. 2015; Xiang et al. 2012; Xu et al. 2008; Yan et al. 2015; Zhang et al. 2013; 2016; Zhou et al. 2012b), five esophageal squamous cell carcinoma (ESCC) studies (Guo et al. 2010; Qu et al. 2014; Shen et al. 2016; Umar et al. 2013; Wei et al. 2013), three oral squamous cell carcinoma (OSCC) studies (Chu et al. 2012; Palmieri et al. 2014; Zhang et al. 2017) and other carcinoma studies (one cholangiocarcinoma study (Mihalache et al. 2012), one GBC study (Srivastava et al. 2010) and one PC study (Pavlakis et al. 2013)). In addition, there were 42 case-control studies on Asians (Ahn et al. 2013; Chae et al. 2013; Chen et al. 2018; Chu et al. 2014, 2012; Cong et al. 2014; Duan Lei 2017; Gao et al. 2018; Guo et al. 2010; Hishida et al. 2011; Huang et al. 2013; Jiang et al. 2016; Lin et al. 2019; Hai-feng et al. 2016; Li et al. 2015; Lv et al. 2013; Ma 2012; Ma et al. 2013; Mao et al. 2014; Min et al. 2012; Okubo et al. 2010; Parlayan et al. 2014; Pu et al. 2014; Qu et al. 2014; Shen et al. 2016; Srivastava et al. 2010; Umar et al. 2013; Wei et al. 2013; Xia et al. 2016; Xiang et al. 2012; Xu et al. 2008; Yan et al. 2015; Ying et al. 2016; Zeng et al. 2010; Zhang et al. 2017; 2013; 2016; Zhou et al. 2012a, 2012b) and 14 case-control studies on Caucasians (Akkiz et al. 2011; Chayeb et al. 2018; Dikaiakos et al. 2015; Dikeakos et al. 2014; Hezova et al. 2012; Kupcinskas et al. 2014a, 2014b; Mihalache et al. 2012; Palmieri et al. 2014; Pavlakis et al. 2013; Rogoveanu et al. 2017; Soleimani et al. 2016; Yadegari et al. 2016). Other characteristics are presented in Table 1. The distributions of genotype and allele in *miR-146a* rs2910164 are listed in Table 2. Table 3 shows the quality assessment of this meta-analysis.

Findings

Table 4 lists the main findings. The results of heterogeneity tests are also summarized in Table 4. Pooling the eligible studies, we found an association of rs2910164 with DSC risk in dominant model (P = .035, Figure 2).

Rs2910164 locus, in Asians subgroup, was correlated with a susceptibility to DSC (GG/CG vs. CC: P = .033). In Caucasians subgroup, this SNP was also associated with a susceptibility to DSC (GG vs. CC/CG: P = .020). Additionally, rs2910164 was suggested to be associated with the occurrence of OSCC (G vs. C: P = .034 and GG/CG vs. CC: P = .022)

Sensitivity analysis

Sensitivity analysis was carried out to determine the influence of each study to the overall ORs and CIs. Our findings revealed that any individual study could not alter the ORs and CIs significantly (Figure 3). These observations further suggested the correlation between rs2910164 locus and DSC risk.

Table 1. Characteristics of the studies in meta-analysis.

