MEDICAL SCIENCE MONITOR

META-ANALYSIS

e-ISSN 1643-3750
© Med Sci Monit, 2018; 24: 7057-7071
DOI: 10.12659/MSM.912534

Received: 2018.08.05
Accepted: 2018.09.22
Published: 2018.10.04

Rs4938723 Polymorphism Is Associated with Susceptibility to Hepatocellular Carcinoma Risk and Is a Protective Factor in Leukemia, Colorectal, and Esophageal Cancer

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Source of support: Departmental sources

Background: Growing evidence indicates that a non-coding RNA named miR-34b/c plays crucial roles in carcinogenesis, and its common polymorphism, pri-miR-34b/c rs4938723, also participates in this process and is associated with cancer susceptibility. However, this association was previously undefined and ambiguous. Therefore, we carried out an updated analysis to evaluate this relationship between rs4938723 polymorphism and cancer susceptibility.

Material/Methods: PubMed, EMbase, Web of Science and Chinese language (WanFang, CNKI and VIP) databases were searched for relevant studies until Sep 10, 2018. Odds ratios and 95% confidence interval were applied to assess this relationship.

Results: Thirty case-control studies were retrieved. No positive association was found in either the overall study population or in the subgroups, based on ethnicity, source of group, sex, smoking, and drinking status. The main results were observed in the stratified analysis subgroups in cancer type subgroup: rs4938723 polymorphism may be a protective factor in leukemia, colorectal cancer, and esophageal cancer; however, C-allele was a risk factor in carriers for hepatocellular carcinoma. Last but not the least, poor positive results were discovered in the age subgroup.

Conclusions: Current meta-analysis suggested that rs4938723 polymorphism was potentially associated with hepatocellular carcinoma risk, but this polymorphism had a decreased association for susceptibility to esophageal cancer, leukemia, and colorectal cancer. Furthermore, studies with larger sample sizes and including gene-gene or gene-environment interactions should be carried out to elucidate the role of rs4938723 polymorphism in cancer risk.

MeSH Keywords: Early Detection of Cancer • Ethnic Groups • Polymorphism, Genetic

Full-text PDF: https://www.medscimonit.com/abstract/index/idArt/912534

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Background

Cancer is a leading cause of death worldwide. To make things worse, the number of cancer cases and deaths is expected to grow rapidly with increase in populations, age, and adaptation to lifestyle behaviors that increase cancer risk [1]. One of the major reasons for variability among individuals is the presence of single-nucleotide polymorphisms (SNPs), which makes individuals more susceptibility to cancer [2]. Several explorations related to genome-wide associations have suggested there are many *loci* in the genome that have signs of low tumor susceptibility for common tumors [3–5].

MicroRNAs (miRNAs) are a type of single-stranded non-encoded small RNA that can inhibit the transcription of mRNA or promote its degradation at the post-transcription level by binding to the target mRNA 3' UTR region to regulate gene expression [6,7]. There is growing evidence that misalignment of miRNA expression affects tumorigenesis based on activation of either tumor suppressor or oncogene [8–12]. miRNA gene polymorphism affects tumor susceptibility by destroying miRNA biosynthesis and target gene expression, changing mature miRNA, or by affecting its interaction with target genes [13–16]. The relationship between miRNA gene polymorphisms is complicated. For example, in each case, the rs11614913 variant homozygote CC was associated with increased cancer risk. Risk of developing oesophageal cancer in Caucasian males and never-smokers was significantly associated with the rs11614913 variant homozygote TT, the minor allele in this population [17]. Rs11614913 is located on the 3' passenger (3p) strand mature sequence of mir-196a-2, thereby possibly affecting both maturation and the repertoire of target mRNAs with which it interacts. Indeed, previous studies have shown that sequence variations in mature and precursor miRNA sequences affect miRNA biogenesis [18,19], and levels of mature miR-196a-2 were lower in CC carriers than in TT carriers [20,21]. Notably, this SNP has also been associated with poor survival in patients with lung cancer.

The miR-34 family members include miR-34a, miR-34b, and miR-34c. miR-34a is encoded by its own transcription, while the miR-34b and miR-34c share a primary transcription (pri-miR-34b/c) [22]. In the promoter region of Pri-miR-34b/c, a potentially functional rs4938723 T/C variant may affect the binding of transcription factor Gata-X, thereby changing the expression of pri-miR-34b/c [23–25]. The rs4938723 T>C variant may potentially influence the expression of miR-34b/c via genetic and epigenetic mechanisms, leading to increased or decreased risk of cancer. Previous studies proposed that miR-34b/c is dysregulated in various cancers [26–28].

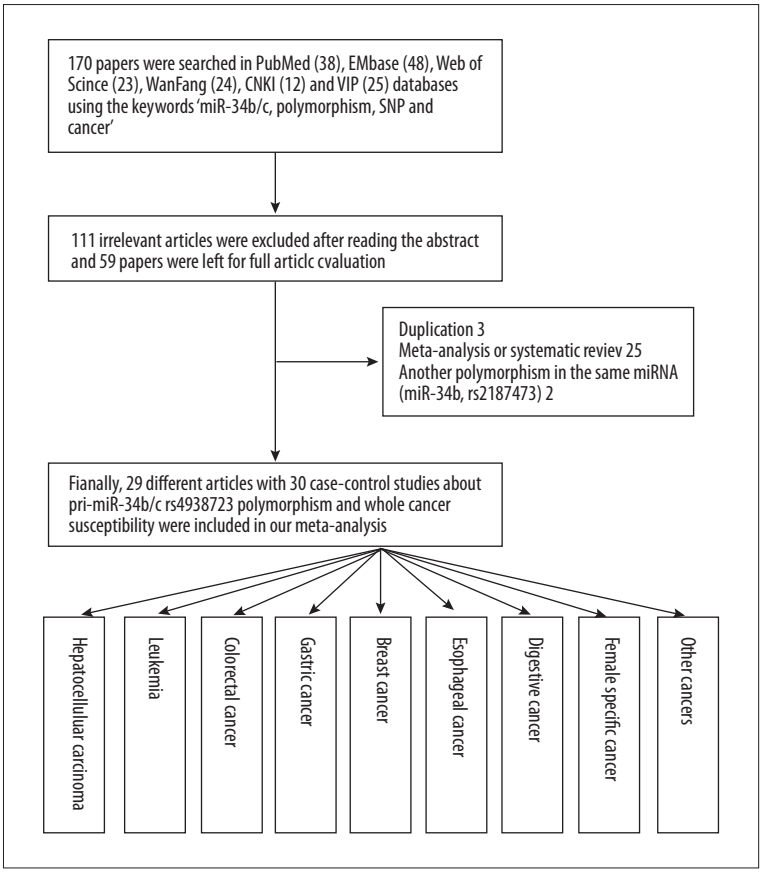

Figure 1. Flowchart illustrating the search strategy used to identify association studies for pri-miR-34b/c rs4938723 polymorphism and whole cancer risk.

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Table 1. Basic information for included studies of the association between pri-miR-34b/c rs4938723 polymorphism site and whole cancer susceptibility.

