Original Article
Polymorphisms in the *intercellular adhesion molecule 1* gene and cancer risk: a meta-analysis

Weifeng Tang[1*], Yafeng Wang[2*], Yuanmei Chen[3*], Haiyong Gu[4], Shuchen Chen[1], Mingqiang Kang[1]

[1]Department of Thoracic Surgery, The Union Clinical Medical College of Fujian Medical University, Fuzhou, Fujian Province, China; [2]Department of Cardiology, The People's Hospital of Xishuangbanna Dai Autonomous Prefecture, Jinghong, Yunnan Province, China; [3]Department of Thoracic Surgery, Fujian Provincial Cancer Hospital, Fuzhou, Fujian Province, China; [4]Department of Cardiothoracic Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu Province, China. *Equal contributors.

Abstract: *Objectives*: The correlation between *intercellular adhesion molecule 1* (*ICAM-1*) common polymorphisms (rs5498 A>G and rs3093030 C>T) and cancer susceptibility has been explored in various ethnic groups and different cancer types; however, these investigations have yielded contradictory results. To address the relationship more precisely, we performed this meta-analysis. *Design and methods*: EmBase, PubMed and China National Knowledge Infrastructure (CNKI) databases were searched by two authors independently for eligible publications before April 8, 2015. Random-effects or fixed-effects model was harnessed to calculate the pooled odds ratios (ORs) and 95% confidence intervals (CIs) when appropriate. *Results*: The result suggested that the *ICAM-1* rs5498 A>G polymorphism is not associated with cancer susceptibility in overall cancer. In a stratified analysis by ethnicity, a significant increased cancer risk was identified among Asians, but the inverse association was found among Caucasians. In a stratified analysis by cancer type, *ICAM-1* rs5498 A>G polymorphism was associated with a significantly increased risk of oral cancer, but with protection from colorectal cancer and melanoma. *ICAM-1* rs3093030 C>T polymorphism is not correlated with cancer susceptibility. *Conclusions*: In summary, this meta-analysis highlights that the *ICAM-1* rs5498 A>G polymorphism probably contributes to decreased susceptibility to cancer, especially in Caucasians, in melanoma and colorectal cancer subgroup, but it may be a risk factor for oral cancer and Asians.

Keywords: Cancer, polymorphism, *ICAM-1*, cancer susceptibility, meta-analysis

Introduction

Based on full GLOBOCAN database, an estimated 14.1 million new cancer patients and 8.2 million cancer-associated deaths occurred in 2012 worldwide [1]. The global incidence and mortality rate of cancer boost largely because of the growth and aging of the world population, as well as a promoting prevalence of established cancer-related lifestyles, such as heavy drinking, smoking, physical inactivity, changing reproductive patterns and 'westernized' diets [2]. However, the mechanism and etiology of carcinogenesis are very complicated and remain largely unclear, although a number of investigations have focused on the relationship of the chronic inflammation and immune system with cancer [3-6].

The *intercellular adhesion molecule 1* (*ICAM-1*) gene (cluster of differentiation 54 [CD54]) is located on chromosome 19q13.3. ICAM-1, a 76-115 KDa surface glycoprotein, is a cell adhesion molecule which is a member of the immunoglobulin (Ig) superfamily. It has three important components which involve five extracellular IgG-like binding domains, a transmembrane region and a cytoplasmic tail that correlates with a few cytoskeletal linker proteins [7-9]. ICAM-1 is presented on the surface of a few cell types, such as endothelial cells, epithelial cells, fibroblasts, leukocytes and keratinocytes [10]. ICAM-1 acts as a moderator in cell-extracellular matrix and cell-cell interactions, and then mediates the invasion of activated immune cells into damaged organ or tissue during immune responses and the inflammatory. Previous studies have highlighted that *ICAM-1* single nucleotide polymorphisms (SNPs) are associated with the risk of multiple human diseases, such as asthma [11], falciparum malaria [12], coronary
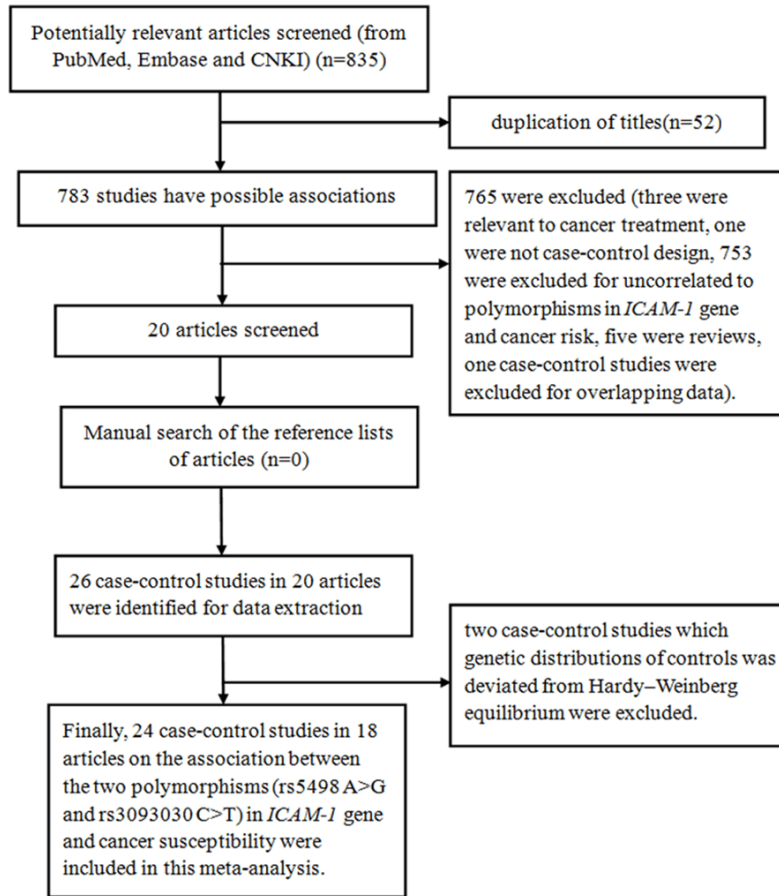
Figure 1. Flow diagram of articles selection process for meta-analysis.

gested that these two SNPs were involved in the aetiology of different cancer types, including urothelial cell carcinoma [20], oral cancer [21, 22], colorectal cancer [23, 24], ovarian cancer [25], breast cancer [26], gastric cancer [27] and so on. However, all available results from those studies remain inconsistent rather than conclusive. Considering the vital role of *ICAM-1* gene in carcinogenesis, we conducted a meta-analysis on all included publications to assess the cancer susceptibility associated with these two SNPs. To the best of our knowledge, the present study is the most comprehensive analysis performed to date with respect to the correlations between polymorphisms in the *ICAM-1* gene and cancer risk.

Materials and methods

Search strategy

PubMed, EMBASE and China National Knowledge Infrastructure (CNKI) databases (the last online literature search was updated in April 8, 2015) were searched simultaneously using the following terms: 'Intercellular adhesion molecule-1' or 'ICAM-1', 'SNP' or 'polymorphism' or 'variant', and 'cancer' or 'malignance' or 'carcinoma'. The literature search was limited to English or Chinese articles. Additional publications were manually searched based on the bibliographies provided in reviews and the retrieved studies.

Inclusion and exclusion criteria

The major selection criteria were: (1) evaluating the correlation of *ICAM-1* rs5498 A>G and rs3093030 C>T polymorphisms with cancer susceptibility, (2) case-control study design, (3) containing data on genotype and allele frequency. Accordingly, reports without complete data, not case-control study design, reviews, duplicated data and comments were excluded.

artery disease, Behçets disease [13] and diabetic nephropathy among type 1 diabetes [14] et al.