First Author	Year	Country	Ethnicity	Cancer type	Source of control	Number of cases	Number of controls
Okubo et al.	2010	Japan	Asians	GC	H-B	552	697
Zeng et al.	2010	China	Asians	GC	H-B	304	304
Hishida et al.	2011	Japan	Asians	GC	H-B	583	1637
Zhou et al.	2012	China	Asians	GC	H-B	1686	1895
Ma et al.	2012	China	Asians	GC	H-B	86	42
Ahn et al.	2013	Korea	Asians	GC	H-B	461	447
Parlayan et al.	2014	Japan	Asians	GC	H-B	160	524
Pu et al.	2014	China	Asians	GC	H-B	220	530
Kupcinskas et al.	2014	Germany, Lithuania and Latvia	Caucasians	GC	H-B	363	351
Dikeakos et al.	2014	Greece	Caucasians	GC	H-B	163	480
Yadegari et al.	2016	Iran	Caucasians	GC	H-B	120	120
Jiang et al.	2016	China	Asians	GC	H-B	898	992
Xia et al.	2016	China	Asians	GC	*P*-B	1125	1196
Soleimani et al.	2016	Iran	Caucasians	GC	H-B	130	130
Rogoveanu et al.	2017	Romania	Caucasians	GC	H-B	142	288
Lin et al.	2017	China	Asians	GC	H-B	490	1476
Chen et al.	2018	China	Asians	GC	H-B	1063	1677
Hezova et al.	2012	Czech Republic	Caucasians	CRC	H-B	197	212
Min et al.	2012	Korea	Asians	CRC	H-B	251	502
Min et al.	2012	Korea	Asians	CRC	H-B	184	502
Chae et al.	2013	Korea	Asians	CRC	H-B	176	568
Chae et al.	2013	Korea	Asians	CRC	H-B	221	568
Lv et al.	2013	China	Asians	CRC	H-B	353	540
Ma et al.	2013	China	Asians	CRC	H-B	588	1203
Ma et al.	2013	China	Asians	CRC	H-B	559	1203
Kupcinskas et al.	2014	Lithuania and Latvia	Caucasians	CRC	H-B	193	428
Mao et al.	2014	China	Asians	CRC	*P*-B	554	566
Dikaiakos et al.	2015	Greece	Caucasians	CRC	H-B	157	299
Ying et al.	2016	China	Asians	CRC	H-B	1358	1079
Zhang et al.	2016	China	Asians	CRC	H-B	106	53
Chayeb et al.	2018	Tunisia	Caucasians	CRC	H-B	57	161
Chayeb et al.	2018	Tunisia	Caucasians	CRC	H-B	95	161
Gao et al.	2018	China	Asians	CRC	H-B	560	780
Guo et al.	2010	China	Asians	ESCC	H-B	444	468
Wei et al.	2013	China	Asians	ESCC	H-B	380	380
Shen et al.	2016	China	Asians	ESCC	*P*-B	1400	2185
Umar et al.	2013	India	Asians	ESCC	H-B	289	309
Qu et al.	2014	China	Asians	ESCC	*P*-B	381	426
Xu et al.	2008	China	Asians	HCC	H-B	479	504
Akkiz et al.	2011	Turkey	Caucasians	HCC	*P*-B	222	222
Xiang et al.	2012	China	Asians	HCC	H-B	100	100
Zhou et al.	2012	China	Asians	HCC	H-B	186	483
Chu et al.	2014	China	Asians	HCC	H-B	188	337
Cong et al.	2014	China	Asians	HCC	H-B	206	217
Zhang et al.	2013	China	Asians	HCC	*P*-B	1000	1000
Huang et al.	2013	China	Asians	HCC	H-B	110	110
Palmieri et al.	2014	Italy	Caucasians	OSCC	H-B	337	1176
Chu et al.	2012	China	Asians	OSCC	H-B	470	425
Mihalache et al.	2012	Germany	Caucasians	CC	H-B	182	350
Srivastava et al.	2010	India	Asians	GBC	*P*-B	230	230
Pavlakis et al.	2013	Greece	Caucasians	PC	H-B	93	122
Zhang et al.	2017	China	Asians	OSCC	H-B	340	340
Yan et al.	2015	China	Asians	HCC	H-B	274	328
Li ei al.	2015	China	Asians	HCC	H-B	266	266
Duan et al.	2017	China	Asians	HCC	H-B	188	186
Zhang et al.	2016	China	Asians	HCC	H-B	175	302

GC: gastric cancer;
CRC: Colorectal cancer;
HCC: hepatocellular cancer;
ESCC: esophageal squamous cell carcinoma;
OSCC: oral squamous cell carcinoma;

PC: pancreatic cancer;
CC: cholangiocarcinoma;
GBC: gallbladder cancer;
P-B: population-based;
H-B: hospital-based

Publication bias

In our study, the bias of publication was assessed by using Bgger's funnel plots and the Egger's test. After these evaluations, no significant bias was found among these included studies (Figure 4).

Heterogeneity

Significant heterogeneity was identified in our study. To identify the major source of heterogeneity, we conducted a heterogeneity analysis by stratified analyses. We suggested a correlation of Asians, GC, CRC, HCC, ESCC, hospital-based study, small sample size (<1000 subjects) and high-quality score (≥7.0) subgroups with significant heterogeneity. In addition, we used Galbraith radial plot to determine the heterogeneity (Figure 5). Among the eligible studies, eleven outliers (Chae et al. 2013; Dikaiakos et al. 2015; Duan Lei 2017; Guo et al. 2010; Kupcinskas et al. 2014a; Li et al. 2015; Lv et al. 2013; Ma 2012; Srivastava et al. 2010; Zhang et al. 2016) were found, which contributed to the main heterogeneity.

The power of the present study (α = 0.05)

For overall comparison, the power value was 0.994 in the dominant model. It was 0.989 in dominant model for Asians. The power value of other subgroups was less than 0.8 (data were not shown).

Discussion

The risk of malignancy may be diverse among different ethnicity. A number of investigations have clarified that miRs may influence the development of DSC. Recently, rs2910164 polymorphism and its importance to the initiate of DSC has been widely explored. In the past years, several pooled-analyses have explored the relationship of rs2910164 locus with the development of DSC. However, the conflicting results have been observed. Thus, an updated meta-analysis should be carried out.

A vital characteristic of this pooled-analysis was that our study included the largest sample sizes to determine a potential relationship between rs2910164 polymorphism and DSC risk comprehensively. Here, this meta-analysis identified that rs2910164 SNP conferred an increased risk to overall DSC and Asian populations. The previous pooled-analyses have been conducted to determine a relationship of rs2910164 variants to the development of DSC. The forepassed meta-analyses showed that G allele in rs2910164 polymorphism might not influence the initiate of DSC (B. Chen et al. 2014; Wang et al. 2012; Wu et al. 2013). Of late, some previous published meta-analyses identified that *miR-146a* rs2910164 could be implicated in the risk of DSC in Asian populations (Li et al. 2014; Xie et al. 2015; Xu et al. 2014). In addition, another meta-analysis indicated that rs2910164

Table 2. Distribution of miR-146a rs2910164 C > G genotypes and alleles.