First author (year) [ref no.]	Origin	Ethnicity	Design	Case	Control	Case			Control				Method	Cancer type (1)	Cancer type (2)
						CC	CT	TT	CC	CT	TT	HWE			
Bensen (2013) [34]	USA	African	PB	742	658	63	317	362	58	257	343	0.32	Illumina	Breast cancer	Female specific cancer
Sanaei (2016) [47]	Canada	Caucasian	PB	263	221	23	115	125	15	106	100	0.06	PCR-RFLP	Breast cancer	Female specific cancer
bensen (2013) [34]	USA	Caucasian	PB	1203	1088	144	563	496	155	503	430	0.68	Illumina	Breast cancer	Female specific cancer
gao (2013) [38]	China	Asian	HB	347	488	28	144	175	62	210	216	0.33	PCR-RFLP	Colorectal cancer	Digestive cancer
Oh (2014) [45]	South Korea	Asian	HB	545	428	40	233	272	41	171	216	0.40	PCR-RFLP	Colorectal cancer	Digestive cancer
yin (2013) [52]	China	Asian	HB	600	673	45	278	277	73	290	310	0.67	PCR-LDR	Esophageal cancer	Digestive cancer
zhu (2015) [31]	China	Asian	PB	237	274	25	99	113	30	122	122	0.95	MALDI-TOF-MS	Esophageal cancer	Digestive cancer
zhang (2) (2014) [55]	China	Asian	PB	1109	1275	84	536	489	133	573	569	0.52	SNaPshot Multiplex System	Esophageal cancer	Digestive cancer
you (2011) [53]	China	Asian	PB	251	189	28	103	120	15	86	88	0.34	MALDI-TOF-MS	Esophageal cancer	Digestive cancer
yang (2014) [51]	China	Asian	HB	419	402	40	186	193	62	184	156	0.52	PCR-RFLP	Gastric cancer	Digestive cancer
pan (2015) [46]	China	Asian	HB	197	289	19	76	102	31	137	121	0.39	PCR-RFLP	Gastric cancer	Digestive cancer
son (2013) [49]	South Korea	Asian	HB	157	201	13	75	69	17	74	110	0.37	PCR-RFLP	Hepato-cellular carcinoma	Digestive cancer
han (2013) [39]	China	Asian	HB	1013	999	118	444	451	119	424	456	0.18	fluorescent-probe real-time quantitative PCR	Hepato-cellular carcinoma	Digestive cancer
xu (2011) [25]	China	Asian	PB	502	549	62	236	204	54	229	266	0.65	PCR-RFLP	Hepato-cellular carcinoma	Digestive cancer
chen (2016) [30]	China	Asian	HB	286	572	38	146	102	33	267	272	0.00	PCR-RFLP	Hepato-cellular carcinoma	Digestive cancer
tong (2016) [29]	China	Asian	HB	570	673	35	281	254	76	296	301	0.80	TaqMan	Leukemia	Other cancers
hashemi (2017) [41]	Iran	Caucasian	PB	110	120	2	31	77	6	52	62	0.24	PCR-RFLP	Leukemia	Other cancers
yuan (2016) [54]	China	Asian	HB	328	568	36	175	117	68	258	242	0.95	PCR-RFLP	Cervical cancer	Female specific cancer
li (2013) [43]	China	Asian	PB	217	360	31	104	82	37	155	168	0.89	PCR-RFLP	Nasoph-aryngeal carcinoma	Other cancers

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Table 1 continued. Basic information for included studies of the association between pri-miR-34b/c rs4938723 polymorphism site and whole cancer susceptibility.

First author (year) [ref no.]	Origin	Ethnicity	Design	Case	Control	Case			Control				Method	Cancer type (1)	Cancer type (2)
						CC	CT	TT	CC	CT	TT	HWE			
tian (2014) [50]	China	Asian	PB	133	133	30	62	41	18	53	62	0.22	TaqMan	Osteo-sarcoma	Other cancers
hashemi (2016) [40]	Iran	Caucasian	HB	152	152	10	56	85	5	38	109	0.46	PCR-RFLP	Prostate cancer	Other cancers
Zhang (1) (2014) [22]	China	Asian	HB	710	760	84	324	302	64	344	352	0.11	TaqMan	Renal cell cancer	Other cancers
carvalho (2017) [36]	Brazil	Mixed	PB	130	105	14	64	52	16	44	45	0.34	sequencing	Retino-blastoma	Other cancers
liu (2017) [44]	China	Asian	HB	164	305	26	80	58	22	141	142	0.10	PCR-RFLP	Hepato-cellular carcinoma	Digestive cancer
Chen (2015) [37]	China	Asian	HB	784	1006	111	402	271	99	451	456	0.41	PCR-RFLP	Thyroid carcinoma	Other cancers
Bulibu (2018) [35]	China	Asian	PB	175	186	37	74	64	53	81	52	0.08	PCR-DHPLC	Esophageal cancer	Digestive cancer
Wu (2017) [56]	China	Asian	PB	893	990	92	396	405	84	430	476	0.34	MassARRAY	Gastric cancer	Digestive cancer
Singh (2017) [48]	China	Asian	HB	324	598	44	148	132	66	262	270	0.84	PCR-LDR	Gastric cancer	Digestive cancer
He (2018) [42]	China	Asian	HB	377	810	49	107	221	75	358	377	0.45	TaqMan	Neuro-blastoma	Other cancers
Pu (2012) [57]	China	Asian	HB	1013	999	118	444	451	119	424	456	0.18	Fluorescent Probe-Real-time Quantitative PCR	Hepato-cellular carcinoma	Digestive cancer

HWE – Hardy-Weinberg equilibrium; HB – hospital-based; PB – population-based; PCR-FLIP – polymerase chain reaction and restrictive fragment length polymorphism; MALDI-TOF-MS – matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; DHPLC – denaturing high performance liquid chromatography; LDR – ligation detection reaction.

Similar to other kinds of polymorphisms, miR-34b/c rs4938723 polymorphism may influence its own expression, then affect its target genes' expression, finally promoting or inhibiting translation of target proteins to act on several biological functions. For example, Tong (2016) [29] reported rs4938723 CC genotype was significantly associated with reduced lymphoblastic leukemia risk, and C-allele may increase the transcription activity of miR-34b/c. However, Chen (2016) [30] found that TC+CC genotype was correlated with an increased risk of hepatocellular carcinoma compared to the TT genotype, which disagrees with Tong's results. In addition, Zhu (2015) [31] indicated no association between this polymorphism and esophageal squamous cell carcinoma.

A number of meta-analyses with respect to association between this polymorphism and cancer susceptibility have been reported, but with some limitations and false-positive conclusions. Li (2017) [32] indicated a rs4938723 polymorphism

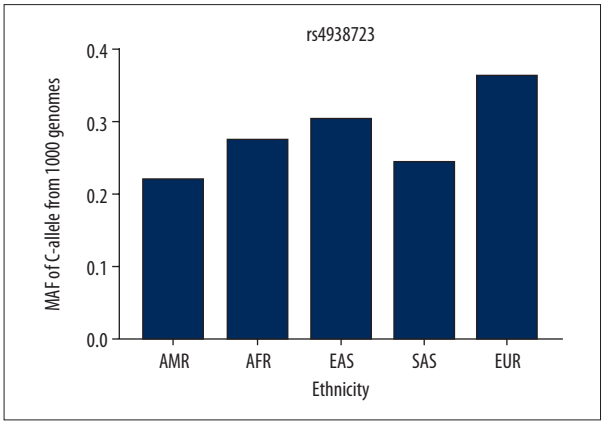

Figure 2. The MAF of minor allele (mutant-allele) for pri-miR-34b/c rs4938723 polymorphism from the 1000 Genomes online database and present analysis. EAS – East Asian; EUR – European; AFR – African; AMR – American; SAS – South Asian.