Some prior studies indicated that ICAM-1 is overexpressed in a number of malignancies such as thyroid carcinoma [15], gastric cancer [16], renal cell carcinoma [17] and oral cancer [18] and may contribute to carcinogenesis, tumor progression and metastasis. Accumulating evidence demonstrates *ICAM-1* SNPs play important roles in tumorigenesis and progression, specifically by facilitating malignance invasion and metastasis [18, 19]. *ICAM-1* gene is polymorphic, and a number of variants have been established, such as rs5498 A>G (K469E), rs3093030 C>T, rs5030382 A>G, rs1799969 G>A, rs5490 A>C, rs5496 A>G, rs281432 C>G and rs281428 C>T polymorphisms etc. Among them, the *ICAM-1* rs5498 A>G and rs3093030 C>T SNPs were the most widely explored for their implication in cancer susceptibility. Several previous studies sug-

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

Study	Year	Country	Ethnicity	Cancer type	Genotype method	No.of cases/ controls	Polymorphism
Lu et al.	2015	China	Asians	ovarian cancer	PCR-RFLP	687/687	rs5498
Wang et al.	2014	China	Asians	urothelial cell carcinoma	TaqMan	279/279	rs5498, rs3093030
Yilmaz et al.	2013	Turkey	Caucasians	brain cancer	PCR-RFLP	92/92	rs5498
Lin et al.	2013	China	Asians	oral cancer	TaqMan	595/561	rs5498, rs3093030
Cai et al.	2013	China	Asians	ovarian cancer	MassARRAY system	480/520	rs5498, rs3093030
Thanopoulou et al.	2012	Greece	Caucasians	Lung cancer	PCR-RFLP	203/175	rs5498
Tian et al.	2012	China	Asians	gastric cancer	PCR-RFLP	332/380	rs5498
Dean Hosgood III et al.	2011	USA	Caucasians	lymphoma	Illumina SNP Genotyping	1946/1808	rs3093030
Han et al.	2010	Korea	Asians	breast cancer	Illumina SNP Genotyping	117/164	rs3093030
Wang et al.	2009	China	Asians	colorectal cancer	PCR-SSP	87/102	rs5498
Bai et al.	2009	China	Asians	oral cancer	PCR-RFLP	112/98	rs5498
Arandi et al.	2008	Iran	Caucasians	breast cancer	PCR-SSP	264/200	rs5498
Theodoropoulos et al.	2006	Greece	Caucasians	colorectal cancer	PCR-RFLP	222/200	rs5498
Chen et al.	2006	USA	Africans	prostate cancer	PCR-RFLP	286/391	rs5498, rs3093030
Cox et al.	2006	USA	mixed	breast cancer	TaqMan	1264/1747	rs5498
Vinceti et al.	2006	Italy	Caucasians	melanoma	PCR-RFLP	59/59	rs5498
Howell et al.	2005	UK	Caucasians	melanoma	TaqMan	164/264	rs5498
Kammerer et al.	2004	German	Caucasians	breast cancer	MassEXTEND	242/265	rs5498
Kammerer et al.	2004	German	Caucasians	breast cancer	MassEXTEND	178/142	rs5498
Kammerer et al.	2004	Australia	Caucasians	breast cancer	MassEXTEND	167/170	rs5498

PCR-SSP: polymerase chain reaction-sequence specific primer; PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism.

Table 2. Distribution of *ICAM-1* polymorphisms genotype and allele

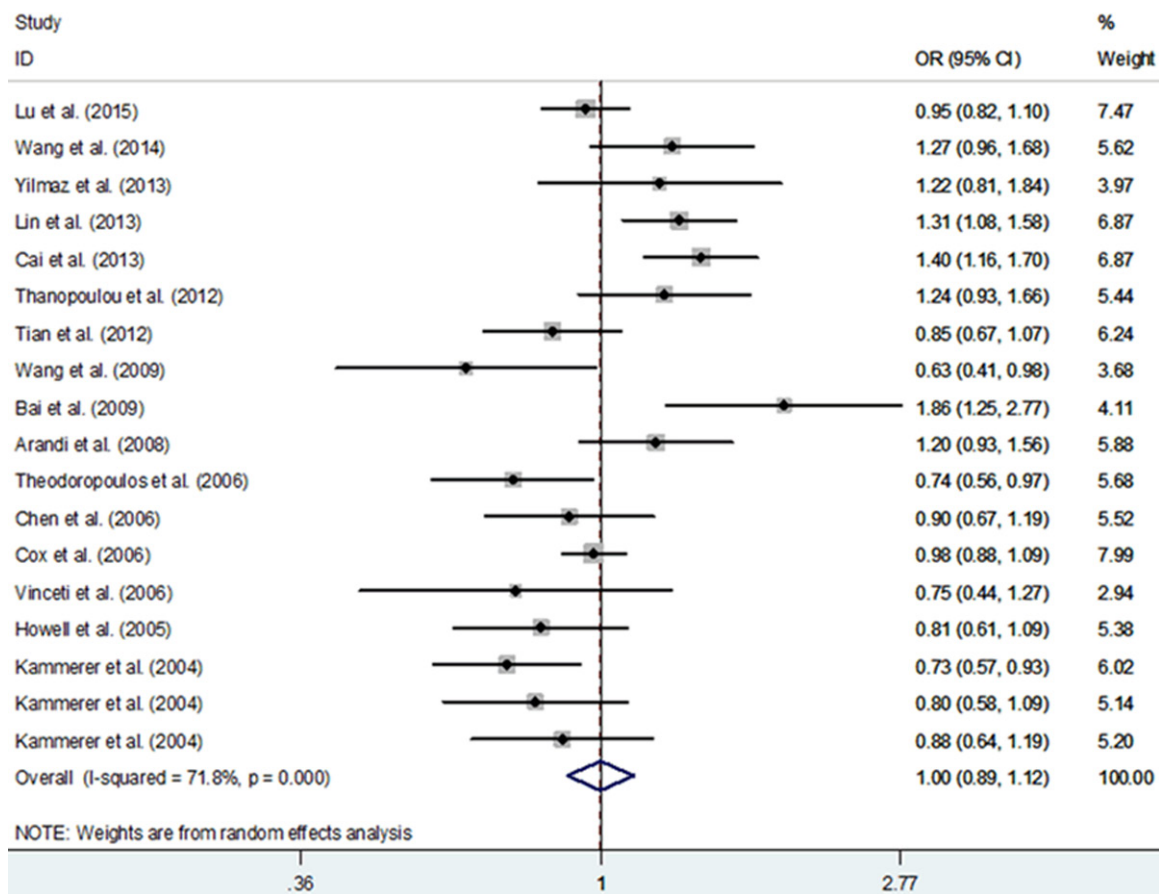| Polymorphisms	Study	Year	Case genotype			Control genotype			Case allele		Control allele		HWE
ICAM-1 rs5498 A>G			AA	AG	GG	AA	AG	GG	A	G	A	G	
	Lu et al.	2015	209	322	156	180	362	145	740	634	722	652	0.137937
	Wang et al.	2014	151	114	14	174	92	13	416	142	440	118	0.850971
	Yilmaz et al.	2013	25	49	18	29	50	13	99	85	108	76	0.246364
	Lin et al.	2013	329	220	46	350	182	29	878	312	882	240	0.402868
	Cai et al.	2013	144	201	60	237	228	50	489	321	702	328	0.651420
	Thanopoulou et al.	2012	70	87	46	66	82	27	227	179	214	136	0.854302
	Tian et al.	2012	190	116	26	187	169	24	496	168	543	217	0.079239
	Wang et al.	2009	50	28	9	43	44	15	128	46	130	74	0.498977
	Bai et al.	2009	38	43	31	44	45	9	119	105	133	63	0.602349
	Arandi et al.	2008	53	144	67	52	104	44	250	278	208	192	0.555690
	Theodoropoulos et al.	2006	56	96	70	35	88	77	208	236	158	242	0.261476
	Chen et al.	2006	197	83	6	265	110	16	477	95	640	142	0.290310
	Cox et al.	2006	388	585	196	543	798	294	1361	977	1884	1386	0.978208
	Vinceti et al.	2006	22	27	8	14	35	8	71	43	63	51	0.067884
	Howell et al.	2005	58	63	30	67	109	48	179	123	243	205	0.767737
	Kammerer et al.	2004	94	109	39	77	130	58	297	187	284	246	0.822276
	Kammerer et al.	2004	60	84	34	40	67	35	204	152	147	137	0.510933
	Kammerer et al.	2004	67	72	28	62	75	33	206	128	199	141	0.234396
ICAM-1 rs3093030 C>T			CC	CT	TT	CC	CT	TT	T	C	T	C	
	Wang et al.	2014	176	92	11	178	93	8	114	444	109	449	0.313530
	Lin et al.	2013	384	183	28	365	179	17	239	951	213	909	0.377044
	Cai et al.	2013	183	172	51	271	207	36	274	538	279	749	0.678157
	Dean Hosgood III et al.	2011	524	695	236	607	878	305	1167	1743	1488	2092	0.680035
	Han et al.	2010	59	54	4	75	65	24	62	172	113	215	0.116842
	Chen et al.	2006	241	44	1	315	72	4	46	526	80	702	0.959563

HWE: Hardy-Weinberg equilibrium.