First Author	Year	Case CC	Case CG	Case GG	Control CC	Control CG	Control GG	Case G	Case C	Control G	Control C	HWE
Okubo et al.	2010	236	243	73	254	322	121	389	715	564	830	Yes
Zeng et al.	2010	89	153	62	119	132	53	277	331	238	370	Yes
Hishida et al.	2011	230	271	82	633	775	229	435	731	1233	2041	Yes
Zhou et al.	2012	286	822	578	393	951	551	1978	1394	2053	1737	Yes
Ma et al.	2012	14	44	20	14	19	6	84	72	31	47	Yes
Ahn et al.	2013	159	231	71	164	221	62	373	549	345	549	Yes
Parlayan et al.	2014	61	79	20	216	237	71	119	201	379	669	Yes
Pu et al.	2014	65	96	36	143	274	96	168	226	466	560	Yes
Kupcinskas et al.	2014	16	94	252	16	108	223	598	126	554	140	Yes
Dikeakos et al.	2014	105	45	13	307	149	24	71	255	197	763	Yes
Yadegari et al.	2016	73	38	9	81	34	5	56	184	44	196	Yes
Jiang et al.	2016	303	441	154	325	457	207	749	1047	871	1107	Yes
Xia et al.	2016	397	536	192	420	577	199	920	1330	975	1417	Yes
Soleimani et al.	2016	13	42	75	10	40	80	192	68	200	60	Yes
Rogoveanu et al.	2017	8	48	86	19	109	160	220	64	429	147	Yes
Lin et al.	2017	182	223	81	583	683	206	385	587	1095	1849	Yes
Chen et al.	2018	327	543	171	644	787	243	885	1197	1273	2075	Yes
Hezova et al.	2012	12	70	115	9	79	124	300	94	327	97	Yes
Min et al.	2012	76	144	31	188	245	69	206	296	383	621	Yes
Min et al.	2012	69	87	28	188	245	69	143	225	383	621	Yes
Chae et al.	2013	66	87	23	165	282	121	133	219	524	612	Yes
Chae et al.	2013	90	93	38	165	282	121	169	273	524	612	Yes
Lv et al.	2013	47	230	54	143	274	96	338	324	466	560	Yes
Ma et al.	2013		CG/CC:359	229		CG/CC:806	397					Yes
Ma et al.	2013		CG/CC:344	215		CG/CC:806	397					Yes
Kupcinskas et al.	2014	2	50	140	15	134	275	330	54	684	164	Yes
Mao et al.	2014	186	291	70	205	271	85	431	663	441	681	Yes
Dikaiakos et al.	2015	101	48	8	158	120	21	64	250	162	436	Yes
Ying et al.	2016	473	655	223	383	529	163	1101	1601	855	1295	Yes
Zhang et al.	2016	16	62	28	18	25	10	118	94	45	61	Yes
Chayeb et al.	2018	6	31	20	23	89	49	71	43	187	135	Yes
Chayeb et al.	2018	9	46	40	23	89	49	126	64	187	135	Yes
Gao et al.	2018	145	285	130	220	411	149	545	575	709	851	Yes
Guo et al.	2010	20	190	234	42	220	206	658	230	632	304	Yes
Wei et al.	2013	117	184	67	122	181	67	318	418	315	425	Yes
Shen et al.	2016	495	685	220	780	1060	345	1125	1675	1750	2620	Yes
Umar et al.	2013	163	102	24	155	127	27	150	428	181	437	Yes
Qu et al.	2014	116	203	62	123	228	75	327	435	378	474	Yes

(*Continued*)

Table 2. (Continued).

First Author	Year	Case CC	Case CG	Case GG	Control CC	Control CG	Control GG	Case G	Case C	Control G	Control C	HWE
Xu et al.	2008	158	241	80	197	249	58	401	557	365	643	Yes
Akkiz et al.	2011	10	75	137	11	67	144	349	95	355	89	Yes
Xiang et al.	2012	28	45	27	33	46	21	99	101	88	112	Yes
Zhou et al.	2012	67	86	33	158	254	71	152	220	396	570	Yes
Chu et al.	2014	84	82	22	141	146	50	126	250	246	428	Yes
Cong et al.	2014	94	85	27	117	84	17	139	273	118	318	Yes
Zhang et al.	2013	331	503	163	367	475	156	829	1165	787	1209	Yes
Huang et al.	2013	40	58	12	54	41	15	82	138	71	149	Yes
Palmieri et al.	2014	19	121	197	93	436	647	515	159	1730	622	Yes
Chu et al.	2012	174	242	54	175	196	54	350	590	304	546	Yes
Mihalache et al.	2012	11	53	118	17	122	211	289	75	544	156	Yes
Srivastava et al.	2010	11	90	129	5	81	138	348	112	357	91	Yes
Pavlakis et al.	2013	4	38	51	4	39	79	140	46	197	47	Yes
Zhang et al.	2017	189	124	27	207	114	19	178	502	152	528	Yes
Yan et al.	2015	94	145	35	123	169	36	215	333	241	415	Yes
Li ei al.	2015	29	86	151	19	81	166	388	144	413	119	Yes
Duan et al.	2017	37	93	58	18	75	93	209	167	261	111	Yes
Zhang et al.	2016	52	86	37	137	135	30	160	190	195	409	Yes

Hardy-Weinberg equilibrium: HWE.

