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Original Article

The role of *HRAS* rs12628 polymorphism in cancer risks: evidence from a meta-analysis of 19 case-control studies

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Abstract: There was inconsistent conclusion on the association between rs12628 polymorphism of *HRAS* gene and human cancer risks. Therefore, we systematically carried out an updated meta-analysis to determine whether *HRAS* rs12628 polymorphism is associated with the susceptibility to cancer. The literature retrieval based on PUBMED, Web of Science, EMBASE and WANFANG databases was performed with publication date before July 1st, 2016. After screening, 19 case-control studies were enrolled for meta-analysis. The overall cancer risk was statistically higher in the case group than the control group, under C vs T (OR=1.48, 95% CI=1.12-1.96, $P_{association}$=0.006), TC vs TT (OR=1.50, 95% CI=1.08-2.08, $P_{association}$=0.015), TC+CC vs TT (OR=1.56, 95% CI=1.11-2.18, $P_{association}$=0.009), carrier C vs carrier T (OR=1.38, 95% CI=1.08-1.72, $P_{association}$=0.008), but not CC vs TT and CC vs TT+TC model (all $P_{association}$>0.05). Furthermore, the similar significant difference was observed in the stratification analysis by Asian population, thyroid cancer and P_{HWE}>0.05 (all OR>1, $P_{association}$<0.05). Our data supported the genetic relationship between TC genotype of *HRAS* rs12628 and an increased risk of cancer, particularly in the Asian population.

Keywords: Meta-analysis, *HRAS*, polymorphism, cancer, susceptibility

Introduction

Three types of rat sarcoma viral oncogene homologue (RAS) gene, namely *HRAS*, *KRAS* and *NRAS*, encode the small guanosine-5'-triphosphate (GTP)-binding proteins, also known as p21 ras, and modulate the inactive GTP-bound/active GDP-bound switch to control the growth and proliferation of mammalian cells [1-3]. An increasing number of studies reported that *RAS* gene contributes to the occurrence of human cancer [2, 3].

Human *HRAS* (*Harvey RAS*) gene on chromosome 11 comprises one 5' terminal noncoding exon and 3' terminal four encoding exons [4, 5]. Several single nucleotide polymorphisms (SNP), such as rs12628, rs35601764 and rs112587690, have been identified in *HRAS* gene [6, 7]. *HRAS* rs12628 T/C polymorphism (T81C) fails to disturb the structure of p21 ras protein, because that both CAT and CAC encode the same histidine in the codon 27 of first exon (his27his) [5, 8]. In spite of that, it was reported that *HRAS* rs12628 was involved in the presence of Costello syndrome (CS), a rare congenital disorder [9]. In addition, accumulating but conflicting results have been reported on the role of *HRAS* polymorphisms in the susceptibility to different cancers [7, 10-13].

Three meta-analyses on the association between *HRAS* rs12628 and cancer risks have been reported [5, 12, 14]. However, an updated comprehensive systematic review and meta-analysis was still needed to evaluate the association between more *HRAS* variants and cancer susceptibility, considering the publication of more potential studies. After the systematic review, only the common genetic rs12628 polymorphism of *HRAS* was chosen, due to the limited data. Here, our results revealed that TC

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

First author (Year)	Ethnicity	Country	Genotyping method	Control			Source*	P_{HWE}	Case			Disease
				TT	TC	CC			TT	TC	CC	
Castro (2006)	Caucasian	Portugal	SSCP	50	36	16	PB	0.04	32	38	15	Thyroid cancer
Catela (2009)	Caucasian	Croatia	PCR-RFLP	85	85	30	PB	0.26	121	73	6	Colon cancer
Guan (2014)	Asian	China	PCR-RFLP	159	39	2	PB	0.82	107	89	4	Thyroid cancer
Johne (2003)	Caucasian	Germany	PCR-RFLP	106	130	18	HB	0.01	151	119	42	Bladder cancer
				58	40	8	PB	0.76	151	119	42	Bladder cancer
Khan (2013)	Asian	India	PCR-RFLP	143	20	7	PB	0.00	58	54	28	Thyroid cancer
Mir (2015)	Asian	India	PCR-RFLP	92	8	0	PB	0.68	38	61	1	Chronic myeloid leukemia
Ni (2012)	Asian	China	PCR-RFLP	660	170	8	PB	0.42	141	30	7	Colon cancer
				660	170	8	PB	0.42	142	53	0	Rectal cancer
Oh (2010)	Asian	Korea	GoldenGate Assay	184	126	11	HB	0.06	95	51	5	Gastric cancer
Pandith (2013)	Asian	India	PCR-RFLP	135	25	0	PB	0.28	90	42	8	Bladder cancer
Rostami (2013)	Asian	Iran	PCR-RFLP	60	33	7	PB	0.41	69	29	2	Gastric cancer
Sanyal (2004)	Caucasian	Sweden	PCR-RFLP	54	61	6	PB	0.03	153	147	2	Bladder cancer
Sathyan (2006)	Asian	India	PCR-SSCP	92	43	7	HB	0.50	94	70	12	Oral cancer
Tomei (2012)	Caucasian	North America	sequencing and fragment analysis	55	57	6	PB	0.07	65	52	24	Melanoma
Traczyk (2012)	Caucasian	Poland	SSCP and DNA sequencing	49	48	9	PB	0.56	45	64	23	Bladder cancer
Zhang (2008)	Asian	China	PCR-RFLP	355	89	4	PB	0.54	48	40	2	Gastric cancer
				355	89	4	PB	0.54	71	20	2	Colon cancer
				355	89	4	PB	0.54	85	28	0	Rectal cancer