Figure 2. Meta-analysis with a random-effects model for the association between *ICAM-1* rs5498 A>G polymorphism and cancer risk (G vs. A compare genetic model).

Data extraction

For each recruited study, the following original data were extracted by two independent authors (W. Tang and Y. Wang): (1) the surname of first author and published year, (2) country of origin and ethnicity, (3) cancer type, (4) case/control number, (5) data of allele and genotype frequency, (6) evidence of Hardy-Weinberg equilibrium (HWE) in controls and (7) genotyping method. When come to conflicting evaluations, disputes were settled based on the discussion among all reviewers.

Statistical analysis

The crude odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated to assess the strength of correlation between *ICAM-1* polymorphisms and cancer susceptibility. A $P<0.05$ (two-tailed) was accepted as statistically significant. A Chi-square-based I^2 test

was used to detect heterogeneity [28] and an $I^2<25\%$ indicates low heterogeneity, $25\%≤I^2≤50\%$ indicates moderate heterogeneity, and $I^2>50\%$ indicates large heterogeneity [29]. When $I^2>50\%$ or $P<0.10$ (two-sided), the random-effects model (the DerSimonian-Laird method) was utilized to pool the data [30], otherwise the fixed-effects model (the Mantel-Haenszel method) was used [31]. Sub-group analyses were harnessed according to cancer type and ethnicity to identify the specific effects of heterogeneity. Galbraith radial plot was used to detect the major source of heterogeneity [32]. Publication bias was assessed by Begg's funnel plot and Egger's test [33]. One-way sensitivity analysis was also used to confirm the stability of our findings. In addition, for publication bias test, a $P<0.1$ (two-sided) was accepted as statistical significance. All statistical analyses were performed using STATA version 12.0 software (Stata Corporation, College Station, TX).
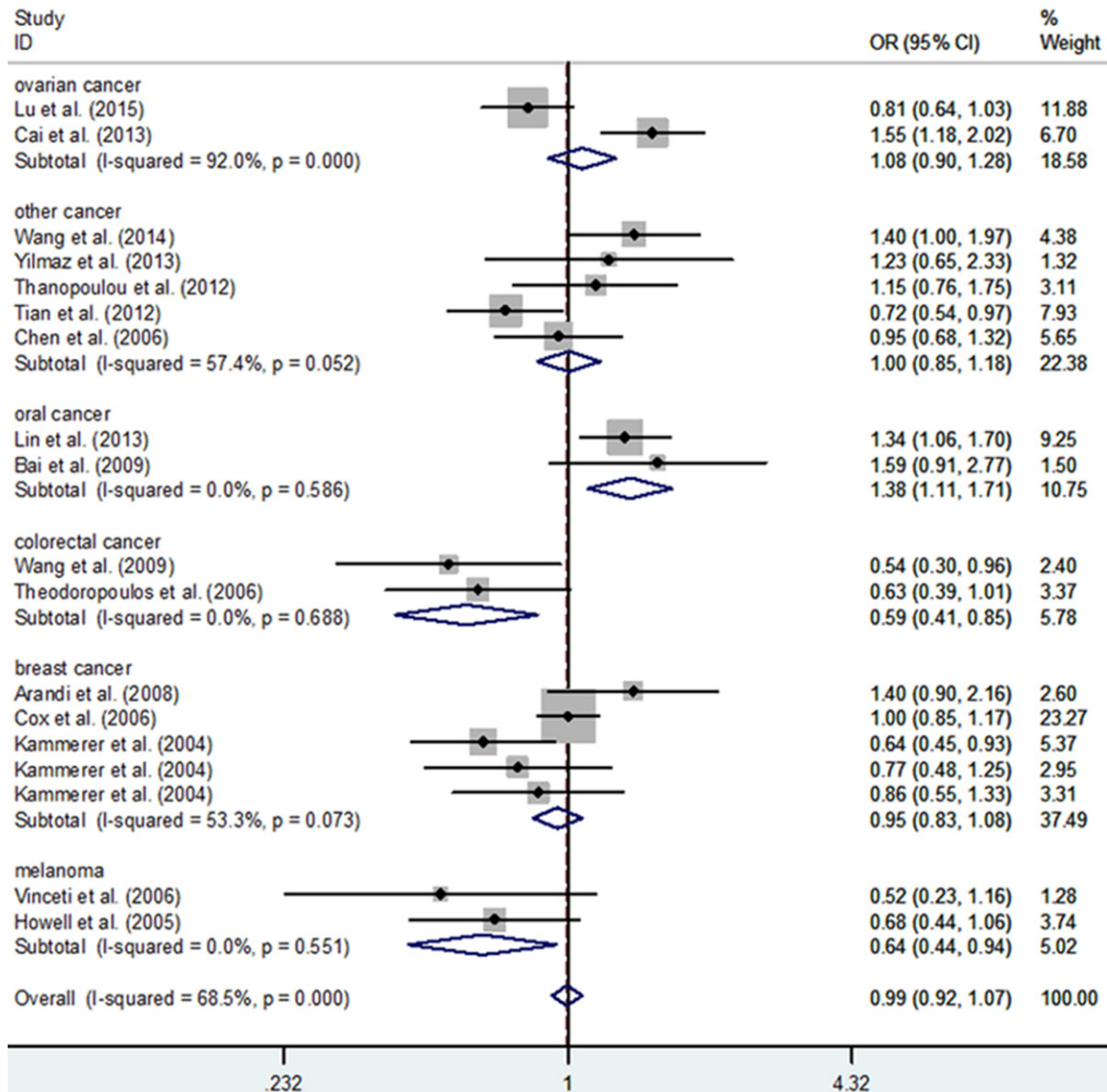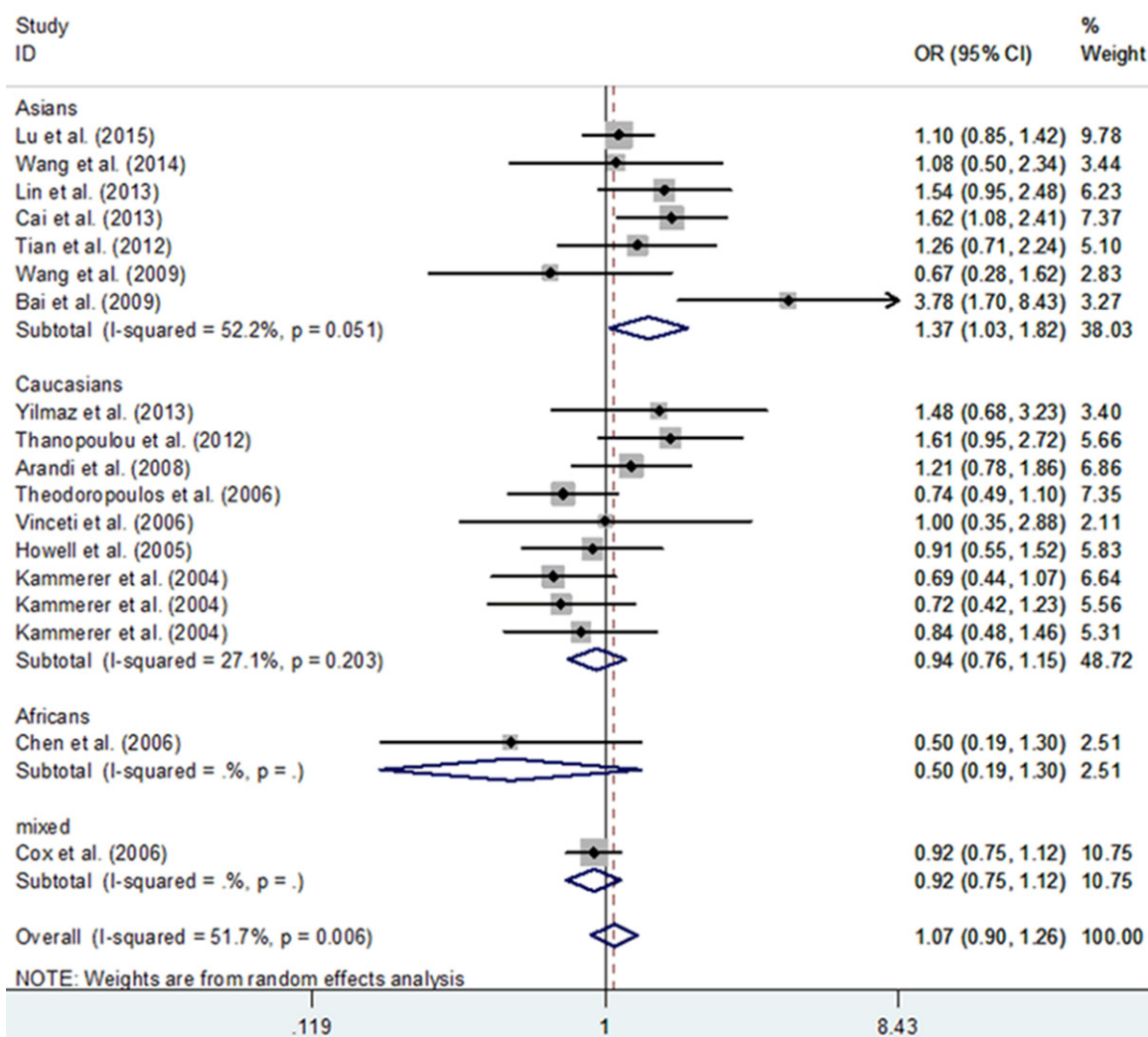
Figure 3. Meta-analysis with a random-effects model for the association between *ICAM-1* rs5498 A>G polymorphism and cancer risk in different cancer type (GG+AG vs. AA compare genetic model).