Table 3. Quality assessment of the meta-analysis.

		Selection					Exposure			
Study	Year	Adequate case definition	Representativeness of the cases	Selection of the controls	Definition of Controls	Comparability of the cases and controls	Ascertainment of exposure	Same ascertainment method for cases and controls	Non-Response rate	Total Stars
Okubo et al.	2010	★	★	-	★	-	★	★	-	5
Zeng et al.	2010	★	★	-	★	★★	★★	★	-	8
Hishida et al.	2011	★	★	-	★	★★	★★	★	-	8
Zhou et al.	2012	★	★	-	★	★★	★	★	-	7
Ma et al.	2012	★	★	-	-	★	★	★	-	5
Ahn et al.	2013	★	★	-	★	★★	★	★	-	7
parlayan et al.	2014	★	★	-	★	★★	★	★	-	7
Pu et al.	2014	★	★	-	★	★★	★	★	-	7
Kupcinskas et al.	2014	★	★	-	★	★★	★	★	-	7
Dikeakos et al.	2014	★	★	-	★	★	★	-	-	5
Yadegari et al.	2016	★	★	-	★	★★		-	-	5
Jiang et al.	2016	★	★	-	★	★★	★	★	-	7
Xia et al.	2016	★	★	★	★	★★	★	★	-	8
Soleimani et al.	2016	★	★	-	★	★★	-	★	-	6
Rogoveanu et al.	2017	★	★	-	★	★★	★	-	-	6
Lin et al.	2017	★	★	-	★	★★	★★	★	-	8
Chen et al.	2018	★	★	-	★	★★	★★	★	-	8
Hezova et al.	2012	★	★	-	★	★	★	★	-	6
Min et al.	2012	★	★	-	★	★★	★	★	-	7
Min et al.	2012	★	★	-	★	★★	★★	★	-	7
Chae et al.	2013	★	★	-	★	★★	★	★	-	7
Chae et al.	2013	★	★	-	★	★★	★	★	-	7
Lv et al.	2013	★	★	-	★	★	★	★	-	6
Ma et al.	2013	★	★	-	★	★★	★★	★	-	8
Ma et al.	2013	★	★	-	★	★★	★★	★	-	8
Kupcinskas et al.	2014	★	★	-	★	-	★	★	-	5
Mao et al.	2014	★	★	★	★	★★	★	★	-	8
Dikaiakos et al.	2015	★	★		★	★★	★	★	-	7
Ying et al.	2016	★	★	-	★	-	★	★	-	5
Zhang et al.	2016	★	★	-	★	★★	★	★	-	7
Chayeb et al.	2018	★	★	-	★	★★	★★	★	-	8
Chayeb et al.	2018	★	★	-	★	★★	★★	★	-	8
Gao et al.	2018	★	★	-	★	★★	★	★	-	7
Guo et al.	2010	★	★	-	★	★★	★	★	-	7

(*Continued*)

Table 3. (Continued).

		Selection					Exposure			
Study	Year	Adequate case definition	Representativeness of the cases	Selection of the controls	Definition of Controls	Comparability of the cases and controls	Ascertainment of exposure	Same ascertainment method for cases and controls	Non-Response rate	Total Stars
Wei et al.	2013	★	★	-	★	★★	★★	★	-	8
Shen et al.	2016	★	★	★	★	★★	★★	★	★	10
Umar et al.	2013	★	★	-	★	★★	★	★	-	7
Qu et al.	2014	★	★	★	★	★★	★★	★	-	9
Xu et al.	2008	★	★		★	★★	★	★	-	7
Akkiz et al.	2011	★	★	★	★	★★	★★	★	-	9
Xiang et al.	2012	★	★	-	★	★	★	★	-	6
Zhou et al.	2012	★	★	-	★		★	★	-	5
Chu et al.	2014	★	★	-	★	★★	★★	★	-	8
Cong et al.	2014	★	★	-	★	★	★	★	-	6
Zhang et al.	2013	★	★	★	★	★★	★★	★	-	9
Huang et al.	2013	★	★	-	★	★★	★	★	-	7
Palmieri et al.	2014	★	★	-	-	-	-	★	-	3
Chu et al.	2012	★	★	-	★	★	★★	★	-	7
Mihalache et al.	2012	★	★	-	★		★	★	-	5
Srivastava et al.	2010	★	★	★	★	★★	★	★	-	8
Pavlakis et al.	2013	★	★	-	★	★★	★	★	-	7
Zhang et al.	2017	★	★	-	★	★★	★	★	-	7
Yan et al.	2015	★	★	-	★	★	★	★	-	6
Li ei al.	2015	★	★	-	★	★★	★	★	-	7
Duan et al.	2017	★	★	-	★	★★	★	★	-	7
Zhang et al.	2016	★	★	-	★	★	★	★	-	6

Table 4. Results of the meta-analysis from different comparative genetic models.