*, Source of controls; SSCP: single-strand conformation polymorphism; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; PB: population-based; HB: hospital-based; P_{HWE}: *P* value for Hardy-Weinberg equilibrium.

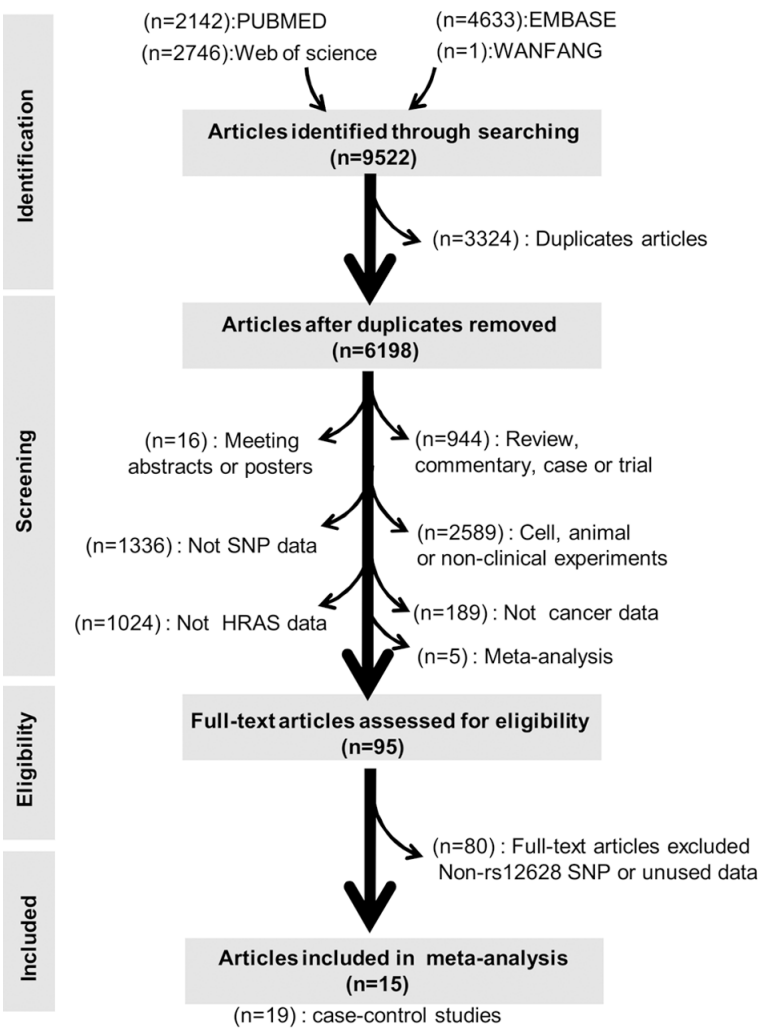

Figure 1. The selection flowchart of eligible studies.

genotype of *HRAS* rs12628 may be linked to the increased risks of cancer, particularly in the Asian population.

Materials and methods

Literature retrieval strategy

Meta-analysis was performed in accordance with the slightly modified "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) [15]. The literatures were retrieved in the databases of PUBMED, Web of Science, EMBASE and WANFANG (update to July 1st, 2016). One of search terms: ("HRAS" or "H-RAS" or "H-ras") and ("polymorphism" or "Single Nucleotide Polymorphism" or "SNP" or "rs12628" or "T81C" or "mutation").

Study selection and data extraction

We excluded the literature with the following features: "Duplicated articles; Review, commentary, case or trial; Meeting abstracts or posters; Cell, animal or non-clinical experiments; Not SNP data; Not HRAS data; Not cancer data; Meta-analysis; Non-rs12628 SNP or unused data". All selected case-control studies could provide the genotype data of *HRAS* rs12628 polymorphism in both control and case group.

The following information was extracted by the investigators independently: First author, Year of publication, Ethnicity, Country, Genotyping method, genotype frequencies in case/control groups, Source of control, *P* value of HWE (Hardy-Weinberg equilibrium) in the control group and Disease type. A meeting for conflicting evaluation and an E-mail for unavailable data were required.

