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META-ANALYSIS

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Association of Polymorphisms in Intercellular Adhesion Molecule 1 (ICAM-1) Gene with Cancer Susceptibility: A Meta-Analysis of 14 Case-Control Studies

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Background: Many epidemiology studies have indicated that polymorphisms in *ICAM-1* are associated with a variety of cancers, but published data are contradictory and inconclusive. Therefore, we conducted the current meta-analysis to elaborate the effects of *ICAM-1* polymorphisms (rs5491, rs3093030, rs281432, and rs1799969) on cancer susceptibility.

Material/Methods: We conducted a comprehensive literature search in PubMed, Web of Science, and Google Scholar. Odds ratios (ORs) with 95% confidence intervals (CIs) were estimated to assess the association between *ICAM-1* polymorphisms and cancer susceptibility.

Results: We enrolled 14 published case-control studies including 4608 cancer cases and 4913 controls. We found an increased susceptibility of cancer in polymorphism rs1799969 (C *vs.* T: OR=1.662, 95%CI=1.288–2.143, p=0141; CT *vs.* TT: OR=1.860, 95%CI=1.398–2.474, p=0.507; CC+CT *vs.* TT: OR=1.812, 95%CI=1.373–2.391, p=0.284) of *ICAM-1* among the overall population. However, no association between polymorphisms rs5491, rs3093030, or rs281432 of *ICAM-1* and cancer susceptibility was identified. In the stratification analysis by ethnicity, we identified an increased susceptibility for Asians in rs3093030 polymorphism (CC *vs.* TC+TT: OR=1.728, 95% CI=1.234–2.421, p=0.787).

Conclusions: Our results suggest that the *ICAM-1* polymorphism rs1799969 is significantly associated with increased susceptibility to overall cancer. Further studies (preferably prospective) are warranted to validate these relationships.

MeSH Keywords: Genetic Predisposition to Disease • Meta-Analysis • Polymorphism, Genetic

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Background

Cancer is a major public health problem all over the world, and has become one of the primary causes of morbidity and mortality [1]. The epidemiology of cancer is influenced by the aging and growth of the world population and a rise in cancer-causing behaviors; therefore, the global burden of cancer is rapidly increasing [1,2]. The etiology of cancer is complex and is still obscure. Recent research suggests that single-nucleotide polymorphisms (SNPs) in genes play critical roles in cancer development and progression [3–6]. Among these SNPs, *ICAM-1* polymorphisms have been shown to be particularly important.

ICAM-1, a single-chain 76–110 kDa glycoprotein, is a member of the immunoglobulin superfamily, which is involved in cell adhesion and signalling [7]. Studies indicate that ICAM-1 plays an important role in tumorigenesis and tumor progression, specifically by facilitating tumor invasion and metastases [8,9]. Many case-control studies have demonstrated that *ICAM-1* polymorphisms (rs5491, rs3093030, rs281432, and rs1799969) are associated with susceptibility to many cancers, including colorectal cancer [10], breast cancer [11,12], diffuse astrocytoma [13], prostate cancer [14], cutaneous malignant melanoma [15], ovarian cancer [16], urothelial cell carcinoma [17], oral cancer [18], and acute promyelocytic leukanemia (APL) [19].

In view of the relevance of *ICAM-1* polymorphisms (rs5491, rs3093030, rs281432, and rs1799969) in susceptibility to cancer, many studies have been conducted [9–18] but the results were inconclusive and inconsistent. In 2014, Wang et al. [20] performed a meta-analysis of 14 studies and concluded that *ICAM-1* rs5498 polymorphism was associated with cancer susceptibility. In the present study, we aimed to clarify the relationship between other *ICAM-1* polymorphisms (rs5491, rs3093030, rs281432, and rs1799969) and cancer susceptibility based on all eligible published case-control studies.

Material and Methods

Literature search strategy

All eligible case-control studies on the relationship between polymorphisms of *ICAM-1* (rs5491, rs3093030, rs281432, and rs1799969) and cancer susceptibility up to June 16, 2015 were identified by a systematic literature search in PubMed, Web of Science, and Google Scholar. The search terms were: ("Intercellular adhesion molecule-1" OR"ICAM -1") AND ("cancer" OR "carcinoma" OR "neoplasms") AND ("polymorphism" OR "variant" OR "mutation"). In addition, for each retrieved publication, a manual search for relevant references was also conducted to find additional case-control studies.