		G vs. C				GG vs. CC				GG+CG vs. CC				GG vs. CG+CC			
	No. of studies	OR(95% CI)	*P*	I^2	*P*(Q-test)	OR(95% CI)	*P*	I^2	*P*(Q-test)	OR(95% CI)	*P*	I^2	*P*(Q-test)	OR(95% CI)	*P*	I^2	*P*(Q-test)
Total	56	1.05(1.00–1.11)	0.051	66.1%	<0.001	1.11(1.00–1.23)	0.058	60.4%	<0.001	**1.09(1.01–1.17)**	**0.035**	62.8%	<0.001	1.06(0.99–1.14)	0.082	50.1%	<0.001
Ethnicity																	
Asians	42	1.05(0.99–1.11)	0.116	71.1%	<0.001	1.09(0.98–1.23)	0.128	67.6%	<0.001	**1.09(1.01–1.19)**	**0.033**	69.2%	<0.001	1.04(0.96–1.13)	0.295	56.6%	<0.001
Caucasians	14	1.08(0.96–1.20)	0.210	37.8%	0.075	1.21(0.97–1.51)	0.088	0.0%	0.452	1.01(0.86–1.20)	0.881	13.1%	0.310	**1.14(1.02–1.28)**	**0.020**	12.0%	0.322
Cancer type																	
GC	17	1.06(0.99–1.15)	0.109	62.6%	<0.001	1.11(0.96–1.30)	0.164	57.9%	0.002	1.08(0.97–1.20)	0.152	56.7%	0.002	1.08(0.97–1.20)	0.167	41.4%	0.040
CRC	16	1.04(0.93–1.17)	0.494	69.5%	<0.001	1.08(0.85–1.37)	0.553	63.6%	0.001	1.10(0.89–1.37)	0.383	77.3%	<0.001	1.07(0.95–1.22)	0.272	47.3%	0.019
HCC	12	1.06(0.91–1.23)	0.480	77.8%	<0.001	1.14(0.83–1.56)	0.418	74.0%	<0.001	1.11(0.93–1.34)	0.254	62.0%	0.002	1.07(0.84–1.37)	0.582	72.1%	<0.001
ESCC	5	1.03(0.90–1.18)	0.666	64.0%	0.025	1.09(0.82–1.45)	0.537	58.0%	0.049	1.03(0.84–1.26)	0.806	58.5%	0.047	1.07(0.94–1.21)	0.299	34.3%	0.192
OSCC	3	**1.14(1.01–1.29)**	**0.034**	0.0%	0.641	1.26(0.95–1.69)	0.114	0.0%	0.387	**1.24(1.03–1.50)**	**0.022**	0.0%	0.814	1.11(0.91–1.35)	0.301	0.0%	0.370
Others	3	0.90(0.73–1.09)	0.270	36.5%	0.207	0.66(0.37–1.18)	0.159	0.0%	0.583	0.66(0.38–1.17)	0.156	0.0%	0.701	0.89(0.63–1.26)	0.518	51.1%	0.129
Sample sizes																	
≥1,000	15	1.05(0.99–1.11)	0.136	65.0%	0.001	1.09(0.96–1.24)	0.177	63.1%	0.001	1.08(0.99–1.17)	0.084	55.8%	0.007	1.08(0.99–1.18)	0.080	54.0%	0.007
<1,000	41	1.06(0.98–1.14)	0.156	67.2%	<0.001	1.12(0.96–1.31)	0.152	60.5%	<0.001	1.09(0.97–1.23)	0.140	65.2%	<0.001	1.06(0.95–1.17)	0.297	49.3%	<0.001
Source of control																	
H-B	49	1.07(1.00–1.13)	0.036	68.9%	<0.001	**1.14(1.01–1.29)**	**0.039**	63.6%	<0.001	1.10(1.00–1.20)	0.040	66.2%	<0.001	**1.09(1.01–1.18)**	**0.035**	52.4%	<0.001
P-B	7	1.01(0.95–1.06)	0.828	0.0%	0.597	1.01(0.89–1.13)	0.930	0.0%	0.644	1.04(0.96–1.13)	0.368	0.0%	0.523	0.97(0.87–1.07)	0.485	0.0%	0.782
Quality scores																	
≥7.0	39	1.02(0.96–1.08)	0.527	68.0%	<0.001	1.04(0.93–1.17)	0.490	60.8%	<0.001	1.05(0.97–1.14)	0.224	61.4%	<0.001	1.03(0.95–1.11)	0.530	53.4%	<0.001
<7.0	17	**1.15(1.04–1.27)**	**0.009**	61.5%	<0.001	**1.34(1.06–1.70)**	**0.014**	59.9%	0.001	1.21(1.00–1.46)	0.049	67.1%	<0.001	1.18(1.03–1.35)	0.019	41.7%	0.037

GC: gastric cancer;
CRC: Colorectal cancer;
HCC: hepatocellular cancer;
ESCC: esophageal squamous cell carcinoma;
OSCC: oral squamous cell carcinoma;
P-B: population-based;
H-B: hospital-based.