Statistical analysis

The STATA software (version 12.0, STATA Corporation, TX, USA) was utilized to assess the strength of genetic relationship. The odd radios (OR), 95% confidence intervals (95% CI) andtwo-tailed $P_{association}$ value were yielded through Mantel-Haenszel method, based on the allele model (C vs T), homozygote model (CC vs TT), heterozygote model (TC vs TT), dominant model (TC+CC vs TT), recessive model (CC vs TT+TC) and carrier model (carrier C vs carrier T), respectively. A $P_{association}$ value <0.05 was considered as the presence of a statistically significant difference. The between-study heterogeneity was evaluated by Cochran's Q statistic test and inconsistency index (I^2) value, ranging from 0% to 100%. The low, moderate, and high degrees of heterogeneity were defined by the I^2 value of 25%, 50%, and 75%, respec-

Table 2. Pooled analysis of the association between *HRAS* rs12628 polymorphism and cancer risks

Comparison	Association' test			Studies number	Heterogeneity		Model	Begg' test		Egger' test	
	OR	95% CI	$P_{association}$		I^2	$P_{heterogeneity}$		z	P_{Begg}*	t	P_{Egger}
C vs T	1.48	1.12-1.96	0.006	19	90.2%	<0.001	Random	2.38	0.017	2.88	0.010
CC vs TT	1.57	0.89-2.77	0.116	19	76.1%	<0.001	Random	0.00	1.000	-0.31	0.762
TC vs TT	1.50	1.08-2.08	0.015	19	88.6%	<0.001	Random	2.73	0.006	2.91	0.010
TC+CC vs TT	1.56	1.11-2.18	0.009	19	89.9%	<0.001	Random	2.17	0.030	3.00	0.008
CC vs TT+TC	1.45	0.88-2.40	0.149	19	71.1%	<0.001	Random	0.49	0.624	-0.63	0.537
Carrier C vs carrier T	1.38	1.08-1.72	0.008	19	82.1%	<0.001	Random	2.24	0.025	3.11	0.006

*continuity corrected.

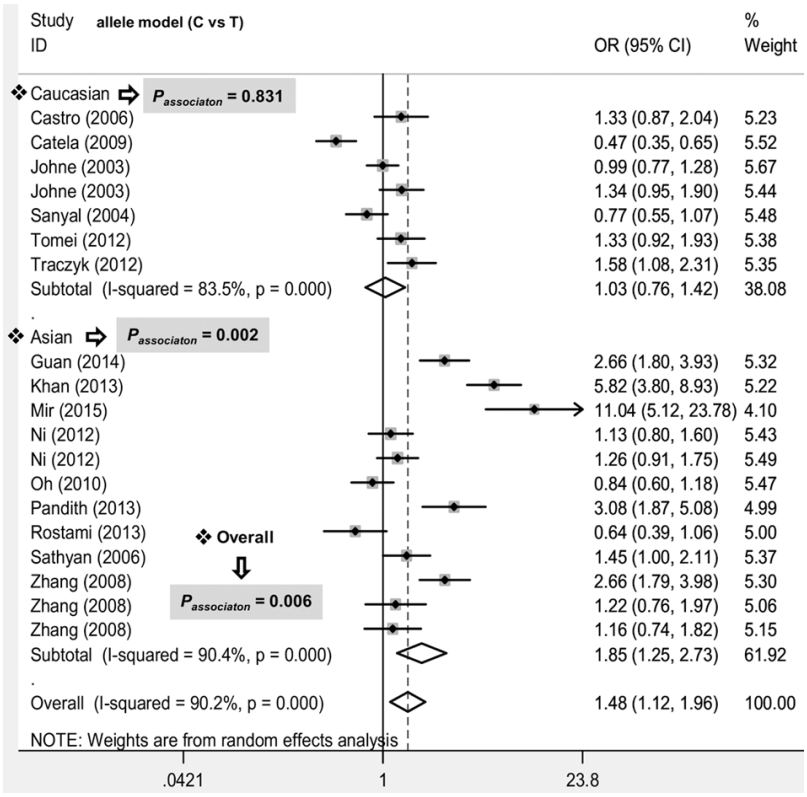

Figure 2. Stratification analysis by ethnicity for the association between *HRAS* rs12628 polymorphism and cancer risks under C vs T model.

tively. *P* value of Cochran's Q statistic test >0.1 or I^2<25% excludes the existence of heterogeneity. Fixed-effect model was thus adopted for Mantel-Haenszel statistics. Otherwise, random-effect model was used. To analyze the potential sources of heterogeneity, sensitivity analysis via sequentially omitting each study and stratification analysis by ethnicity, disease type or P_{HWE} value were performed. Also, Begg's test and Egger's test were performed to assess the potential publication bias [16-18].

Results

Characteristics of included studies

The databases (PUBMED, Web of Science, EMBASE and WANFANG) were systematically retrieved with publication date before July 1st, 2016. After the screening based on the selection criteria, 19 case-control studies from 15 eligible articles were selected for our meta-analysis [4, 5, 7, 8, 10-14, 19-24]. The genotype frequency and characteristics of included studies are shown in **Table 1**.