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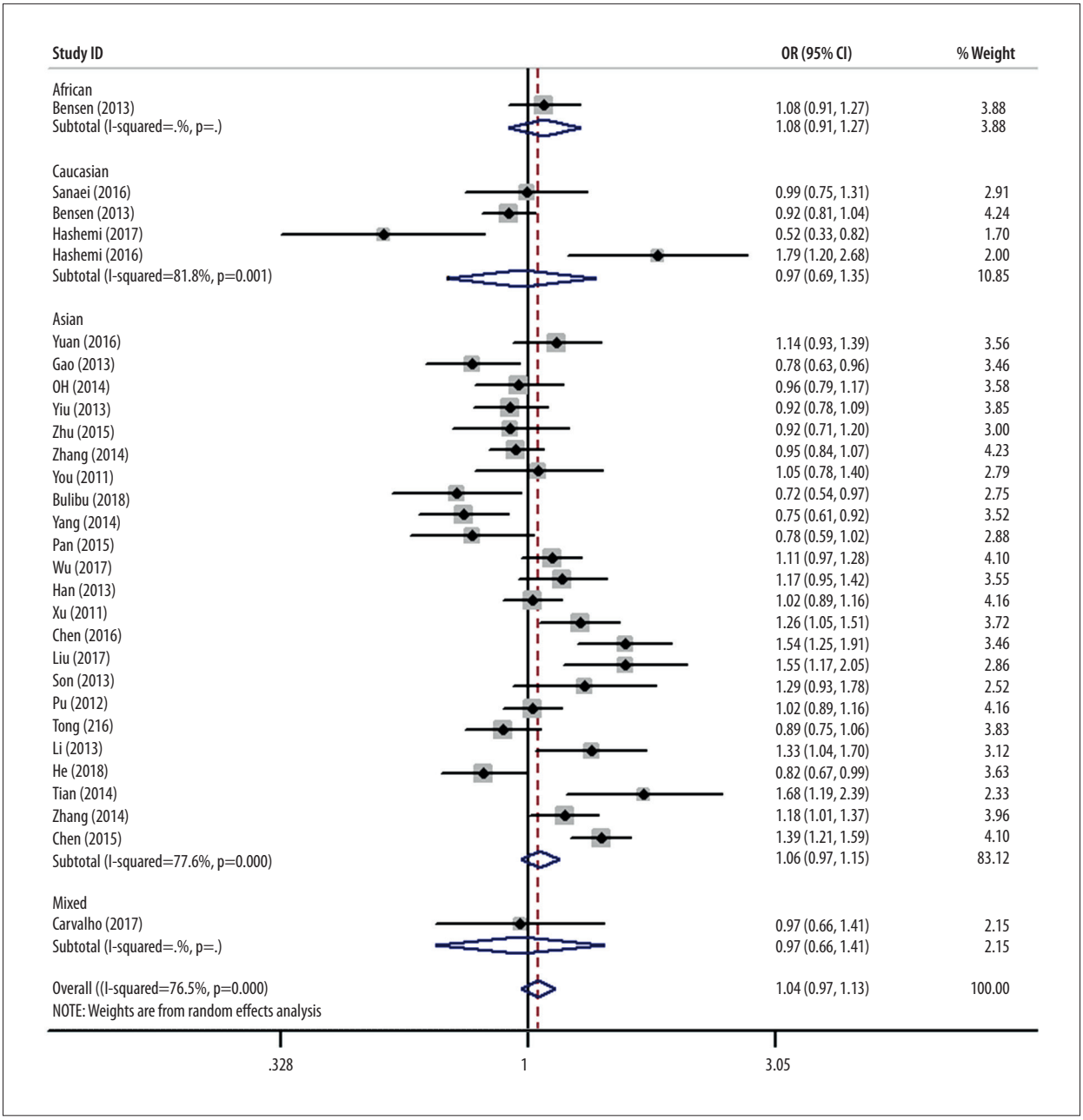

Figure 3. Forest plot of cancer risk associated with pri-miR-34b/c rs4938723 polymorphism (C-allele *vs.* T-allele) in the whole. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

had a significant relationship with the whole cancer risk. In addition, this polymorphism played an increased risk in hepatocellular carcinoma, but a decreased risk for colorectal, gastric, and esophageal squamous cell cancer. Furthermore, Wang (2014) [33] suggested that this polymorphism may be associated with the risk of various types of cancers, including nasopharyngeal cancer, osteosarcoma, and renal cell cancer, especially in Asians. In addition to these 2 meta-analyses, some vital case-control studies were included, and some novel studies were also reported. We considered that it was necessary to re-analyze all case-control studies to assess the association between rs4938723 variant and tumor susceptibility [22,25,29–31,34–57].

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Table 2. Total and stratified subgroup analysis for pri-miR-34b/c rs4938723 polymorphism site and cancer susceptibility.