Results

Characteristics

In total, 835 potentially relevant publications were retrieved. **Figure 1** showed the detailed selecting process. Finally, a total of twenty-four case-control studies from eighteen articles were identified. Overall, there were sixteen publications (including eighteen case-control studies) on the *ICAM-1* rs5498 A>G polymorphism and six articles (including six case-control studies) on the rs3093030 C>T polymorphism. Of these articles, four investigated breast cancer, two investigated ovarian cancer, two investigated oral cancer, two investigated colorectal can-

cer and two investigated melanoma. Others investigated urothelial cell carcinoma, lung cancer, brain cancer, gastric cancer, lymphoma and prostate cancer. Among twenty case-control studies, eight were from Asia, ten were from Caucasians, one was mixed populations and one was from American Africans. The characteristics of the eligible studies and the distribution of *ICAM-1* variants as well as alleles are listed in **Tables 1**, **2**, respectively.

Quantitative synthesis

ICAM-1 rs5498 A>G polymorphism: There were sixteen papers met the inclusion criteria with

Figure 4. Meta-analysis with a random-effects model for the association between *ICAM-1* rs5498 A>G polymorphism and cancer risk in different populations (GG vs. AG+AA compare genetic model).

5528 cases and 6173 controls, one article (Kammerer et al.) [26] provided three subgroups, thus, we treated them separately. In total, there were eighteen case-control studies included in the present meta-analysis. Nine case-control studies were from Caucasians, seven were from Asia, one was from American Africans and one was from mixed populations. Overall, there was null correlation of *ICAM-1* rs5498 A>G polymorphism with overall cancer risk (**Figure 2**). In a subgroup analysis by cancer type, *ICAM-1* rs5498 A>G polymorphism was associated with a significantly increased risk of oral cancer (OR, 1.49; 95% CI, 1.07-2.09; *P* = 0.020 for G vs. A; OR, 2.41; 95% CI, 1.05-5.52; *P* = 0.038 for GG vs. AA; OR, 1.38; 95% CI, 1.11-1.71; *P* = 0.004 for GG+AG vs. AA and OR, 1.26; 95% CI, 1.00-1.58; *P* = 0.049 for AG vs. AA), but with protection from colorectal cancer (OR, 0.71; 95% CI, 0.56-0.89; *P* = 0.004 for G vs. A; OR, 0.55; 95% CI, 0.35-0.88; *P* = 0.012 for GG vs. AA; OR, 0.59; 95% CI, 0.41-0.85; *P* = 0.005 for GG+AG vs. AA and OR, 0.62; 95% CI, 0.42-0.93; *P* = 0.020 for AG vs. AA) and melanoma (OR, 0.64; 95% CI, 0.44-0.94; *P* = 0.023 for GG+AG vs. AA and OR, 0.62; 95% CI, 0.41-0.93; *P* = 0.022 for AG vs. AA) (**Figure 3**). In a subgroup analysis by ethnicity, a significant increased cancer risk was identified among Asians (OR, 1.37; 95% CI, 1.03-1.82; *P* = 0.032 for GG vs. AG+AA) but the inverse association was found among Caucasians (OR, 0.84; 95% CI, 0.72-0.99; *P* = 0.043 for GA vs. AA) (**Figure 4**). Other comparison results are listed in **Table 3**.

ICAM-1 rs3093030 C>T polymorphism: A total of 3138 cases and 3699 controls from six

Table 3. Meta-analysis of the *ICAM-1* rs5498 A>G polymorphism and cancer risk

	No. of study	G vs. A			GG vs. AA			GG+AG vs. AA			GG vs. AG+AA			AG vs. AA		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95%CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95%CI)	*P*	*P* (Q-test)
Total	18	1.00 (0.89-1.12)	0.974	<0.001	1.02 (0.82-1.27)	0.542	<0.001	0.96 (0.82-1.11)	0.564	<0.001	1.07 (0.90-1.26)	0.457	0.006	0.94 (0.82-1.08)	0.401	0.001
Ethnicity																
Asians	7	1.13 (0.92-1.39)	0.253	<0.001	1.36 (0.92-2.00)	0.123	0.002	1.07 (0.81-1.42)	0.631	<0.001	1.37 (1.03-1.82)	0.032	0.051	1.00 (0.76-1.32)	0.997	<0.001
Caucasians	9	0.91 (0.78-1.06)	0.225	0.023	0.86 (0.63-1.17)	0.355	0.029	0.84 (0.68-1.04)	0.117	0.069	0.93 (0.78-1.10)	0.404	0.203	0.84 (0.72-0.99)	0.043	0.280
Cancer type																
Ovarian cancer	2	1.15 (0.78-1.69)	0.479	0.002	1.33 (0.63-2.79)	0.449	0.005	1.12 (0.59-2.01)	0.732	<0.001	1.23 (0.99-1.52)	0.061	0.110	1.05 (0.56-1.96)	0.877	0.001
Oral cancer	2	1.40 (1.18-1.66)	<0.001	0.116	2.41 (1.05-5.52)	0.038	0.088	1.38 (1.11-1.71)	0.004	0.586	2.27 (0.95-5.46)	0.066	0.058	1.26 (1.00-1.58)	0.049	0.651
Colorectal cancer	2	0.71 (0.56-0.89)	0.004	0.546	0.55 (0.35-0.88)	0.012	0.859	0.59 (0.41-0.85)	0.005	0.688	0.72 (0.50-1.04)	0.082	0.848	0.62 (0.42-0.93)	0.020	0594
Breast cancer	5	0.92 (0.78-1.07)	0.270	0.056	0.85 (0.63-1.14)	0.278	0.080	0.91 (0.72-1.15)	0.426	0.073	0.89 (0.77-1.04)	0.153	0.419	0.98 (0.85-1.12)	0.734	0.208
Melanoma	2	0.80 (0.62-1.03)	0.087	0.783	0.71 (0.42-1.18)	0.186	0.851	0.64 (0.44-0.94)	0.023	0.551	0.93 (0.58-1.47)	0.742	0.874	0.62 (0.41-0.93)	0.022	0.530
Other cancer	5	1.06 (0.88-1.27)	0.533	0.094	1.19 (0.87-1.62)	0.288	0.320	1.04 (0.80-1.34)	0.791	0.052	1.23 (0.92-1.66)	0.166	0.317	1.00 (0.76-1.33)	0.980	0.038