Selection criteria

The inclusion criteria were: 1) evaluation of the *ICAM-1* polymorphisms and cancer susceptibility, 2) case-control studies, and 3) presenting available information to assess the odds ratio (OR) with 95% confidence interval (CI). Major reasons for exclusion of studies were: 1) no control population, 2) abstracts and reviews, 3) no available genotype frequency, 4) duplication of the previous publication, and 5) non-human studies.

Data extraction

Two investigators (Xiaolong Zhang and Junjie Huang) independently extracted data on *ICAM-1* polymorphisms, first author, year of publication, ethnicity of the case-control studies, genotyping methods, source of controls, type of cancer, and genotype number in cancer cases and controls. Any disagreements were resolved by discussion and consensus.

Statistical analysis

We evaluated the association between *ICAM-1* polymorphisms and cancer susceptibility by OR and 95% CI. The significance of the pooled OR was determined by the Z-test and $P<0.05$ was considered statistically significant. A total of 4 genetic models were selected: allele contrasts, additive genetic model, recessive genetic model, and dominant genetic model separately. Heterogeneity was detected by the χ^2-based Q statistic test to assess the heterogeneity within the case-control studies [21]. When there was heterogeneity ($p<0.10$, $I^2>50\%$), the random-effects model was used to calculate the pooled ORs [22]; otherwise, the fixed-effects model was used [23]. *P* values of the HWE for control groups were tested by χ^2 test. Stratification analyses of cancer type, genotyping method, and source of control were conducted. Sensitivity analyses were further performed to calculate the stability of the results by removing each case-control study from the enrolled pooled data to detect the influence of the respective data set on the pooled ORs. To examine the potential publication bias, Begg's funnel plot and Egger's regression test were used [24,25]. The STATA 12.0 (Stata Corporation, College Station, TX) was used to conduct all statistical analyses.

Quality evaluation

The study quality was assessed independently by Xiaolong Zhang and Junjie Huang by referring to the Newcastle-Ottawa scale (NOS), which examines the quality of non-randomized studies by the selection of participants, comparability of groups, and exposure assessment. Any disagreements were resolved by discussion and consensus.

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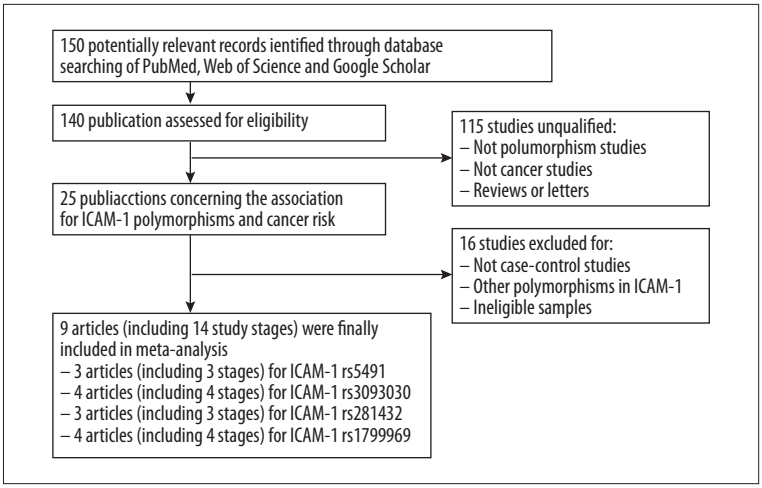

Figure 1. Flow chart displaying the selection procedure.

Table 1. Polymorphisms and characteristics of studies involved in this meta-analysis.