Variables	N	Case/ control	C-allele *vs.* T-allele		CT *vs.* TT		CC *vs.* TT		CC+CT *vs.* TT		CC *vs.* CT+TT	
			OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h
Total	30	13950/ 16071	1.04 (0.97–1.13)	<0.001	1.07 (0.98–1.17)	<0.001	1.07 (0.91–1.27)	<0.001	1.07 (0.97–1.18)	<0.001	1.03 (0.89–1.19)	<0.001
HWE	29	13664/ 15499	1.03 (0.95–1.12)	<0.001	1.09 (0.99–1.20)	<0.001	0.99 (0.83–1.19)	<0.001	1.07 (0.97–1.19)	<0.001	0.94 (0.81–1.10)	<0.001
Ethnicity												
Asian	24	10351/ 13727	1.06 (0.97–1.15)	<0.001	1.08 (0.97–1.19)	<0.001	1.10 (0.91–1.32)	<0.001	1.08 (0.97–1.20)	<0.001	1.05 (0.89–1.24)	<0.001
Caucasian	4	1727/ 1581	0.97 (0.69–1.35)	0.001	0.95 (0.64–1.40)	0.004	1.00 (0.56–1.78)	0.076	0.95 (0.63–1.43)	0.001	0.88 (0.71–1.10)	0.151
African	1	742/ 658	–		–		–		–		–	
Mixed	1	130/ 105	–		–		–		–		–	
China	22	10649/ 13098	1.05 (0.96–1.15)	<0.001	1.06 (0.96–1.18)	<0.001	1.11 (0.91–1.36)	<0.001	1.07 (0.96–1.20)	<0.001	1.07 (0.90–1.27)	<0.001
Non-China	8	3301/ 2973	1.02 (0.87–1.18)	0.004	1.09 (0.89–1.33)	0.006	0.90 (0.75–1.07)	0.286	1.06 (0.87–1.30	)0.002	0.87 (0.74–1.03)	0.479
Source of control												
HB	17	7985/ 9923	1.07 (0.95–1.20)	<0.001	1.09 (0.94–1.27)	<0.001	1.10 (0.85–1.43)	<0.001	1.10 (0.95–1.28)	<0.001	1.05 (0.84–1.32)	<0.001
PB	13	5965/ 6149	1.02 (0.92–1.14)	<0.001	1.05 (0.93–1.18)	0.022	1.05 (0.84–1.31)	0.002	1.04 (0.91–1.19)	0.002	1.01 (0.84–1.21)	0.018
Cancer type												
Hepatocellular carcinoma	6	5421/ 6411	1.23 (1.06–1.44)	0.001	1.19 (1.07–1.32)	0.156	1.53 (1.04–2.23)	<0.001	1.29 (1.08–1.53)	0.019	1.34 (0.97–1.86)	0.002
Leukemia	2	680/ 793	0.71 (0.42–1.20)	0.031	0.76 (0.33–1.75)	0.006	0.52 (0.34–0.79)	0.411	0.71 (0.33–1.52)	0.009	0.50 (0.33–0.75)	0.657
Colorectal cancer	2	892/ 916	0.87 (0.75–1.01)	0.154	0.97 (0.79–1.17)	0.222	0.66 (0.47–0.92)	0.342	0.90 (0.75–1.09)	0.157	0.67 (0.48–0.93)	0.519
Gastric cancer	4	1833/ 2279	0.94 (0.75–1.18)	0.001	0.93 (0.75–1.17)	0.381	0.92 (0.58–1.47)	0.400	0.92 (0.71–1.20)	0.007	0.96 (0.66–1.47)	0.022
Breast cancer	3	2208/ 1967	0.97 (0.89–1.07)	0.304	1.02 (0.90–1.16)	0.289	0.90 (0.73–1.10)	0.386	1.00 (0.88–1.13)	0.287	0.89 (0.73–1.08)	0.387
Esophageal cancer	5	2372/ 2597	0.93 (0.85–1.01)	0.475	1.02 (0.90–1.14)	0.049	0.76 (0.62–0.92)	0.346	0.97 (0.86–1.08)	0.500	0.76 (0.63–0.91)	0.251
Digestive cancer	17	8232/ 9417	1.02 (0.92–1.13)	<0.001	1.05 (0.96–1.16)	0.019	1.02 (0.80–1.29)	<0.001	1.04 (0.93–1.17)	<0.001	0.99 (0.81–1.22)	<0.001
Female specific cancer	4	2535/ 2536	1.00 (0.92–1.09)	0.228	1.09 (0.91–1.31)	0.098	0.93 (0.77–1.12)	0.473	1.05 (0.93–1.17)	0.109	0.89 (0.75–1.07)	0.593
Other cancers	8	2830/ 3894	1.22 (1.04–1.24)	<0.001	1.24 (0.92–1.17)	<0.001	1.50 (1.26–1.77)	0.102	1.29 (0.99–1.70)	<0.001	1.37 (1.17–1.60)	0.249

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Table 2 continued. Total and stratified subgroup analysis for pri-miR-34b/c rs4938723 polymorphism site and cancer susceptibility.

Variables	N	Case/ control	C-allele *vs.* T-allele		CT *vs.* TT		CC *vs.* TT		CC+CT *vs.* TT		CC *vs.* CT+TT	
			OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h	OR (95%CI)	P_h
Sex												
Male	6	2674/ 3099	–		–		–		0.90 (0.53–1.52)	<0.001	0.92 (0.55–1.55)	0.007
female	6	1042/ 1369	–		–		–		0.75 (0.48–1.17)	0.085	0.80 (0.56–1.14)	0.234
Somking status												
Ever	5	1669/ 1488	–		–		–		1.04 (0.53–2.02)	0.046	0.92 (0.47–1.79)	0.006
Never	5	1670/ 2170	–		–		–		1.03 (0.56–1.89)	0.014	0.85 (0.65–1.11)	0.141
Drinking												
Ever	3	968/ 778	–		–		–		–		0.94 (0.55–1.62)	0.062
Never	3	1451/ 1930	–		–		–		–		0.81 (0.48–1.37)	0.013
Age												
<62	2	814/ 938	–		–		–		–		0.70 (0.50–0.98)	0.654
≥62	2	895/ 1010	–		–		–		–		0.68 (0.50–0.93)	0.942

P_h – value of *Q*-test for heterogeneity test.

Material and Methods

Identification strategy

We searched in PubMed, EMbase, Web of Science, CNKI, VIP, and WanFang databases (updated on Sep 10, 2018) using 'polymorphism' or 'variant' or 'single-nucleotide polymorphism (SNP)' or 'mutation', 'cancer' or 'tumor', and 'miR-34b/c' or 'pri-miR-34'. Each publication that assessed the relationship between rs4938723 polymorphism and cancer risk was collected.

Search criterion

The selection criteria were: (1) evaluation of pri-miR-34b/c rs4938723 and all types of cancer risks, (2) case-control design, and (3) available genotype frequency. Exclusion criteria were: (1) studies with duplicate data (the most recent or complete study with the largest number of cases and controls were included), and (2) studies that have not yet been published.

Data extraction

The following data were collected: first author, year of publication, race of origin, cancer type by traditional classification, cancer type by our own standard, sample size (cases/controls), each kind of genotype both for case and control groups, study design (HB: hospital-based and PB: population-based), source of control, Hardy-Weinberg equilibrium (HWE) of controls, and genotyping method.

Statistical analysis

Odds ratio (OR) with 95% confidence interval (CI) was used to measure the strength of the association between pri-miR-34b/c rs4938723 and cancers. We analyzed this correlation by using 5 different genetic models: C-allele *vs.* T-allele, CC *vs.* TT, CT *vs.* TT, CC+CT *vs.* TT, and CC *vs.* CT+TT. Ethnicity subgroup were categorized as Caucasian, Asian, African, or mixed (if study population was not a pure race). We divided the control group into 4 classes based on source: HB or PB. In the cancer type subgroup, we included hepatocellular carcinoma, leukemia, colorectal cancer, gastric cancer, breast cancer, esophageal