The flowchart of literature retrieval strategy is shown in **Figure 1**. A total of 9522 available literatures, including PUBMED (n=2142), Web of Science (n=2746), EMBASE (n=4633) and WANFANG (n=1), were initially obtained. We removed 3324 duplicated articles and excluded the following articles: Review, commentary, case or trial (n=944), Meeting abstracts or posters (n=16), Cell, animal or non-clinical experiments (n=2589), Not SNP data (n=1336), Not HRAS data (n=1024), Not cancer data (n=189), and Meta-analysis (n=5). Then, we independently extracted the data from 95 full-text articles. Of which, 80 articles were excluded due to the lack of rs12628 SNP or unused genotype data.

Table 3. Stratification analysis of the association between *HRAS* rs12628 polymorphism and cancer risks

Comparison	Stratification		Studies number	Test of association		
				OR	95% CI	$P_{association}$
C vs T	Ethnicity	Caucasian	7	1.03	0.76-1.42	0.831
		Asian	12	1.85	1.25-2.73	0.002
	Disease	Thyroid cancer	3	2.74	1.22-6.17	0.015
		Colon cancer	3	0.86	0.45-1.62	0.632
		Bladder cancer	5	1.34	0.91-1.97	0.145
		Chronic myeloid leukemia	1	11.04	5.12-23.78	<0.001
		Rectal cancer	2	1.23	0.94-1.60	0.131
		Gastric cancer	3	1.14	0.49-2.63	0.764
		Oral cancer	1	1.45	1.00-2.11	0.051
		Melanoma	1	1.33	0.92-1.93	0.133
	HWE	P_{HWE}<0.05	4	1.55	0.71-3.38	0.276
		P_{HWE}>0.05	15	1.46	1.08-1.96	0.014
CC vs TT	Ethnicity	Caucasian	7	1.05	0.45-2.49	0.903
		Asian	12	2.21	1.06-4.60	0.035
	Disease	Thyroid cancer	3	3.55	0.92-13.68	0.066
		Colon cancer	3	1.09	0.10-12.35	0.945
		Bladder cancer	5	1.60	0.64-4.01	0.312
		Chronic myeloid leukemia	1	7.21	0.29-180.87	0.230
		Rectal cancer	2	0.35	0.05-2.73	0.318
		Gastric cancer	3	0.90	0.23-3.48	0.882
		Oral cancer	1	1.68	0.63-4.45	0.298
		Melanoma	1	3.38	1.29-8.87	0.013
	HWE	P_{HWE}<0.05	4	1.49	0.41-5.45	0.544
		P_{HWE}>0.05	15	1.58	0.82-3.05	0.171
TC vs TT	Ethnicity	Caucasian	7	0.91	0.69-1.19	0.484
		Asian	12	1.99	1.28-3.10	0.002
	Disease	Thyroid cancer	3	3.36	1.65-6.67	0.001
		Colon cancer	3	0.80	0.57-1.12	0.187
		Bladder cancer	5	1.14	0.73-1.80	0.562
		Chronic myeloid leukemia	1	18.46	8.06-42.26	<0.001
		Rectal cancer	2	1.40	1.05-1.87	0.022
		Gastric cancer	3	1.26	0.8-3.35	0.638
		Oral cancer	1	1.59	0.99-2.57	0.055
		Melanoma	1	0.77	0.46-1.30	0.329
	HWE	P_{HWE}<0.05	4	1.53	0.59-3.98	0.382
		P_{HWE}>0.05	15	1.49	1.05-2.12	0.024
TC+CC vs TT	Ethnicity	Caucasian	7	0.97	0.70-1.34	0.860
		Asian	12	2.05	1.30-3.23	0.002
	Disease	Thyroid cancer	3	3.45	1.53-7.78	0.003
		Colon cancer	3	0.81	0.47-1.39	0.442
		Bladder cancer	5	1.27	0.79-2.04	0.318
		Chronic myeloid leukemia	1	18.76	8.20-42.93	<0.001
		Rectal cancer	2	1.34	1.00-1.78	0.047
		Gastric cancer	3	1.22	0.45-3.30	0.699
		Oral cancer	1	1.61	1.02-2.53	0.041
		Melanoma	1	1.02	0.63-1.67	0.935

	HWE	P_{HWE}<0.05	4	1.61	0.60-4.35	0.344
		P_{HWE}>0.05	15	1.54	1.08-2.20	0.017
CC vs TT+TC	Ethnicity	Caucasian	7	1.09	0.49-2.42	0.835
		Asian	12	1.88	1.00-3.54	0.050
	Disease	Thyroid cancer	3	2.41	0.75-7.72	0.138
		Colon cancer	3	1.18	0.12-11.72	0.890
		Bladder cancer	5	1.60	0.69-3.70	0.270
		Chronic myeloid leukemia	1	3.03	0.12-75.28	0.499
		Rectal cancer	2	0.33	0.04-2.53	0.285
		Gastric cancer	3	0.86	0.28-2.63	0.793
		Oral cancer	1	1.41	0.54-3.68	0.482
		Melanoma	1	3.83	1.51-9.72	0.005
	HWE	P_{HWE}<0.05	4	1.38	0.47-4.06	0.558
		P_{HWE}>0.05	15	1.46	0.80-2.67	0.217
carrier C vs carrier T	Ethnicity	Caucasian	7	1.00	0.81-1.23	0.982
		Asian	12	1.66	1.20-2.30	0.002
	Disease	Thyroid cancer	3	2.33	1.19-4.58	0.014
		Colon cancer	3	0.87	0.58-1.30	0.483
		Bladder cancer	5	1.21	0.89-1.65	0.223
		Chronic myeloid leukemia	1	7.83	3.56-17.20	<0.001
		Rectal cancer	2	1.24	0.94-1.63	0.133
		Gastric cancer	3	1.14	0.57-2.28	0.706
		Oral cancer	1	1.35	0.89-2.05	0.160
		Melanoma	1	1.15	0.76-1.76	0.505
	HWE	P_{HWE}<0.05	4	1.43	0.75-2.73	0.283
		P_{HWE}>0.05	15	1.35	1.05-1.73	0.018