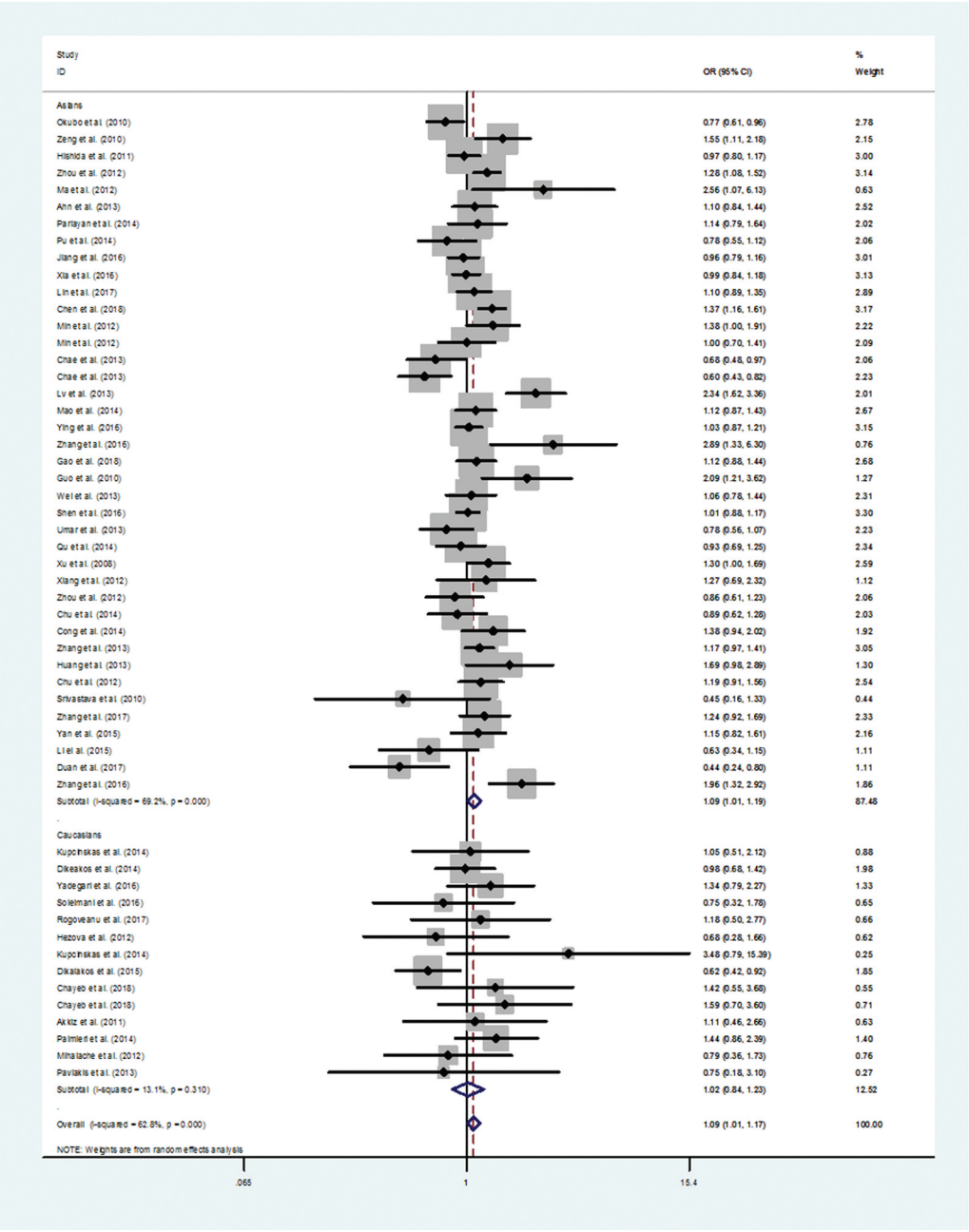

Figure 2. Meta-analysis of the relationship between miR-146a rs2910164 C > G polymorphism and DSC risk (GG/CG vs. CC, random–effects model).