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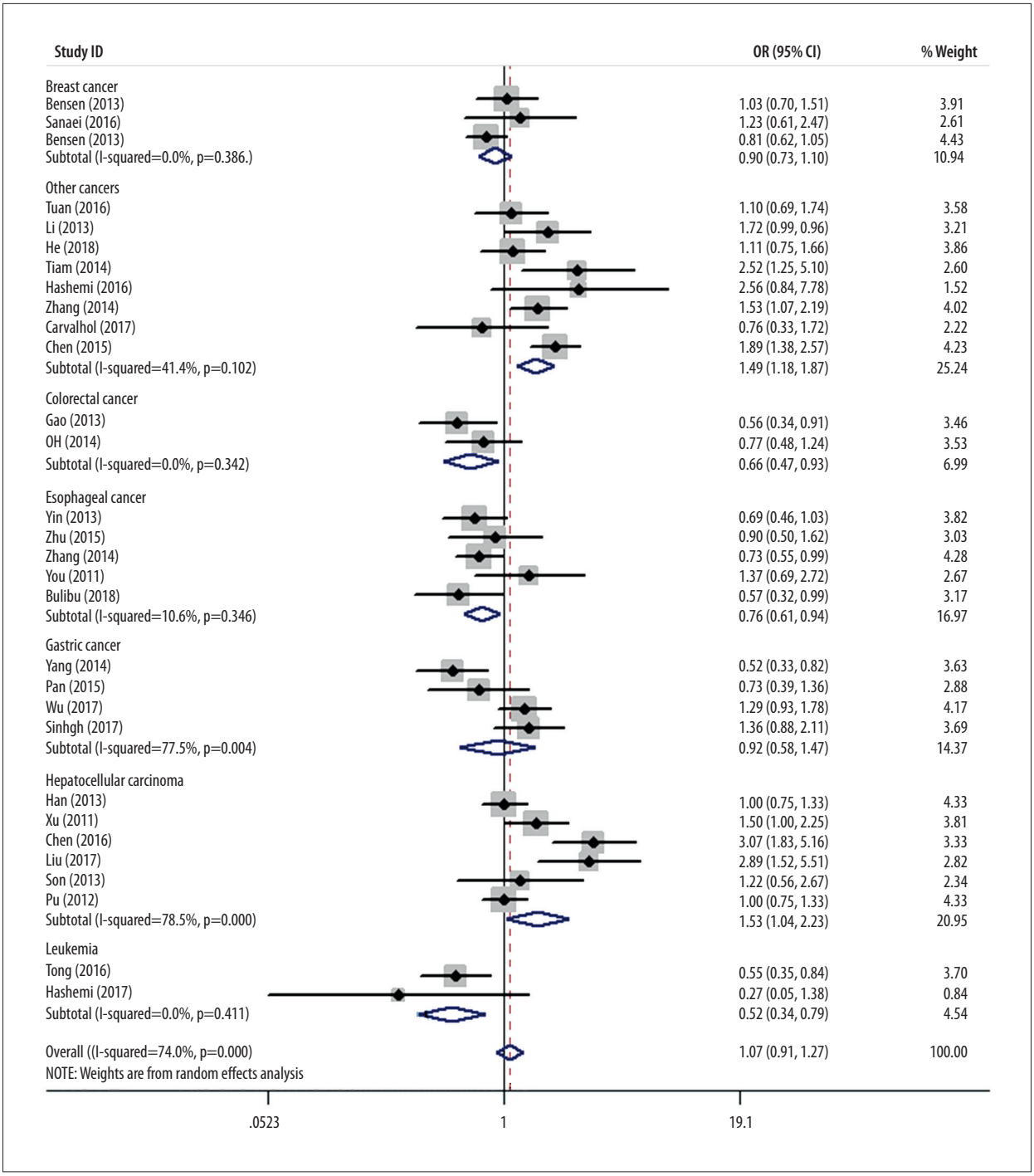

Figure 4. Forest plot of hepatocellular carcinoma associated with pri-miR-34b/c rs4938723 polymorphism (CC *vs.* TT). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

cancer, digestive cancer, female specific cancer, and other cancers (if not in the above types).

Heterogeneity assumption was assessed with a chi-square-based *Q*-test. The statistical significance was calculated with the *Z*-test. When P for the heterogeneity test (*Ph*) was more than 0.10, the fixed-effects model was applied; otherwise, the random-effects model was used [58,59]. The funnel plot asymmetry and publication bias were evaluated by both Egger's test and Begg's test [60,61]. The departure of frequencies of rs4938723 from expected values

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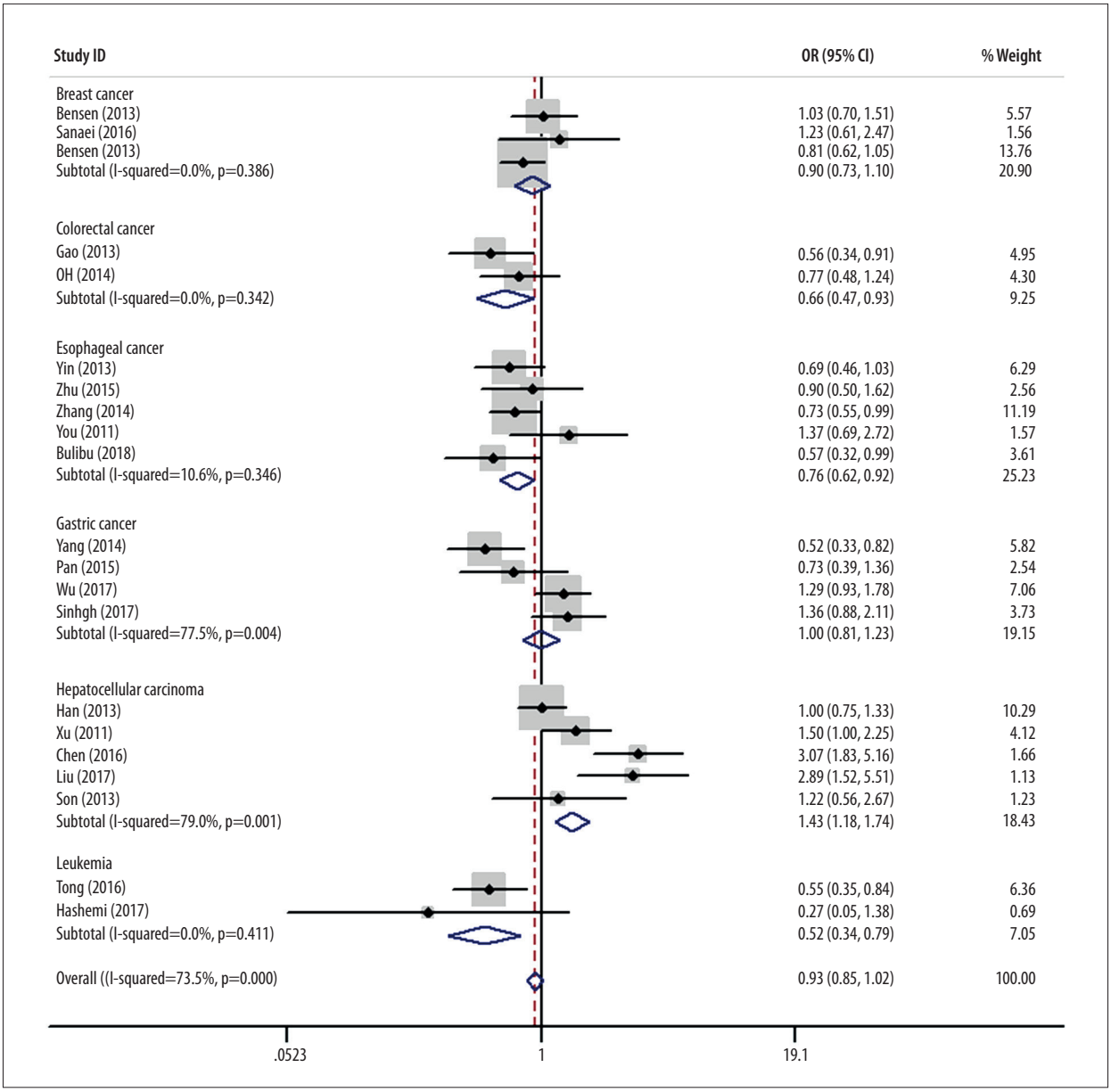

Figure 5. Forest plot of leukemia risk associated with pri-miR-34b/c rs4938723 polymorphism (CC *vs.* TT). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

under HWE was evaluated in controls using the Pearson chi-square test. All these statistical tests were performed using Stata software (version 11.0; StataCorp LP, College Station, TX).