HWE: Hardy-Weinberg equilibrium.

Meta-analysis of the association between HRAS rs12628 and cancer risks

The meta-analysis of 19 case-control studies was performed to determine the association between *HRAS* rs12628 and overall cancer risks. The data of C vs T (I^2 value of 90.2% and $P_{heterogeneity}$<0.001), CC vs TT (I^2=76.1% and $P_{heterogeneity}$<0.001), TC vs TT (I^2=88.6% and $P_{heterogeneity}$<0.001), TC+CC vs TT (I^2=89.9% and $P_{heterogeneity}$<0.001), CC vs TT+TC (I^2=71.1% and $P_{heterogeneity}$<0.001) and carrier C vs carrier T (I^2=82.1% and $P_{heterogeneity}$<0.001) indicated the presence of the high degree of heterogeneity among studies and the utilization of random-effect model (**Table 2**).

The data of pooled analysis (**Table 2**) showed that, compared with the control group, an increased overall cancer risk was observed in the case group under C vs T model (OR=1.48, 95% CI=1.12-1.96, $P_{association}$=0.006), TC vs TT model (OR=1.50, 95% CI=1.08-2.08, $P_{association}$=0.015), TC+CC vs TT model (OR=1.56, 95% CI=1.11-2.18, $P_{association}$=0.009), carrier C vs carrier T model (OR=1.38, 95% CI=1.08-1.72, $P_{association}$=0.008); whereas no significant difference was obtained for CC vs TT model (OR=1.57, 95% CI=0.89-2.77, $P_{association}$=0.116) and CC vs TT+TC (OR=1.45, 95% CI=0.88-2.40, $P_{association}$=0.149). These demonstrated that TC genotype of *HRAS* rs12628 may be closely linked to an increased cancer risk.

Stratification analyses of the association between HRAS rs12628 and cancer risks

Moreover, stratification analyses under all genetic models were performed by ethnicity (Caucasian and Asian), disease type (such as thyroid cancer, colon cancer, bladder cancer and gastric cancer) and P_{HWE} value. As shown in **Figure 2** and **Table 3**, an increased overall cancer risk was observed in the Asian population under C vs T model (OR=1.85, 95% CI=1.25-2.73, $P_{association}$=0.002), CC vs TT model (OR=2.21, 95% CI=1.06-4.60, $P_{association}$=0.035), TC vs TT model (OR=1.99, 95% CI=1.28-3.10,