Table 4. Meta-analysis of the *ICAM-1* rs3093030 C>T polymorphism and cancer risk

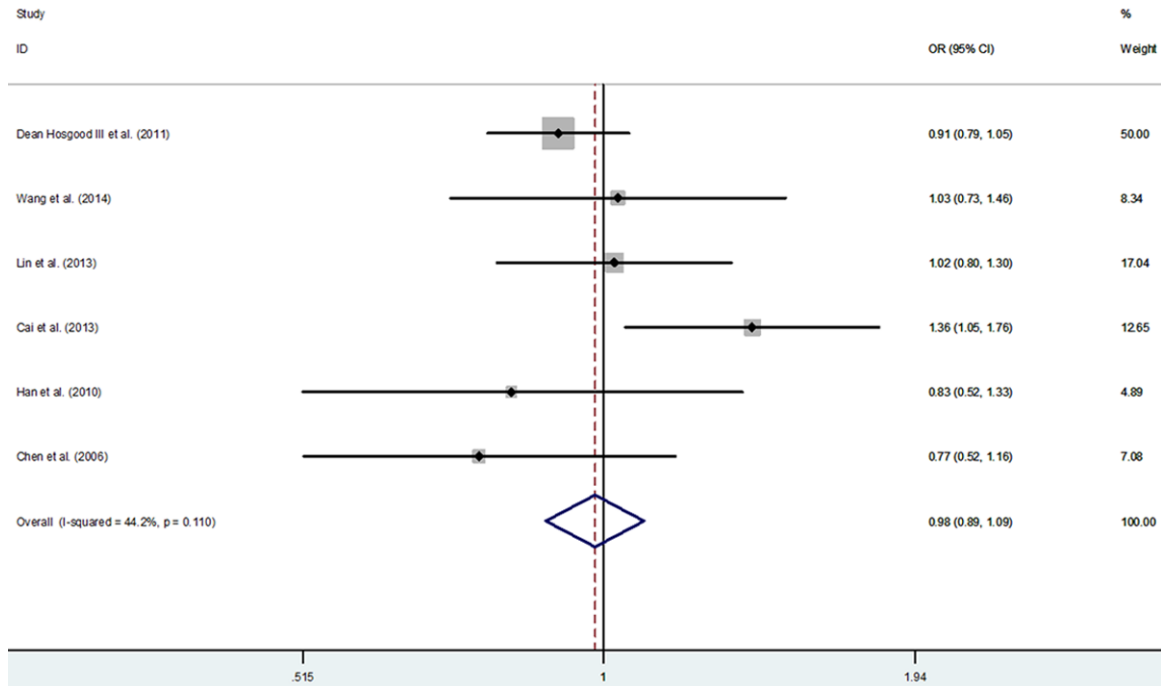|	No. of study	T vs. C			TT vs. CC			TT+CT vs. CC			TT vs. CT+CC			CT vs. CC		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	18	0.99 (0.84-1.18)	0.932	0.004	1.02 (0.60-1.76)	0.930	0.001	0.98 (0.89-1.09)	0.745	0.110	1.03 (0.62-1.70)	0.906	0.001	0.97 (0.87-1.08)	0.600	0.497

Figure 5. Meta-analysis with a fixed-effects model for the association between *ICAM-1* rs3093030 C>T polymorphism and cancer risk (TT+CT vs. CC compare genetic model).
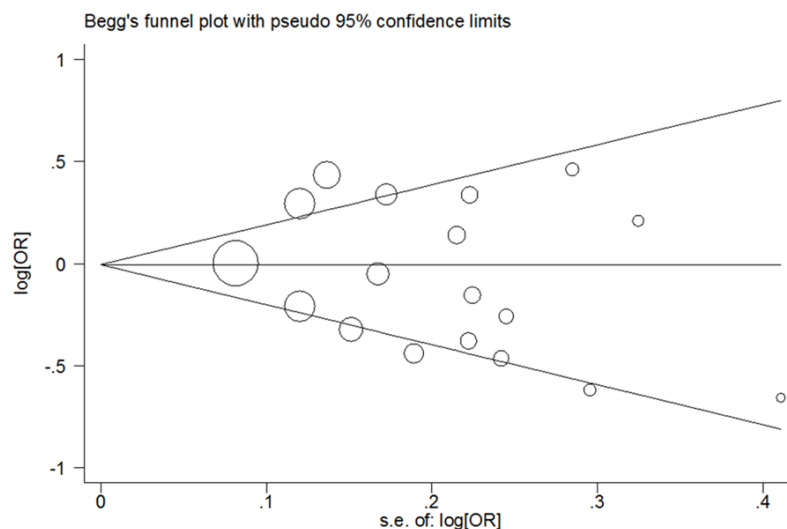

Figure 6. Begg's funnel plot of meta-analysis of the association between the *ICAM-1* rs5498 A>G polymorphism and the risk of cancer (GG+AG vs. AA compare genetic model).

3093030 C>T polymorphism and the overall cancer susceptibility (**Figure 5** and **Table 4**). For limited data, further subgroup analyses were not carried out.

Tests for publication bias, sensitivity analyses, and heterogeneity

No significant publication bias was found with either the Begg's funnel plot or the Egger's test (*ICAM-1* rs5498 A>G: G vs. A: Begg's test *P* = 0.449, Egger's test *P* = 0.772; GG vs. AA: Begg's test *P* = 0.649, Egger's test *P* = 0.886; GG+AG vs. AA: Begg's test *P* = 0.405, Egger's test *P* = 0.339; GG vs. AG+AA: Begg's test *P* = 0.850, Egger's test *P* = 0.555, AG vs. AA: Begg's test *P* = 0.910, Egger's test *P* = 0.204; *ICAM-1* rs3093030 C>T: T vs. C: Begg's test *P* = 0.452, Egger's test *P* = 0.917; TT vs. CC: Begg's test *P* = 0.452, Egger's test *P* = 0.971; TT+CT vs. CC: Begg's test *P* = 1.000, Egger's test *P* = 0.933; TT vs. CT+CC: Begg's test *P* = 0.452, Egger's test *P* =