SNP	First Author	Year	Ethnicity	Genotyping method	Source of control	Cancer type	Case			Control				
							AA	AB	BB	AA	AB	BB	P (HWE)	Y or N
rs5491	Lin et al.	2013	Asian	TaqMan	PB	OC	537	55	3	514	47	0	0.300	Y
	Wang et al.	2014	Asian	PCR	HB	UCC	253	25	1	250	29	0	0.360	Y
	Chen et al.	2006	African	PCR	HB	PC	167	107	12	246	124	21	0.307	Y
rs3093030	Cai et al.	2014	Asian	PCR	PB	OVC	183	172	51	271	207	36	0.678	Y
	Lin et al.	2013	Asian	TaqMan	PB	OC	384	183	28	365	179	17	0.377	Y
	Han et al.	2010	white	PCR	PB	BC	59	54	4	75	65	24	0.117	Y
	Wang et al.	2014	Asian	PCR	HB	UCC	176	92	11	178	93	8	0.314	Y
rs281432	Cai et al.	2014	Asian	PCR	PB	OVC	215	153	37	259	202	57	0.068	Y
	Lin et al.	2013	Asian	TaqMan	PB	OC	332	218	45	324	200	37	0.418	Y
	Wang et al.	2014	Asian	PCR	HB	UCC	136	123	20	146	114	19	0.607	Y
rs1799969	Theodoropoulos et al.	2006	white	PCR	PB	CRC	144	74	4	158	40	2	0.762	Y
	Arandi et al.	2008	white	PCR-RFLP	PB	BC	237	39	0	220	15	0	0.613	Y
	Dore et al.	2007	white	PCR	PB	APL	96	12	2	100	7	0	0.726	Y
	Howell et al.	2005	white	TaqMan	HB	CMM	134	28	2	222	35	7	**0.001**	N

Cancer type: OC – oral cancer; UCC – urothelial cell carcinoma; OVC – ovarian cancer; BC – breast cancer; PC – prostate cancer; APL – acute promyelocytic leukemia; CMM – cutaneous malignant melanoma; CRC – colorectal cancer; DA – diffuse astrocytoma; HWE – Hardy-Weinberg equilibrium; H-B – hospital-based; P-B – population-based; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; Y – conform to HWE; N – do not conform to HWE.

Results

Study characteristics

After a systematic literature search and selection based on the inclusion criteria, 140 publications were considered for eligibility. However, among these eligible articles, 115 are disqualified because they were not about polymorphisms, were not cancer studies, or they were reviews or letters. Of the remaining 25 publications, 7 were based on case-only design, 5 were not polymorphism studies, and 4 were not about susceptibility to cancer. As a result, 9 publications with 14 case-control studies including 4608 cancer cases and 4913 controls were included in the present meta-analysis. We present a flow chart of the study screening process in Figure 1. The characteristics of enrolled studies are presented in Table 1 [9–18]. Eight studies were conducted in people of Asian ethnicity, 6 studies were conducted in people of white ethnicity, and only 1 study

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Table 2A. Results of meta-analysis for polymorphism rs5491 in *ICAM-1* and cancer susceptibility.

	Case/ control	C *vs.* T			CC *vs.* TT			CT *vs.* TT		
		OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)
Variables (rs5491)										
Total	1160/1231	1.109 (0.908–1.355)	0.697	0.0	1.083 (0.559–2.102)	0.320	1.5	1.140 (0.904–1.436)	0.480	0.0
Source of control										
HB	565/670	1.067 (0.844–1.348)	0.571	0.0	0.907 (0.447–1.842)	–	–	1.149 (0.868–1.522)	0.227	9.9
Genotyping method										
PCR	565/670	1.067 (0.844–1.348)	0.571	0.0	0.907 (0.447–1.842)	0.453	0.0	1.149 (0.868–1.522)	0.227	9.9
Ethnicity										
Asian	874/840	1.120 (0.818–1.534)	0.397	0.0	4.847 (0.56–41.659)	0.712	0.0	1.019 (0.733–1.417)	0.440	0.0

	Case/ control	CC+CT *vs.* TT			CC *vs.* CT+TT		
		OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)
Total	1160/1231	1.140 (0.910–1.429)	0.621	0.0	1.000 (0.520–1.922)	0.285	4.1
Source of control							
HB	279/279	1.122 (0.855–1.473)	0.340	0.0	0.835 (0.415–1.679)	0.416	0.0
Genotyping method							
PCR	565/670	1.122 (0.855–1.473)	0.340	0.0	0.835 (0.415–1.679)	0.416	0.0
Ethnicity							
Asian	874/840	1.070 (0.773–1.483)	0.413	0.0	4.848 (0.563–41.713)	0.721	0.0

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Table 2B. Results of meta-analysis for polymorphism rs3093030 in *ICAM-1* and cancer susceptibility.