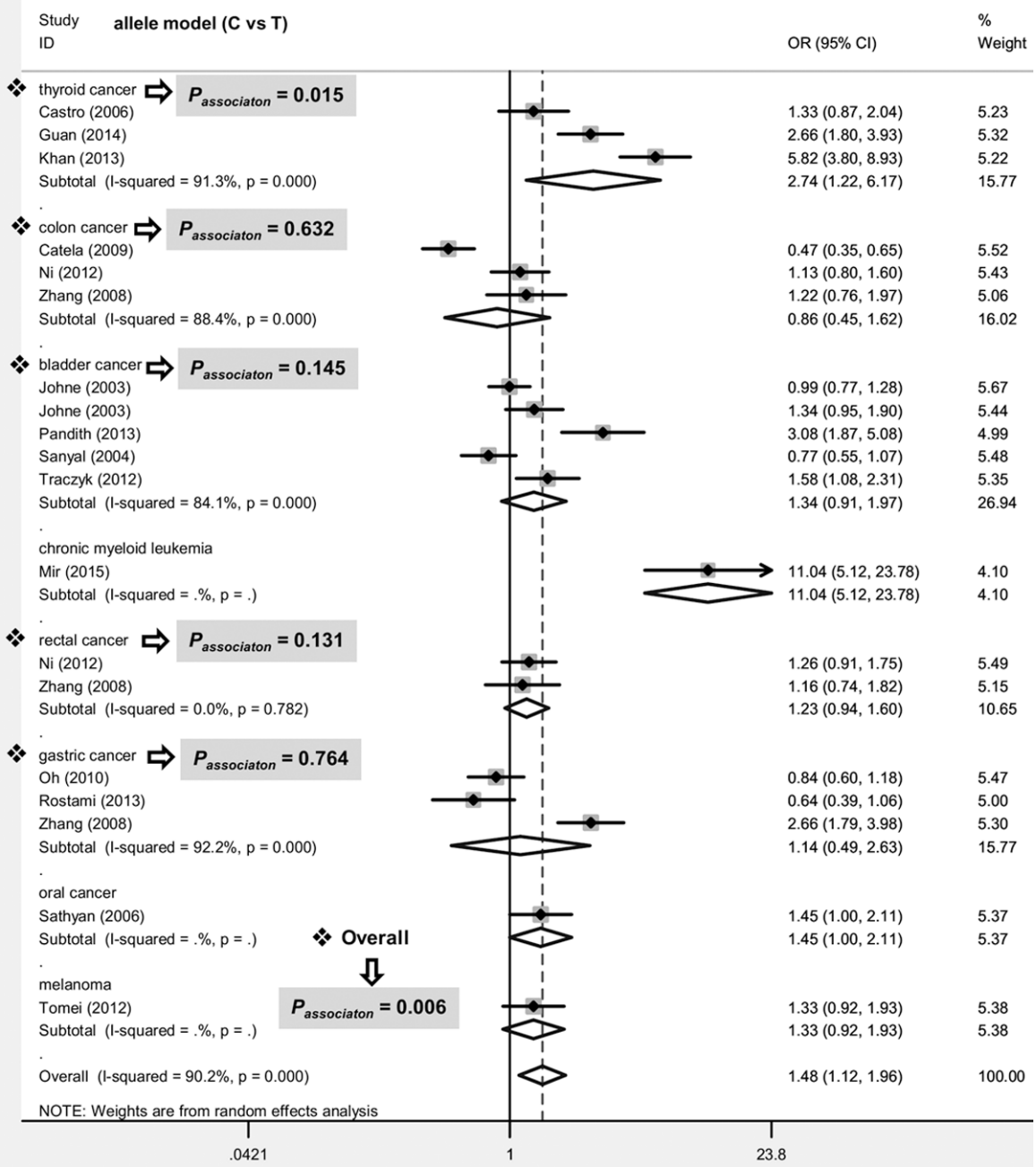

Figure 3. Stratification analysis by disease type for the association between *HRAS* rs12628 polymorphism and cancer risks under C vs T model.

$P_{association}$=0.002), TC+CC vs TT model (OR=2.05, 95% CI=1.30-3.23, $P_{association}$=0.002), carrier C vs carrier T model (OR=1.66, 95% CI=1.20-2.30, $P_{association}$=0.002). And a similar association was obtained in both thyroid cancer and P_{HWE}>0.05 group under allele, heterozygote, dominant and carrier models (**Figure 3** and **Table 3**, all OR>1, *P*<0.05). However, no significant conference was obtained in colon cancer, bladder cancer and gastric cancer groups under all models (all $P_{association}$>0.05). These data highlighted the positive association between TC genotype of *HRAS* rs12628 and the risks of thyroid cancer, particularly in the Asian population.

Publication bias and sensitivity analysis

As shown in **Figure 4** and **Table 2**, the presence of large publication bias was excluded for CC vs

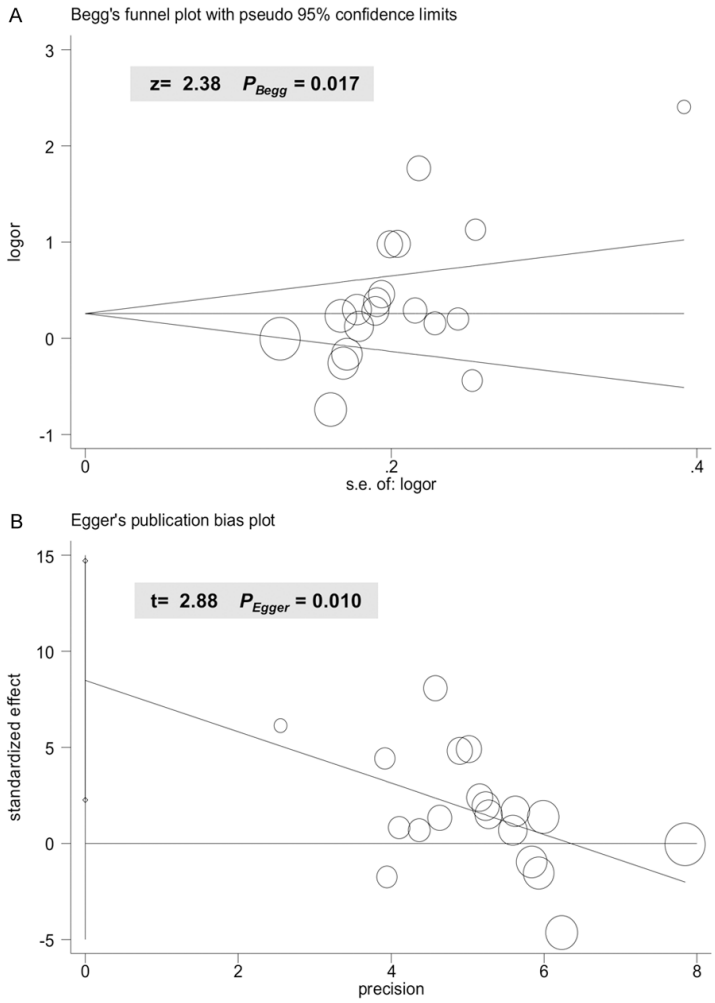

Figure 4. Publication bias analyses under C vs T model.