case-control studies were included in this pooled analysis on the association between the *ICAM-1* rs3093030 C>T polymorphism and cancer susceptibility. Four case-control studies were from Asians, one was from Caucasians, and one was from American Africans. The present findings did not show any statistical evidence of a correlation between the *ICAM-1* rs-
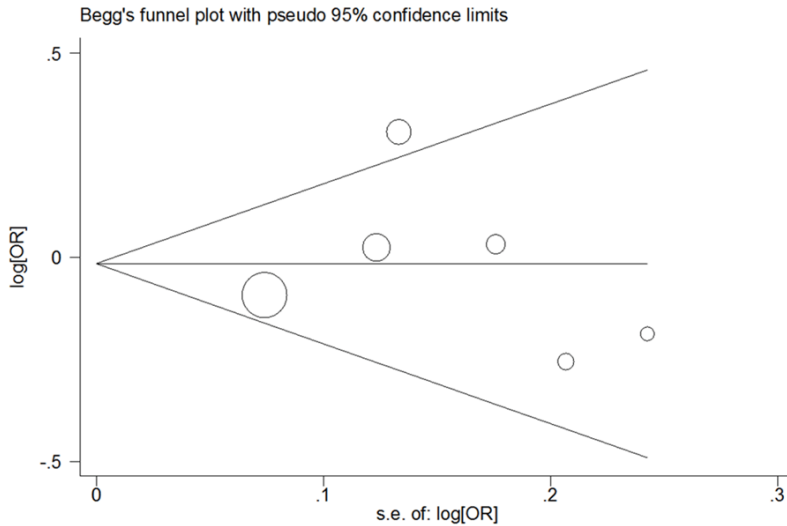
Figure 7. Begg's funnel plot of meta-analysis of the association between the*I-CAM-1* rs3093030 C>T polymorphism and the risk of cancer (TT+CT vs. CC compare genetic model).
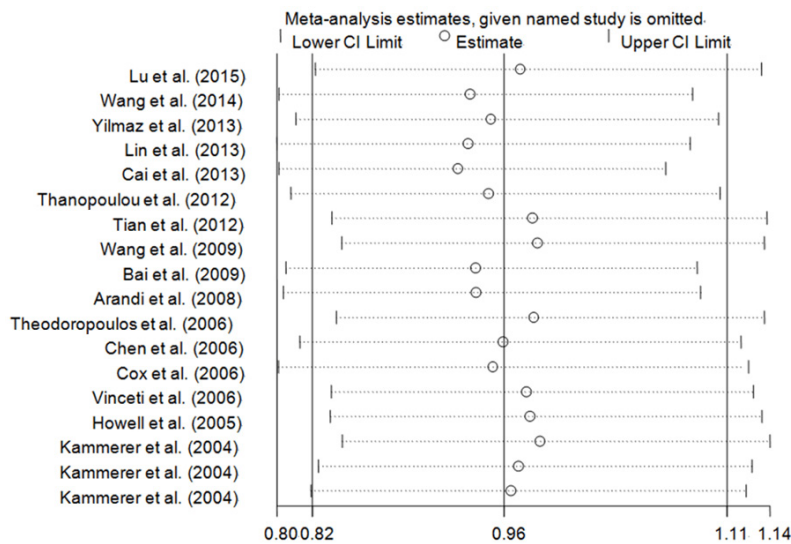

Figure 8. Sensitivity analysis of the influence of GG+AG vs. AA compare genetic model in overall cancer meta-analysis (random-effects estimates for *ICAM-1* rs5498 A>G polymorphism).

0.922; CT vs. CC: Begg's test $P = 0.452$, Egger's test $P = 0.649$) (**Figures 6** and **7**).

We carried out a sensitivity analysis to evaluate the influence of an individual case-control study on the pooled OR by eliding one study in turn. The results highlighted that our findings were relatively stable (**Figures 8** and **9**) (data not shown).

As shown in **Table 3**, heterogeneity was significant in the present study. Thus, we evaluated the sources of heterogeneity by the origin of cancer cells and ethnicity (**Table 3**). The results demonstrated that Asian populations, breast cancer and ovarian cancer subgroup may contribute to the major sources of heterogeneity. Galbraith radial plot was harnessed to analyze the heterogeneity in the allele genetic model. The results showed six outliers [21-26] for *ICAM-1* rs5498 A>G and one outlier [25] for *ICAM-1* rs3093030 C>T, respectively, may contribute to the considerable source of heterogeneity (**Figures 10** and **11**).

Discussion

ICAM-1 is expressed in a number of malignance cells [15-17]. During inflammation process, soluble ICAM-1 (sICAM-1) is shed by several cells which is activated by cytokines and then produce large amounts of membrane ICAM-1 [34]. The level of serum sICAM-1 is very low or cannot be detected in healthy subjects; however, it is elevated with inflammatory diseases and malignances [34-36]. Several prior studies also indicated that the sICAM-1 was a cancer biomarker which was associated with diagnosis, grade, clinical stage and metastasis [37-41].

Recently, a number of case-control studies have focused on the correlation of polymorphisms in *ICAM-1* gene with cancer risk. The most prevalent *ICAM-1* gene mutation, rs5498 A>G polymorphism, has been extensively studied. In 2009, Wang *et al* reported that an A→G mutation in rs5498 polymorphism was associ-

Meta-analysis estimates, given named study is omitted

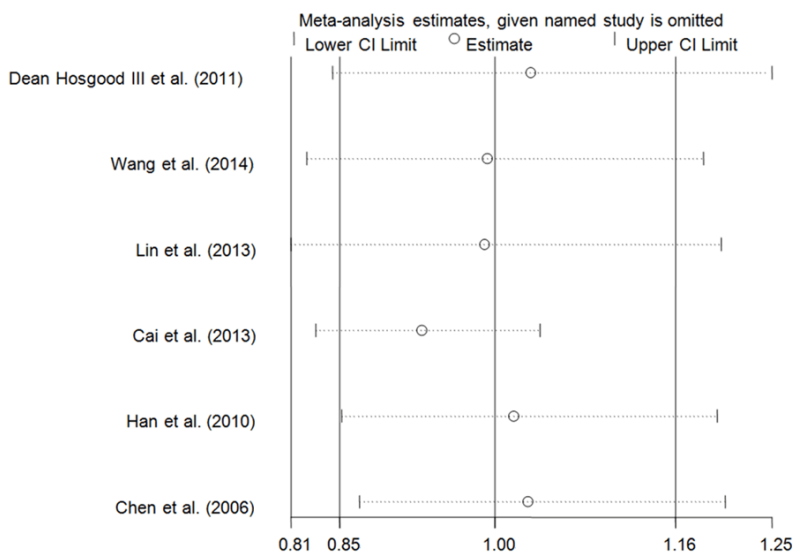| Lower CI Limit | ○ Estimate | | Upper CI Limit |

Figure 9. Sensitivity analysis of the influence of TT+CT vs. CC compare genetic model in overall cancer meta-analysis (random-effects estimates for *ICAM-1* rs3093030 C>T polymorphism).
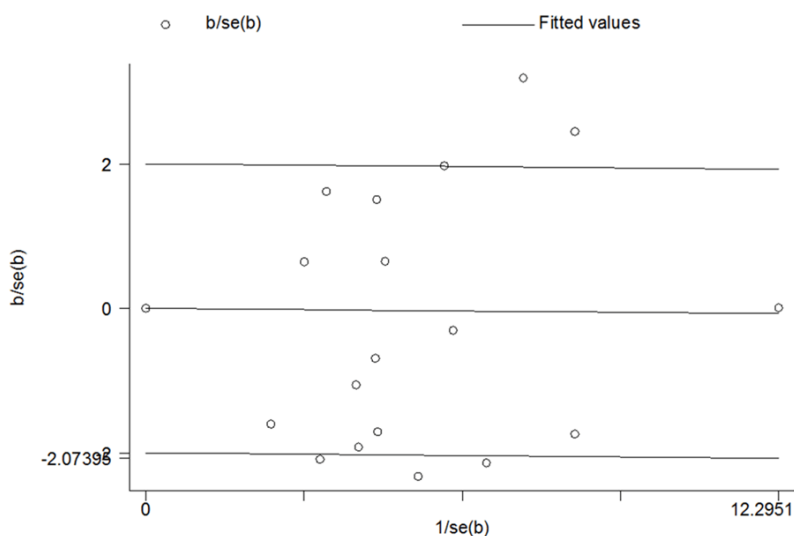

Figure 10. Galbraith radial plot of meta-analysis (GG+AG vs. AA compare genetic model for *ICAM-1* rs5498 A>G polymorphism).