G allele increased the risk of DSC in both Asians and Caucasians (Xie and Wang 2017). However, a more recent meta-analysis reported that the potential relationship disappeared in neither Asians nor Caucasians (Xiong et al. 2017). To our knowledge, the associations were more conflicting. Thus, in this meta-analysis, we included more publications with

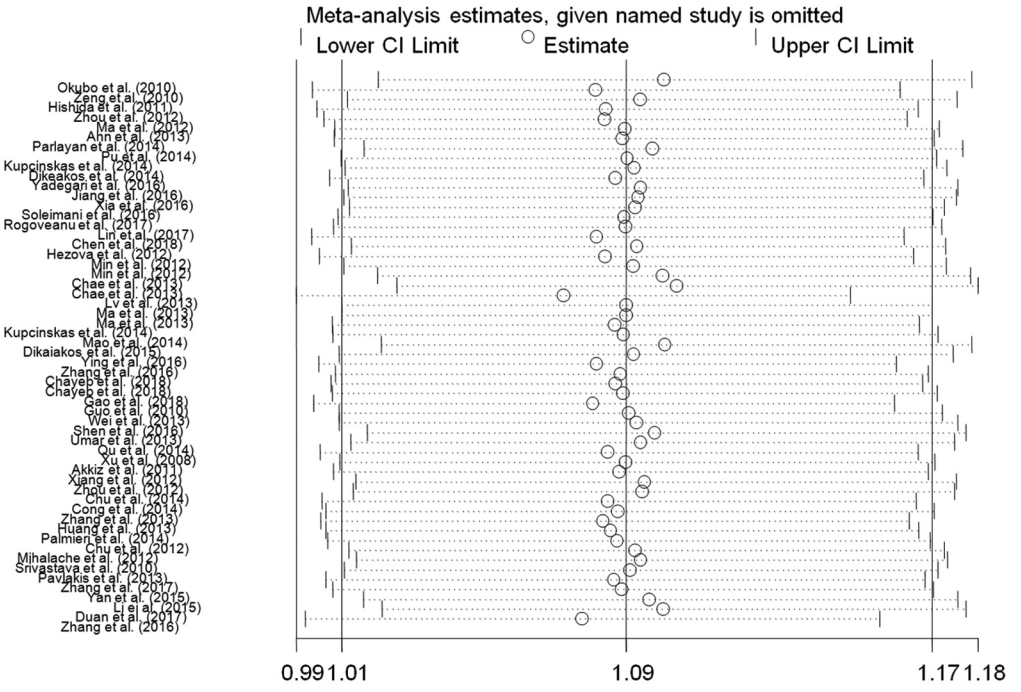

Figure 3. Sensitivity analysis of the influence of GG/CG vs. CC genetic model (random–effects model).

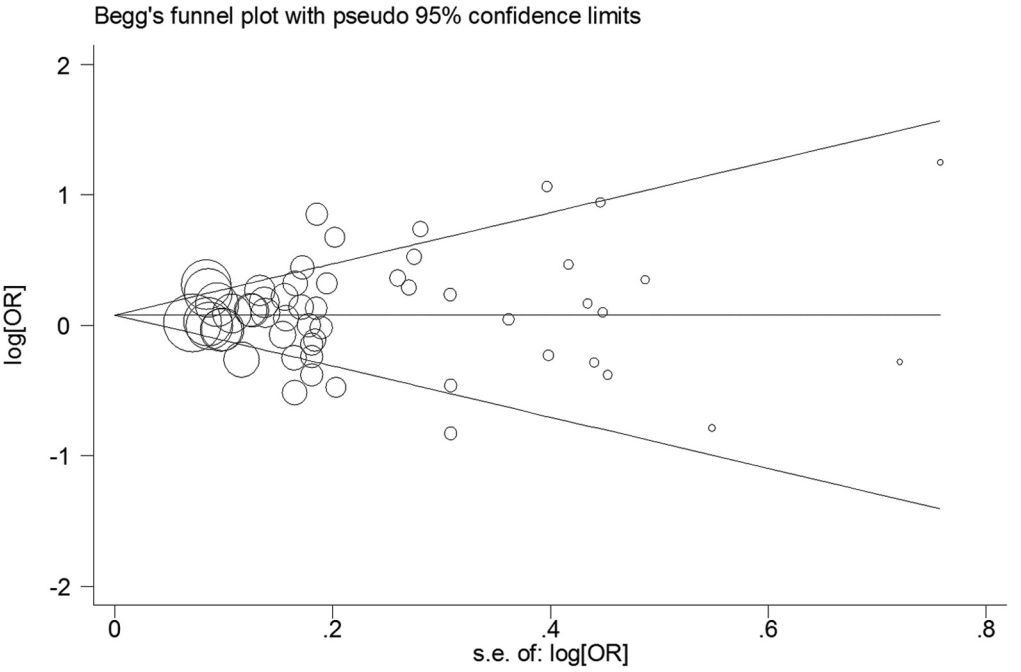

Figure 4. Begg's funnel plot of meta–analysis (GG/CG vs. CC, random–effects model).