	Case/ control	C *vs.* T			CC *vs.* TT			TC *vs.* TT		
		OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)
Variables (rs3093030)										
Total	1397/1518	1.050 (0.823–1.340)	0.012	52.6	1.114 (0.504–2.458)	0.003	62.1	1.063 (0.909–1.242)	0.640	0.0
Source of control										
PB	1118/1239	1.036 (0.745–1.441)	0.005	66.4	1.004 (0.352–2.863)	0.001	73.8	1.078 (0.906–1.283)	0.461	9.9
Genotyping method										
PCR	802/957	1.023 (0.702–1.491)	0.005	66.1	0.919 (0.261–3.243)	0.001	73.8	1.125 (0.921–1.373)	0.642	9.9
Ethnicity										
Asian	1280/1354	1.174 (0.987–1.395)	0.179	17.6	1.810 (1.281–2.558)	0.637	0.0	1.064 (0.902–1.254)	0.431	0.0

	Case/ control	CC+TC *vs.* TT			CC *vs.* TC+TT		
		OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)
Total	1397/1518	1.102 (0.949–1.279)	0.225	9.8	1.079 (0.496–2.345)	0.003	62.1
Source of control							
PB	1118/1239	1.119 (0.948–1.320)	0.123	27.4	0.965 (0.346–2.693)	0.001	73.8
Genotyping method							
PCR	802/957	1.153 (0.953–1.395)	0.151	22.2	0.880 (0.257–3.014)	0.001	73.6
Ethnicity							
Asian	1280/1354	1.137 (0.971–1.331)	0.243	8.6	**1.728 (1.234–2.421)***	0.787	0.0

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Table 2C. Results of meta-analysis for polymorphism rs1799969 in *ICAM-1* and cancer susceptibility.

	Case/ control	C *vs.* T			CC *vs.* TT			CT *vs.* TT		
		OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)
Variables (rs1799969)										
Total	772/806	**1.662 (1.288–2.143)***	0.141	20.3	1.208 (0.462–3.161)	0.261	6.6	**1.860 (1.398–2.474)***	0.507	0.0
Genotyping method										
PCR	332/307	**1.905 (1.327–2.735)***	0.641	0.0	2.812 (0.646–12.251)	0.626	0.0	**1.985 (1.323–2.977)***	0.815	0.0
Source of control										
PB	608/542	**2.007 (1.471–2.737)***	0.778	0.0	2.812 (0.646–12.251)	0.626	0.0	**2.110 (1.502–2.962)***	0.852	0.0

	Case/ control	CC+CT *vs.* TT			CC *vs.* CT+TT		
		OR (95% CI)	P[a]	I^2 (%)	OR (95% CI)	P[a]	I^2 (%)
Total	772/806	**1.812 (1.373–2.391)***	0.284	4.4	1.095 (0.417–2.875)	0.291	3.6
Genotyping method							
PCR	332/307	**2.046 (1.375–3.045)***	0.967	0.0	2.423 (0.560–10.478)	0.571	0.0
Source of control							
PB	608/542	**2.151 (1.539–3.006)***	0.907	0.0	2.423 (0.560–10.478)	0.571	0.0

was conducted in people of African ethnicity. In addition, there were 10 studies done by PCR, 4 performed by TaqMan, and only 1 conducted by PCR-RFLP. The control groups consisted of 10 population-based studies and 5 hospital-based studies. Of these included studies, 3 reported urothelial cell carcinoma and 3 reported oral cancer. Two studies were on breast cancer, 2 were on APL, and 2 were on ovarian cancer. Prostate cancer, cutaneous melanoma, and colorectal cancer were also mentioned in other studies. Only one case-control studies deviated from HWE [15].

Meta-analysis

The results of the meta-analysis for the association between *ICAM-1* polymorphisms (rs5491, rs3093030, rs281432, and rs1799969) and susceptibility to cancer are presented in Table 2. According to the outcomes of heterogeneity analysis, obvious heterogeneity was identified in *ICAM-1* rs3093030 polymorphism (C *vs.* T: P=0.012, I^2=52.6%; CC *vs.* TT: P=0.003, I^2=62.1%; CC *vs.* TC+TT: P=0.003, I^2=62.1%) Therefore, the random-effects model was used to estimate the pooled ORs in these genetic models.