Results

Study characteristics

After reviewing the title, abstract, and full text, we excluded meta-analyses, reviews, case-only studies, and other gene polymorphisms. The flowchart illustrating the search strategy is shown in Figure 1. Finally, 29 different papers describing 30 case-control studies [22,25,29–31,34–57] evaluating the relationship between rs4938723 polymorphism and cancer were identified. Study characteristics are shown in Table 1. The HWE in controls was consistent with 0.05, except for 1 study by Chen (2016) [30]. To observe a representation of our analysis, we investigated the minor allele frequency from 5 main worldwide populations in the 1000 Genomes Browser: East Asian, 0.305; European, 0.365; African, 0.276; American, 0.219; and South Asian, 0.244 (Figure 2).

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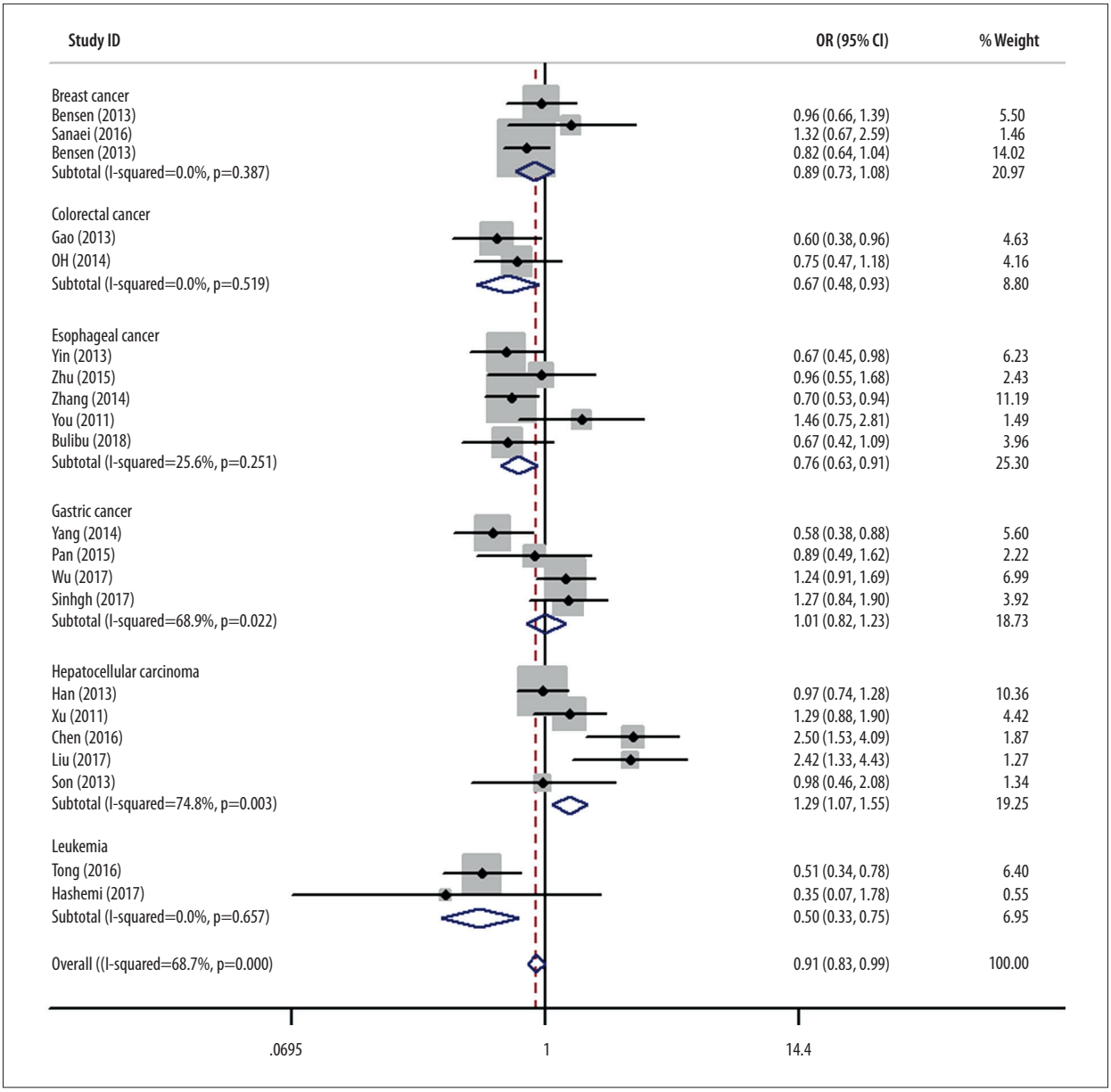

Figure 6. Forest plot of colorectal and esophageal cancer risk associated with pri-miR-34b/c rs4938723 polymorphism (CC *vs.* CT+TT). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

None of the control populations had a history of malignant diseases. Genotyping methods are listed in Table 1.

Quantitative synthesis

Total analysis

In the total group, no vital relationship was found in all comparisons (e.g., C-allele *vs.* T-allele: OR=1.04; 95% CI=0.97–1.13; $P_{(heterogeneity)}$ <0.001, Figure 3). At the same time, if we excluded 1 paper that was not consistent with HWE, a similar association was detected (Table 2). In addition, no association was detected in subgroup analysis based on ethnicity and source of control (Table 2).

Subgroup analysis by cancer type

Detailed results are shown in Table 2. Statistically significant relationships were observed between pri-miR-34b/c rs4938723 and risk of 4 types of cancers: as a risk factor for hepatocellular carcinoma (e.g., CC *vs.* TT: OR=1.53; 95% CI=1.04–2.23; $P_{(heterogeneity)}$<0.001, Figure 4), but as a protective factor for