ancy findings may be partly addressed by the complex etiological link between environmental carcinogens and oral cancer. Exposure to environmental carcinogens, such as somking and betel nut consumption, might implicate the etiology of oral cancer [42-44]. A stratified analysis was also conducted regarding ethnicity for the *ICAM-1* rs5498 A>G polymorphism. This SNP was correlated with the increased susceptibility of cancer in Asian populations, but the decreased risk of cancer in Caucasians. The present analysis highlighted the influence of genetic variants and diversity in different populations to the susceptibility of malignance. To our knowledge, genetic and environmental factors can affect the risk of cancer on different levels. The possible sake of the inconsistent results among different populations could be that different levels of environmental factors and genetic diversity they exposed to may play different roles on cancer risk. Future studies are needed to confirm these correlations, particularly with regard to the interactions of gene-gene and gene-environment.

ated with colorectal cancer differentiation and increased the ICAM-1 expression in tumor tissues [23]. In the present meta-analysis, we found that *ICAM-1* rs5498 A>G polymorphism was correlated with the decreased risk of colorectal cancer and melanoma, suggesting the presence of the A allele, which is associated with increased ICAM-1 expression and activity, might decrease the susceptibility of these malignances. However, the inverse correlation was found in oral cancer. The apparent discrep-

There are only six publications involving 3138 cases and 3699 controls for *ICAM-1* rs3093030 C>T polymorphism and the risk of cancer. Previous study has reported a positive signal of *ICAM-1* rs3093030 C>T polymorphism with ovarian cancer [25]; the other individual investigation has reported negative signal [45]; however, as shown in our findings, there were non-significance. For limited data, further subgroup analyses in different population and different cancer type were not carried out. Further evalu-
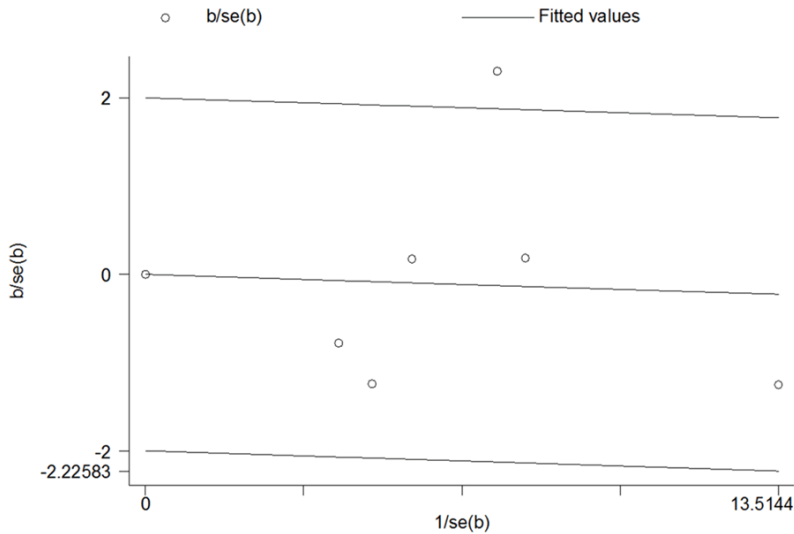
Figure 11. Galbraith radial plot of meta-analysis (TT+CT vs. CC compare genetic model for *ICAM-1* rs3093030 C>T polymorphism).

ations are needed to confirm or refute these results.

Caution must be addressed in the interpretation of these findings because of the large heterogeneity in our study. In subgroup analyses stratified by cancer type and racial descent respectively, this heterogeneity was reduced significantly or removed in some subgroups, implying the relatively large heterogeneity mostly results from differences of cancer type and ethnicity. Simultaneously, the large heterogeneity might also have been prompted by the differences in selection of age distribution and lifestyle factors. Only published studies were enrolled in the present study, and negative or non-significant studies may remain unpublished, thus publication bias may inevitably exist. Finally, due to the lack of sufficient background data, our findings were based on crude estimates, while a more comprehensive analysis should be carried out if the data of individual studies were available.

In conclusion, this meta-analysis highlights that the *ICAM-1* rs5498 A>G polymorphism probably contributes to decreased susceptibility to cancer, especially in Caucasians, in melanoma and colorectal cancer subgroup, but it may be a risk factor for oral cancer and Asians. *ICAM-1* rs3093030 C>T polymorphism is not correlated with cancer susceptibility. Nevertheless, for practical reasons, larger association studies assessing gene-environment, gene-gene interaction and incorporating with functional assessments are warranted to confirm or refute these findings.

Disclosure of conflict of interest

None.

Address correspondence to: Mingqiang Kang, Department of Thoracic Surgery, The Union Clinical Medical College of Fujian Medical University, Fuzhou 350001, China. E-mail: Mingqiang_Kang@126.com; Shuchen Chen, Department of Thoracic Surgery, The Union Clinical Medical College of Fujian Medical University, Fuzhou 350001, China. E-mail: cscdoctor@163.com

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.
[2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90.
[3] Fernandes JV, DE Medeiros Fernandes TA, DE Azevedo JC, Cobucci RN, DE Carvalho MG, Andrade VS, DE Araújo JM. Link between chronic inflammation and human papillomavi-

rus-induced carcinogenesis (Review). Oncol Lett 2015; 9: 1015-1026.

[4] Bremnes RM, Al-Shibli K, Donnem T, Sirera R, Al-Saad S, Andersen S, Stenvold H, Camps C, Busund LT. The role of tumor-infiltrating immune cells and chronic inflammation at the tumor site on cancer development, progression, and prognosis: emphasis on non-small cell lung cancer. J Thorac Oncol 2011; 6: 824-833.

[5] Elinav E, Nowarski R, Thaiss CA, Hu B, Jin C, Flavell RA. Inflammation-induced cancer: crosstalk between tumours, immune cells and microorganisms. Nat Rev Cancer 2013; 13: 759-771.

[6] Nguyen DP, Li J, Tewari AK. Inflammation and prostate cancer: the role of interleukin 6 (IL-6). BJU Int 2014; 113: 986-992.

[7] Lawson C, Wolf S. ICAM-1 signaling in endothelial cells. Pharmacol Rep 2009; 61: 22-32.

[8] Yang L, Froio RM, Sciuto TE, Dvorak AM, Alon R, Luscinskas FW. ICAM-1 regulates neutrophil adhesion and transcellular migration of TNF-alpha-activated vascular endothelium under flow. Blood 2005; 106: 584-592.

[9] Dietrich JB. The adhesion molecule ICAM-1 and its regulation in relation with the blood-brain barrier. J Neuroimmunol 2002; 128: 58-68.

[10] Roebuck KA, Finnegan A. Regulation of intercellular adhesion molecule-1 (CD54) gene expression. J Leukoc Biol 1999; 66: 876-888.

[11] Li YF, Lin CC, Tai CK. Interaction of intercellular adhesion molecule 1 (ICAM1) polymorphisms and environmental tobacco smoke on childhood asthma. Int J Environ Res Public Health 2014; 11: 6504-6516.

[12] Sinha S, Qidwai T, Kanchan K, Anand P, Jha GN, Pati SS, Mohanty S, Mishra SK, Tyagi PK, Sharma SK; Indian Genome Variation Consortium, Venkatesh V, Habib S. Variations in host genes encoding adhesion molecules and susceptibility to falciparum malaria in India. Malar J 2008; 7: 250.

[13] Chmaisse HN, Fakhoury HA, Salti NN, Makki RF. The ICAM-1 (469 T/C) gene polymorphism but not (241 G/A) is associated with Behcet`s disease in the Lebanese population. Neurosciences (Riyadh) 2006; 11: 187-190.

[14] Ma J, Zhang D, Brismar K, Efendic S, Gu HF. Evaluation of the association between the common E469K polymorphism in the ICAM-1 gene and diabetic nephropathy among type 1 diabetic patients in GoKinD population. BMC Med Genet 2008; 9: 47.