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Table 2D. Results of meta-analysis for polymorphism rs281432 in *ICAM-1* and cancer susceptibility.

	Case/ control	C *vs.* T			CC *vs.* TT			CT *vs.* TT		
		OR (95% CI)	P^a	I^2 (%)	OR (95% CI)	P^a	I^2 (%)	OR (95% CI)	P^a	I^2 (%)
Variables (rs281432)										
Total	1279/1358	1.010 (0.895–1.141)	0.286	4.0	0.988 (0.740–1.319)	0.408	0.0	1.028 (0.874–1.209)	0.537	0.0
Genotyping method										
PCR	684/797	0.962 (0.820–1.129)	0.198	15.8	0.877 (0.604–1.273)	0.372	0.0	1.002 (0.807–1.243)	0.291	1.0
Source of control										
PB	1000/1079	0.986 (0.859–1.132)	0.162	24.0	0.958 (0.696–1.320)	0.205	14.2	0.994 (0.828–1.195)	0.417	0.0

	Case/ control	CC+CT *vs.* TT			CC *vs.* TC+TT		
		OR (95% CI)	P^a	I^2 (%)	OR (95% CI)	P^a	I^2 (%)
Total	1279/1358	1.023 (0.877–1.192)	0.377	0.0	0.981 (0.740–1.299)	0.526	0.0
Genotyping method							
PCR	684/797	0.978 (0.797–1.200)	0.215	12.3	0.881 (0.614–1.265)	0.512	0.0
Source of control							
PB	1000/1079	0.989 (0.832–1.177)	0.254	5.4	0.964 (0.706–1.316)	0.269	3.3

I^2 – 0–25, means no heterogeneity; 25–50, means modest heterogeneity; >50, means high heterogeneity; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; PB – population-based; HB – hospital-based; HWE – Hardy-Weinberg equilibrium; Y – polymorphisms conformed to HWE in the control group; N – polymorphisms did not conform to HWE in the control group; P^a – P value of Q test for heterogeneity test; * means statistically significant (P<0.05).

According to the present analysis, we discovered that *ICAM-1* rs1799969 polymorphism was significantly associated with overall cancer susceptibility (Table 2C, C *vs.* T: OR=1.662, 95%CI =1.288–2.143, *p*=0.141, Figure 2A; CT *vs.* TT: OR=1.860, 95%CI=1.398–2.474, *p*=0.507, Figure 2B; CC+CT *vs.* TT: OR=1.812, 95%CI=1.373–2.391, *p*=0.284, Figure 2C). Nevertheless, no relevance was identified between other *ICAM-1* polymorphisms (Table 2A, rs5491; Table 2B, rs3093030; Table 2D, rs281432) and overall cancer susceptibility.

In stratified analysis of the source of controls, an increased susceptibility of the population-based group in rs1799969 polymorphism was found in 3 genetic models (Table 2C, C *vs.* T: OR=2.007, 95%CI=1.471–2.737, p=0.778; CT *vs.* TT: OR=2.110,