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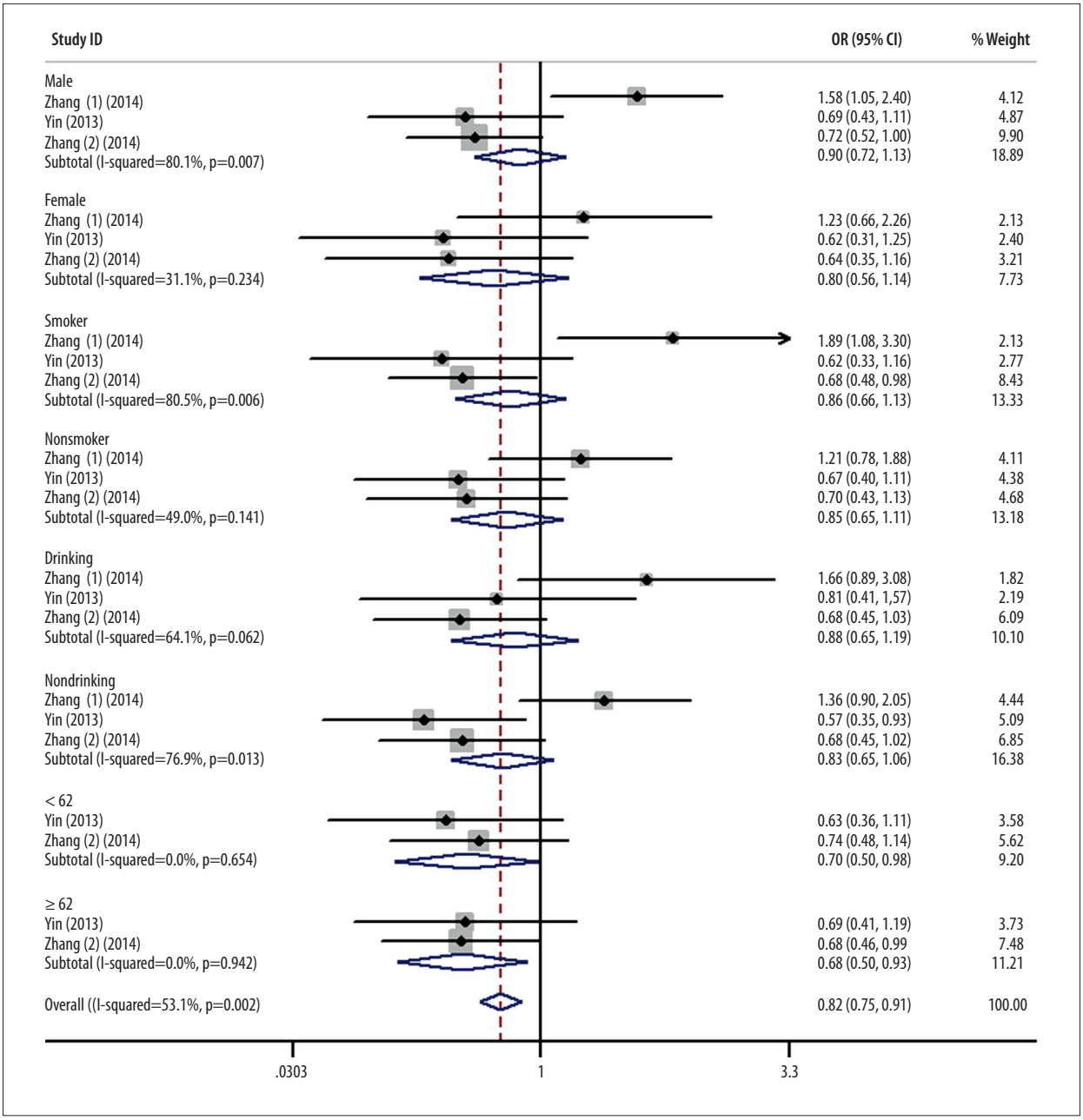

Figure 7. Forest plot of cancer risk associated with pri-miR-34b/c rs4938723 polymorphism (CC *vs.* CT+TT) in the age subgroup. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

leukemia (e.g., CC *vs.* TT: OR=0.52; 95% CI=0.34–0.79; $P_{(heterogeneity)}$=0.411 for heterogeneity, Figure 5), colorectal cancer (CC *vs.* CT+TT: OR=0.67; 95% CI=0.48–0.93; $P_{(heterogeneity)}$=0.519 for heterogeneity, Figure 6), and esophageal cancer (CC *vs.* CT+TT: OR=0.76; 95% CI=0.63–0.91; $P_{(heterogeneity)}$=0.251 for heterogeneity, Figure 6) (Table 2).

Subgroup analysis by age and other kinds of analysis

Interestingly, in the age subgroup, decreased associations were found both in <62 (OR=0.70; 95% CI=0.50–0.98; $P_{(heterogeneity)}$=0.654 for heterogeneity) and ≥62 groups (OR=0.68; 95% CI=0.50–0.93; $P_{(heterogeneity)}$=0.942 for heterogeneity) (Figure 7, Table 2). No association was detected in subgroups based on sex, smoking status, and drinking (Table 2).

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Table 3. Relationship between pri-miR-34b/c rs4938723 polymorphism and cancer prognosis.

Genotype	Localised	Advanced	OR (95%CI)	P_h	*P*
CC+CT	446	261			
TT	317	242	1.15 (0.91–1.46)	0.735	0.237
CC	156	83			
CT+TT	947	605	1.71 (0.79–3.71)	0.001	0.174

P_h – value of *Q*-test for heterogeneity test

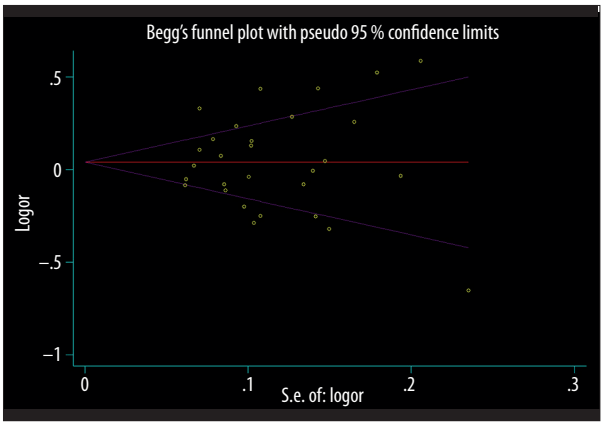

Figure 8. Begg's funnel plot for publication bias test (C-allele *vs.* T-allele). Each point represents a separate study for the indicated association. Log [OR], natural logarithm of OR. Horizontal line, mean effect size.

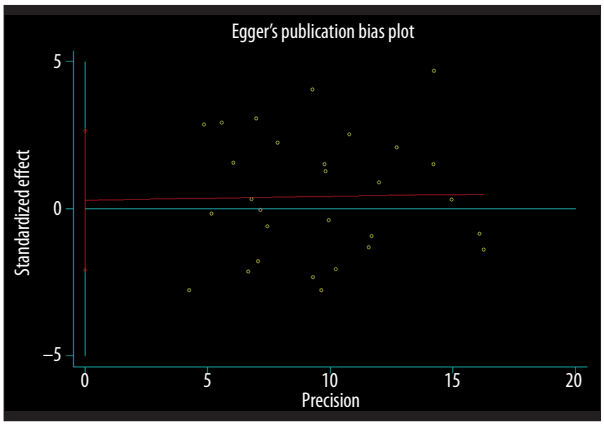

Figure 9. Egger's publication bias plot (C-allele *vs.* T-allele).

Table 4. Publication bias tests (Begg's funnel plot and Egger's test for publication bias test) for pri-miR-34b/c rs4938723 polymorphism.

Genetic type	Egger's test					Begg's test	
	Coefficient	Standard error	*t*	*P* value	95% CI of intercept	z	*P* value
C-allele vs. T-allele	0.282	1.154	0.24	0.809	(–2.082, 2.646)	0.27	0.789
CT *vs.* TT	0.607	0.927	0.65	0.519	(–1.311, 2.526)	0.44	0.657
CC *vs.* TT	0.293	0.509	0.58	0.57	(–0.760, 1.347)	0.68	0.498
CC+TC *vs.* TT	0.651	0.972	0.67	0.51	(–1.360, 2.661)	0.49	0.624
CC *vs.* TC+TT	0.281	0.534	0.53	0.604	(–0.825, 1.387)	0.54	0.591

Relationships between rs4938723 polymorphism and prognosis of cancer

To our regret, no association between this polymorphism and cancer prognosis in 2 models (localized and advanced) (CC+CT *vs.* TT: OR=1.15; 95% CI=0.91–1.46; $P_{(heterogeneity)}$=0.735 for heterogeneity, *P*=0.237 for *Z*-test) was found (Table 3).