TT model (P_{Begg}=1.000, P_{Eegger}=0.762), CC vs TT+TC model (P_{Begg}=0.624, P_{Eegger}=0.537), but not C vs T model (P_{Begg}=0.017, P_{Eegger}=0.010), TC vs TT model (P_{Begg}=0.006, P_{Eegger}=0.010), TC+CC vs TT model (P_{Begg}=0.030, P_{Eegger}=0.008) and carrier C vs carrier T (P_{Begg}=0.025, P_{Eegger}=0.006). Moreover, we performed a sensitivity analysis and observed the similar results after the removal of studies one by one (**Figure 5**).

Discussion

Published conclusions on the effect of *HRAS* rs12628 on the risks of some cancer diseases were inconsistent. For instance, TT genotype of *HRAS* rs12628 was reported to be associated with an increased risk of bladder cancer in the Germanic patients [23], but a decreased risk of bladder cancer in patients of Sweden [10]. *HRAS* rs12628 may be linked to the susceptibility to colon cancer in the Croatian population [11], but not the Chinese patients [12]. The association between *HRAS* rs12628 and gastric cancer susceptibility was also found in the Chinese population [12], but not the Korean population [13].

To our knowledge, three relative meta-analyses were performed previously. In 2008, Zhang, Y. et al performed a meta-analysis of four case-control studies with 388 cases and 391 controls [4, 12, 23, 24], and found that *HRAS* rs12628 seems to be associated with the susceptibility to cancers, including bladder, thyroid and oral cancer [12]. In 2012, Traczyk, M. et al assessed the association between *HRAS* rs12628 and urinary bladder cancer in the polish patients, and conducted another meta-analysis of eight case-control studies [4, 5, 10, 12, 23, 24]. Their meta-analysis results showed that CC genotype of *HRAS* rs12628 is likely to have implications in the overall cancer risk [5]. In 2013, Pandith, A. A. et al evaluated the relationship between *HRAS* rs12628 and urinary bladder cancer in ethnic Kashmiri population, and also performed a meta-analysis with five case-control studies [4, 12, 14, 23, 24], which suggested that *HRAS* rs12628 may act as a kind of risk factor for cancer [14]. Here, we performed a new meta-analysis with 19 case-control studies [4, 5, 7, 8, 10-14, 19-24]. However, it was still hard to conduct the meta-analysis for each type of cancer respectively, due to the limited data. We have to first perform a meta-analysis to investigate the association between *HRAS* rs12628 and overall cancer risks, and then we performed the stratification analyses by the specific cancer type, under the allele, homozygote, heterozygote, dominant recessive and carrier models. We found that *HRAS* rs12628 might be a strong susceptibility factor for the overall cancer, which is in line with the previous conclusion of meta-analyses [5, 12, 14]. Our data further demonstrate that TC genotype of *HRAS* rs12628 seems to be linked to the over-