[15] Buitrago D, Keutgen XM, Crowley M, Filicori F, Aldailami H, Hoda R, Liu YF, Hoda RS, Scognamiglio T, Jin M, Fahey TJ 3rd, Zarnegar R. Intercellular adhesion molecule-1 (ICAM-1) is upregulated in aggressive papillary thyroid

carcinoma. Ann Surg Oncol 2012; 19: 973-980.

[16] Maruo Y, Gochi A, Kaihara A, Shimamura H, Yamada T, Tanaka N, Orita K. ICAM-1 expression and the soluble ICAM-1 level for evaluating the metastatic potential of gastric cancer. Int J Cancer 2002; 100: 486-490.

[17] Tanabe K, Campbell SC, Alexander JP, Steinbach F, Edinger MG, Tubbs RR, Novick AC, Klein EA. Molecular regulation of intercellular adhesion molecule 1 (ICAM-1) expression in renal cell carcinoma. Urol Res 1997; 25: 231-238.

[18] Usami Y, Ishida K, Sato S, Kishino M, Kiryu M, Ogawa Y, Okura M, Fukuda Y, Toyosawa S. Intercellular adhesion molecule-1 (ICAM-1) expression correlates with oral cancer progression and induces macrophage/cancer cell adhesion. Int J Cancer 2013; 133: 568-578.

[19] Schroder C, Witzel I, Muller V, Krenkel S, Wirtz RM, Jänicke F, Schumacher U, Milde-Langosch K. Prognostic value of intercellular adhesion molecule (ICAM)-1 expression in breast cancer. J Cancer Res Clin Oncol 2011; 137: 1193-1201.

[20] Wang SS, Hsieh MJ, Ou YC, Chen CS, Li JR, Hsiao PC, Yang SF. Impacts of ICAM-1 gene polymorphisms on urothelial cell carcinoma susceptibility and clinicopathologic characteristics in Taiwan. Tumour Biol 2014; 35: 7483-7490.

[21] Lin CW, Chuang CY, Tang CH, Chang JL, Lee LM, Lee WJ, Chow JM, Yang SF, Chien MH. Combined effects of icam-1 single-nucleotide polymorphisms and environmental carcinogens on oral cancer susceptibility and clinicopathologic development. PLoS One 2013; 8: e72940.

[22] Bai Y. vascular invasion and eNOS, ICAM-1, E-selection polymorphism in oral cancer. Wuhan university: Wuhan university, China.

[23] Wang QL, Li BH, Liu B, Liu YB, Liu YP, Miao SB, Han Y, Wen JK, Han M. Polymorphisms of the ICAM-1 exon 6 (E469K) are associated with differentiation of colorectal cancer. J Exp Clin Cancer Res 2009; 28: 139.

[24] Theodoropoulos G, Papaconstantinou I, Felekouras E, Nikiteas N, Karakitsos P, Panoussopoulos D, Lazaris ACh, Patsouris E, Bramis J, Gazouli M. Relation between common polymorphisms in genes related to inflammatory response and colorectal cancer. World J Gastroenterol 2006; 12: 5037-5043.

[25] Cai G, Ma X, Zou W, Huang Y, Zhang J, Wang D, Chen B. Prediction value of intercellular adhesion molecule-1 gene polymorphisms for epithelial ovarian cancer risk, clinical features, and prognosis. Gene 2014; 546: 117-123.

[26] Kammerer S, Roth RB, Reneland R, Marnellos G, Hoyal CR, Markward NJ, Ebner F, Kiechle M, Schwarz-Boeger U, Griffiths LR, Ulbrich C,

Chrobok K, Forster G, Praetorius GM, Meyer P, Rehbock J, Cantor CR, Nelson MR, Braun A. Large-scale association study identifies ICAM gene region as breast and prostate cancer susceptibility locus. Cancer Res 2004; 64: 8906-8910.

[27] Tian MM, Sun Y, Li ZW, Wu Y, Zhao AL, Li JY. Polymorphisms of ICAM-1 are associated with gastric cancer risk and prognosis. World J Gastroenterol 2012; 18: 368-374.

[28] Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21: 1539-1558.

[29] Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[30] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[31] Mantel N HW. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.

[32] Wang D, Mou ZY, Zhai JX, Zong HX, Zhao XD. [Application of Stata software to test heterogeneity in meta-analysis method]. Zhonghua Liu Xing Bing Xue Za Zhi 2008; 29: 726-729.

[33] Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[34] Gho YS, Kim PN, Li HC, Elkin M, Kleinman HK. Stimulation of tumor growth by human soluble intercellular adhesion molecule-1. Cancer Res 2001; 61: 4253-4257.

[35] Jun CD, Carman CV, Redick SD, Shimaoka M, Erickson HP, Springer TA. Ultrastructure and function of dimeric, soluble intercellular adhesion molecule-1 (ICAM-1). J Biol Chem 2001; 276: 29019-29027.

[36] Melis M, Pace E, Siena L, Spatafora M, Tipa A, Profita M, Bonanno A, Vignola AM, Bonsignore G, Mody CH, Gjomarkaj M. Biologically active intercellular adhesion molecule-1 is shed as dimers by a regulated mechanism in the inflamed pleural space. Am J Respir Crit Care Med 2003; 167: 1131-1138.

[37] Dymicka-Piekarska V, Guzinska-Ustymowicz K, Kuklinski A, Kemona H. Prognostic significance of adhesion molecules (sICAM-1, sVCAM-1) and VEGF in colorectal cancer patients. Thromb Res 2012; 129: e47-50.

[38] Gogali A, Charalabopoulos K, Zampira I, Konstantinidis AK, Tachmazoglou F, Daskalopoulos G, Constantopoulos SH, Dalavanga Y. Soluble adhesion molecules E-cadherin, intercellular adhesion molecule-1, and E-selectin as lung cancer biomarkers. Chest 2010; 138: 1173-1179.

[39] Toiyama Y, Miki C, Inoue Y, Okugawa Y, Koike Y, Yokoe T, Tanaka K, Kusunoki M. Soluble intercellular adhesion molecule-1 as a prognostic marker for stage II colorectal cancer patients. Ann Surg Oncol 2008; 15: 1617-1624.

[40] Basoglu M, Atamanalp SS, Yildirgan MI, Aydinli B, Ozturk G, Akcay F, Oren D. Correlation between the serum values of soluble intercellular adhesion molecule-1 and total sialic acid levels in patients with breast cancer. Eur Surg Res 2007; 39: 136-140.

[41] Aboughalia AH. Elevation of hyaluronidase-1 and soluble intercellular adhesion molecule-1 helps select bladder cancer patients at risk of invasion. Arch Med Res 2006; 37: 109-116.

[42] Lee CP, Chiang SL, Lee CH, Tsai YS, Wang ZH, Hua CH, Chen YC, Tsai EM, Ko YC. AURKA Phe31Ile polymorphism interacted with use of alcohol, betel quid, and cigarettes at multiplicative risk of oral cancer occurrence. Clin Oral Investig 2015; [Epub ahead of print].

[43] Paulino YC, Hurwitz EL, Warnakulasuriya S, Gatewood RR, Pierson KD, Tenorio LF, Novotny R, Palafox NA, Wilkens LR, Badowski G. Screening for oral potentially malignant disorders among areca (betel) nut chewers in Guam and Saipan. BMC Oral Health 2014; 14: 151.

[44] Amtha R, Razak IA, Basuki B, Roeslan BO, Gautama W, Puwanto DJ, Ghani WM, Zain RB. Tobacco (kretek) smoking, betel quid chewing and risk of oral cancer in a selected Jakarta population. Asian Pac J Cancer Prev 2014; 15: 8673-8678.

[45] Han W, Kang SY, Kang D, Park SK, Lee JY, Kim H, Park AK, Noh DY. Multiplex genotyping of 1107 SNPs from 232 candidate genes identified an association between IL1A polymorphism and breast cancer risk. Oncol Rep 2010; 23: 763-769.