Publication bias diagnosis and sensitivity analysis

Both Begg's funnel plot and Egger's test were applied to assess the publication bias. No publication bias was detected [for example (C-allele *vs.* T-allele) (*z*=0.27, *P*=0.789 for Begg's test; *t*=0.24, *P*=0.809 for Egger's test, Figures 8, 9)] (Table 4). Despite the above results, each study reflected the influence of the individual dataset on the pooled OR, and observed that the corresponding pooled OR was not significantly altered, indicating that our results were statistically robust (for example: allelic contrast, Figure 10).

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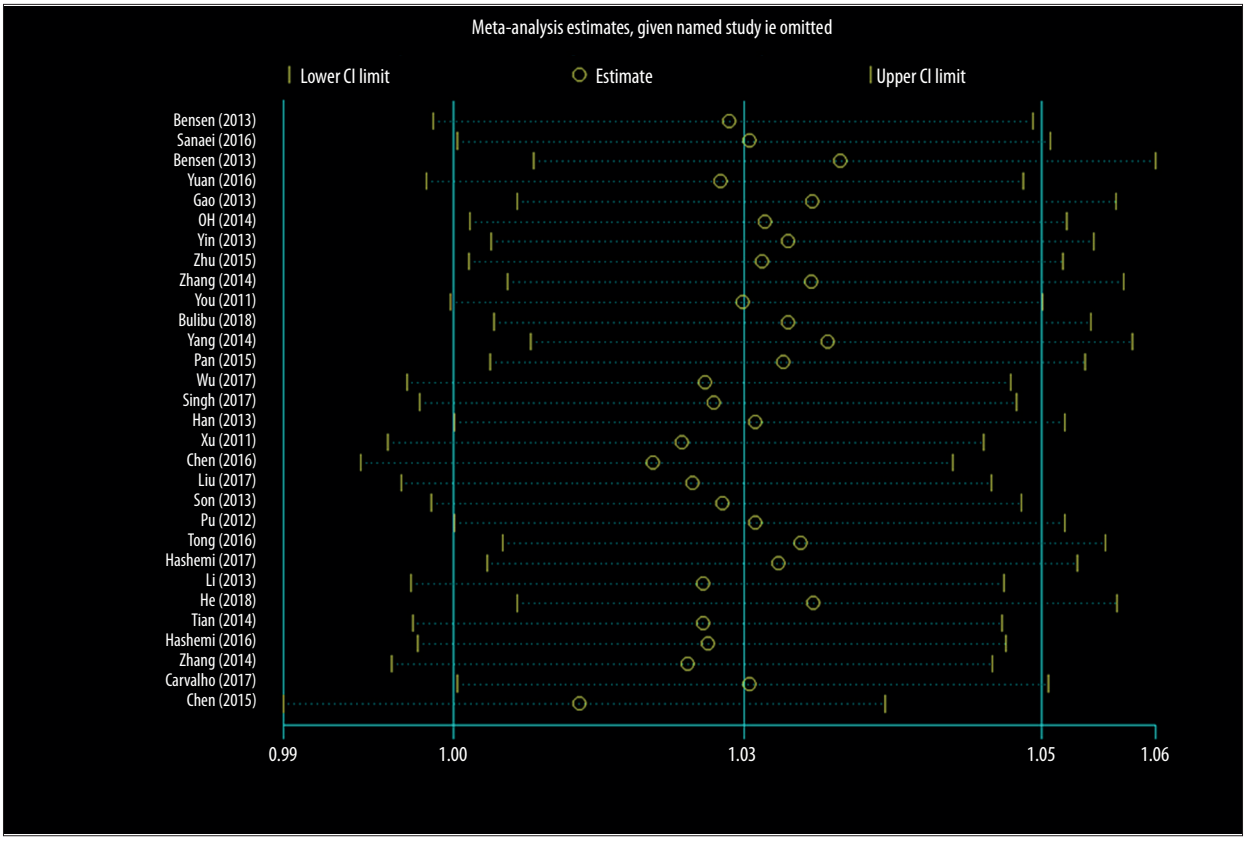

Figure 10. Sensitivity analysis between pri-miR-34b/c rs4938723 polymorphism and TB risk (C-allele *vs.* T-allele).

Discussion

mir-34b/c gene is part of the p53 pathway and enhances its tumor suppressor activities [62, 63]; it transcribes microRNA-34 b and c, which inhibit p53 antagonists [64], cyclin-dependent kinases, and pro-apoptotic proteins [65]. The deregulation of miR-34b/c was observed in several carcinoma cells, and cell proliferation, apoptosis, migration, and invasion were involved. Recently, a SNP located at the promoter region of mir-34b/c gene (rs4938723T/C) was identified, and its role in tumorigenesis has been widely investigated, as it can alter miR-34b/c transcription levels, because it can affect GATA-X binding. Presence of C in this location leads to binding to the GATA-X [33].

Our meta-analysis explored the association between pri-miR-34b/c rs4938723 and overall cancer susceptibility, involving 13 950 cancer cases and 16 071 controls. The main results of our analysis are that this polymorphism has different associations with different types of cancer: increased association for hepatocellular carcinoma, but decreased association for leukemia, colorectal, and esophageal cancer. The following reasons may explain these results. First, differences in the distribution of various cancers between cases and controls might be a source of variability during pooling. Second, rs4938723 polymorphism might carry out different functions in different types of cancers. Third, because cancer is a multi-factorial disease caused by the complex interactions between many genetic and environmental factors, there is no single gene or environmental factor that has a significant effect on cancer susceptibility [66]. The present study differs from previous meta-analyses in that we included some environmental and clinical factors, such as sex, smoking status, age, drinking, and prognosis of cancer. Of note, a positive association was found in the age subgroup. Our results were also different from those of previous meta-analyses [32,33] because previously there had been no association between this polymorphism and the whole cancer risk, as well as no association for Asians and gastric cancer risk. This was because the relatively small samples in previous analysis resulted in false-positive results. So, it made sense to recombine all studies to gain a comprehensive and credible conclusion, and to correct error at the same time.

Some limitations should be considered. First, sample sizes varied widely in the different studies (range of the number of cases/controls: 110/120 to 1109/1275), which may increase the publication bias. Second, there were only 2 case-control studies regarding leukemia, colorectal, and gastric cancer; future studies should also focus on these types of cancers. Third, few studies used mixed, Caucasian, or African populations; future studies should also focus on these races. Fourth,

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additional studies are needed to address the effects of race and sample size on the predicted associations, and more attention must be placed on gene-gene and gene-environment interactions. Fifth, other environmental factors, such as dietary factors and infectious agents, increase the load of carcinogenic substances humans are exposed to.

Conclusions

Our present analysis found novel evidence that the pri-miR-34b/c rs4938723 polymorphism had 2-tier effects on the risk of different types of cancers: rs493723 polymorphism was associated increased risk of hepatocellular carcinoma and decreased risk of leukemia, colorectal and esophageal cancer. Further studies with larger samples are needed to evaluate associations between rs4938723 polymorphism and each type of cancer.

Conflict of interest

None.

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