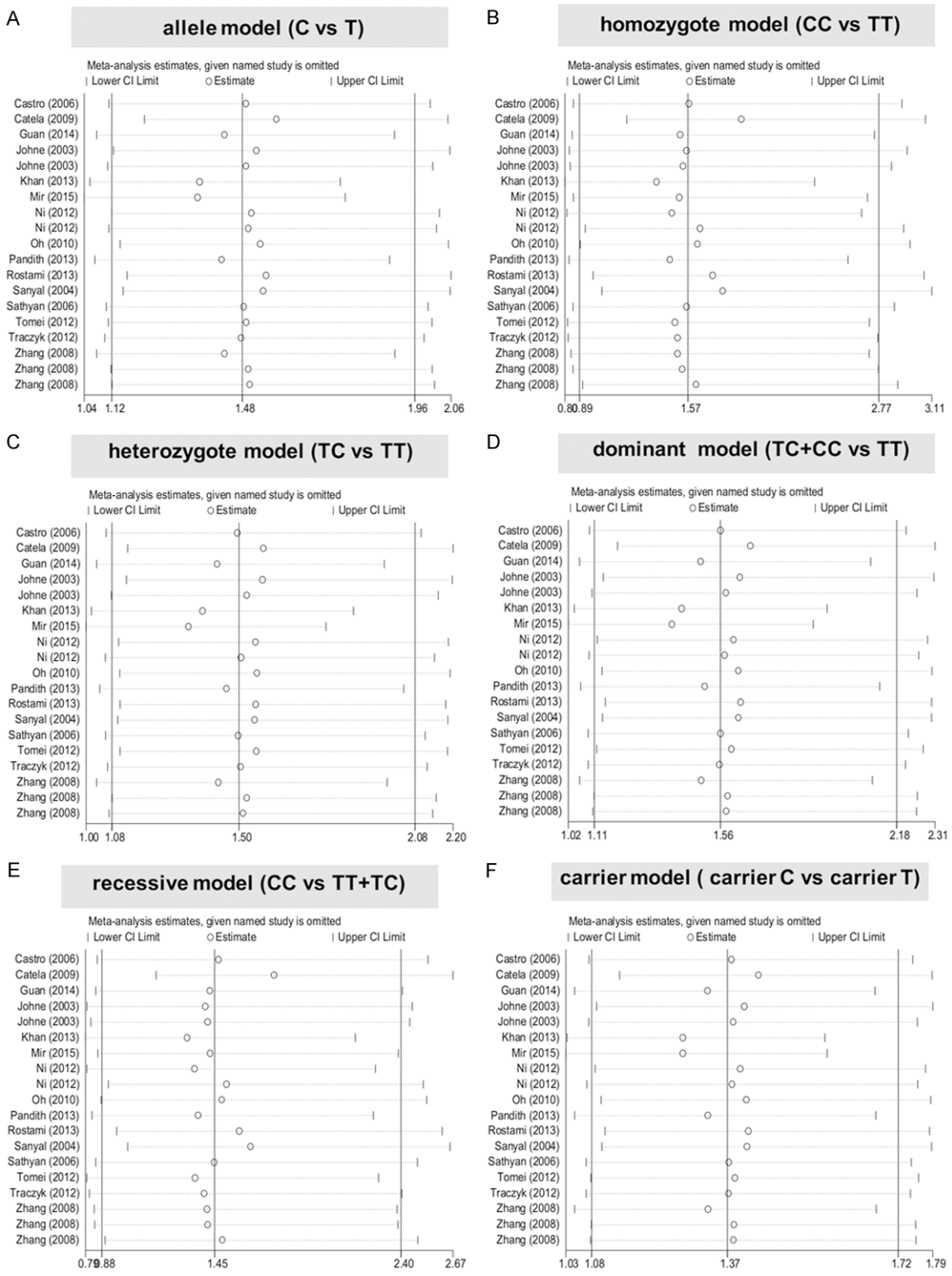

Figure 5. Sensitivity meta-analyses under all genetic models.

all cancer risks, which is different from the conclusion of Traczyk, M. et al [5]. Eleven new published case-control studies [5, 7, 8, 11, 13, 14, 19-22] might account for the difference.

Several genome-wide association studies (GWAS) on the susceptibility to the different cancers were reported. For instance, in 2009, the GWAS data of Gudmundsson J, et al suggested

that rs965513 and rs944289 SNPs might be associated with the susceptibility to thyroid cancer in the European population. And rs965513 and rs944289 were confirmed in the patients of papillary thyroid cancer in the Chinese population [25]. However, we did not obtain the confirmed data on the role of *HRAS* mutation in specific cancer risks. In our stratification analyses, *HRAS* rs12628 was found to be associated with the occurrence of thyroid cancer, but not bladder cancer and gastric cancer. However, we still cannot exclude the potential role of *HRAS* rs12628 in other non-thyroid cancer, due to the relatively weak statistical power for the specific cancer disease. Additionally, seven case-control studies were included in the Caucasian group, while twelve case-control studies were for the Asian group. We found that TC genotype of *HRAS* rs12628 was significantly associated with overall cancer risks in the Asian population, rather than the Caucasian population.

The potential molecular mechanism underlying the role of *HRAS* rs12628 in the overall cancer risks remains unknown. *HRAS* rs12628 may regulate the expression of *HRAS* mRNA and influence the normal function of RAS proteins. It was reported that *HRAS* rs12628 in exon one can be linked to the rs112587690 in intron one and is involved in the development of cutaneous melanoma in the North American population [7]. Additionally, the combination of the *HRAS* rs12628 and *L-myc* rs3134613 was reported to be associated with the colorectal cancer risks in the Chinese population [20]. It is possible that the linkage disequilibrium with other functional *HRAS* SNPs contributes to the role of *HRAS* rs12628 in the cancer risks, considering that *HRAS* rs12628 failed to influence the structure of p21 ras protein.

The limitations in the meta-analysis are noted. First, sample sizes in some enrolled studies are still very limited. For instance, only one case-control study was obtained for the association between *HRAS* rs12628 and some specific cancer diseases, such as chronic myeloid leukemia [21], oral cancer [24] and melanoma [7]. In addition, our conclusion may be influenced by the large between-studies heterogeneity and unpublished studies. More well-powered data and stratification analyses by more factors (e.g. racial differences, etiology, habits or gender), are strongly required.

Conclusion

Our updated meta-analysis demonstrated that TC genotype of *HRAS* rs12628 polymorphism may contribute to the incidence of cancer diseases, including thyroid cancer, in the Asian population.

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Disclosure of conflict of interest

None.

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