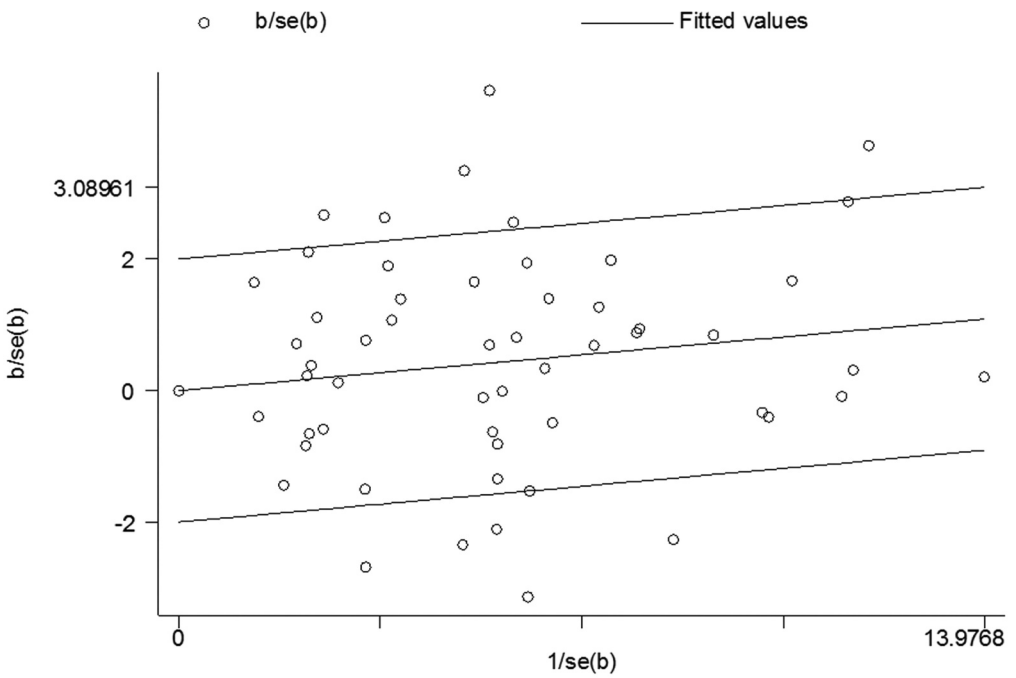

Figure 5. Galbraith radial plot of meta–analysis (GG/CG vs. CC, random–effects model).

24,161 DSC patients and 34,937 cancer-free controls to detect the correlation between rs2910164 G allele and its importance to the initiate of DSC. And we found that rs2910164 G allele might confer risk to DSC.

A previous study identified that the expression of *miR-146a* promoted in acute myeloid leukemia and acute lymphoblastic leukemia cases (Wang et al. 2019). As well, Khorrami et al. suggested that the higher level of *miR-146a* was importance for the milieu of immune suppression and drug-resistant CRC cells (Khorrami et al. 2017). Additionally, *MiR-146a* was found to be correlated with the invasion and migration in CRC patients (Lu et al. 2017). Compared with C allele carriers, the level of *miR-146a* was higher in G allele carriers (Jeon et al. 2014; Jia et al. 2014; Mohamed et al. 2019). Here, we might speculate that the *miR-146a* C→G mutation could increase the expression of *miR-146a* and lead to immune suppression. Finally, this SNP could increase the risk of DSC.

In this meta-analysis, we observed significant heterogeneities among the eligible studies. When the source of heterogeneity was analyzed, we found that high-quality score (≥7.0), small sample size (<1000 subjects), CRC, HCC, GC, ESCC, Asians and hospital-based study subgroups increased it greatly. Additionally, in dominant model (Figure 2), Galbraith radial plot and the forest plot identified eleven outliers (Chae et al. 2013; Dikaiakos et al. 2015; Duan Lei 2017; Guo et al. 2010; Kupcinskas et al. 2014a; Li et al. 2015; Lv et al. 2013; Ma 2012; Srivastava et al. 2010; Zhang et al. 2016).

In current meta-analysis, some merits should be considered. Firstly, this is a large sample size study exploring the relationship of rs2910164 locus with the susceptibility of DSC. Secondly, we only included the case-control studies which were consistent with HWE. Our

findings were less bias. Thirdly, we evaluated the quality scores of the included studies. Fourthly, no significant bias of publication was found in our analysis. Finally, in this study, the power value was also calculated ($\alpha = 0.05$).

The potential limitations also should be addressed. Firstly, all of the publications were performed in Caucasians and Asians, and none was conducted in other populations. Thus, our findings might be only adapted to these ethnicities. Secondly, for lack of original information of participants (e.g. family history, smoking, drinking, nutrient intake, gender, age and lifestyle), the influence of these environmental factors was not considered. Thirdly, gene–environment interactions were not performed. Finally, in this study, we only included one miR-SNP. And another SNPs in miR should not been ignored.

In summary, this study identifies that rs2910164 participates in the development of DSC. In stratified analyses, we find that this SNP also significantly increased cancer susceptibility in Asians. More studies with detailed gene-environment factors are, therefore, needed to confirm our results.

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Author contribution

All authors contributed significantly to this study.
Conceived and designed the experiments: SZ, ZL
Performed the experiments: LL, HG, ZC
Analyzed the data: WT, SZ
Contributed reagents/materials/analysis tools: ZL
Wrote the manuscript: LL, HG, ZC
Other (please specify): None

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