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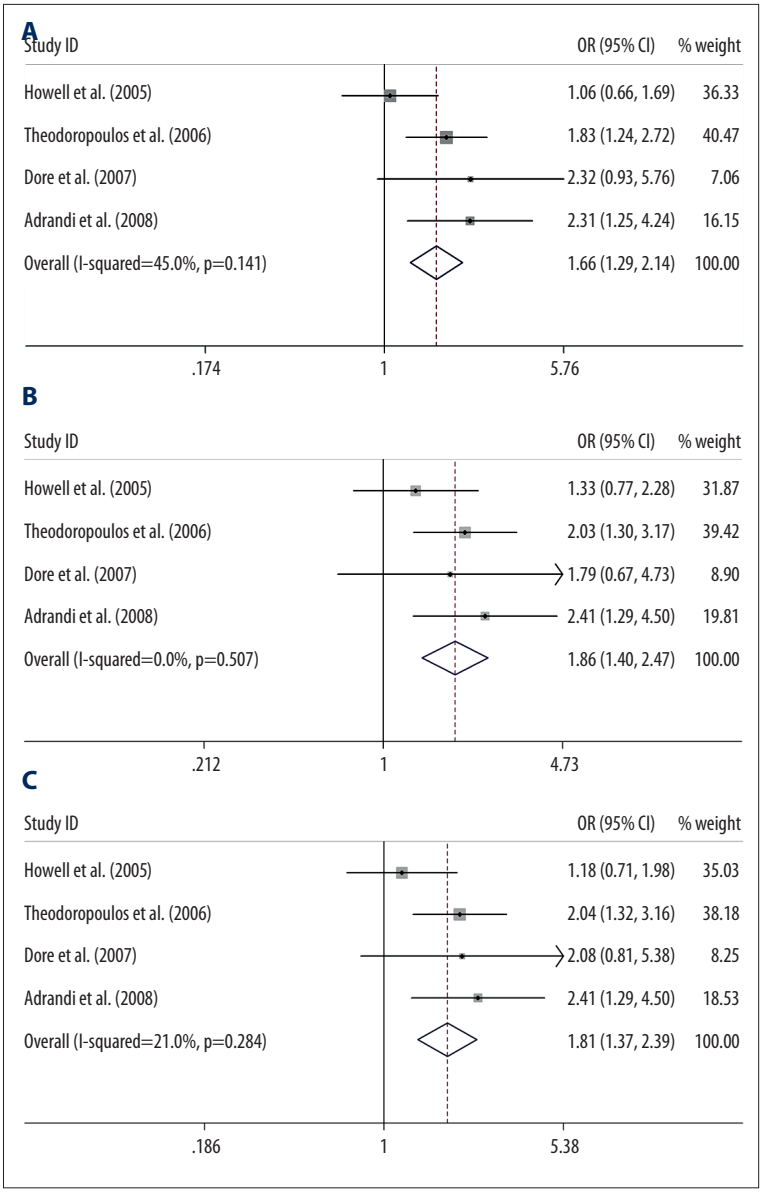

Figure 2. (**A**) OR estimates with the corresponding 95% CI for the association of *ICAM-1* polymorphism rs1799969 with overall cancer risk (C *vs.* T). The sizes of the squares represent the weighting of included studies; OR – odds ratio; CI – confidence interval. (**B**) OR estimates with the corresponding 95% CI for the association of *ICAM-1* polymorphism rs1799969 with overall cancer risk (CT *vs.* TT). The sizes of the squares represent the weighting of included studies; OR – odds ratio; CI – confidence interval. (**C**) OR estimates with the corresponding 95% CI for the association of *ICAM-1* polymorphism rs1799969 with overall cancer risk (CC+CT *vs.* TT). The sizes of the squares represent the weighting of included studies; OR – odds ratio; CI – confidence interval.

95%CI=1.502–2.962, p=0.852; CC+CT *vs.* TT: OR=2.151, 95%CI=1.539–3.006, p=0.907). Interestingly, we also identified an increased susceptibility for Asians in rs3093030 polymorphism (Table 2B, CC *vs.* TC+TT: OR=1.728, 95%CI=1.234–2.421, p=0.787, Figure 3) in the stratification analysis by ethnicity.

Sensitivity analyses and publication bias

Sensitivity analysis confirmed the pooled results (data not shown). Egger's test and Begg's funnel plot were performed to examine the publication bias risk and we found no publication bias (Figure 4A–4D).

Additionally, the quality of the enrolled studies is shown in Table 3.

Discussion

ICAM-1, a cell adhesion molecule with a key role in inflammation and immune surveillance, has been implicated in carcinogenesis by facilitating instability of the tumor environment [26,27]. In 2014, Wang et al. conducted a meta-analysis and concluded that *ICAM-1* rs5498 polymorphism was associated with cancer susceptibility. However, the association between cancer susceptibility and other polymorphisms of *ICAM-1* (rs5491, rs3093030, rs281432, and rs1799969) remained unclear. Recently, Dore et al. [19] demonstrated that no significant association was detected between *ICAM-1* rs1799969 polymorphism and APL in whites. Nevertheless, Theodoropoulos et al, Arandi et al, and Howell et al. obtained the opposite results in breast cancer, colorectal cancer, and cutaneous malignant melanoma,

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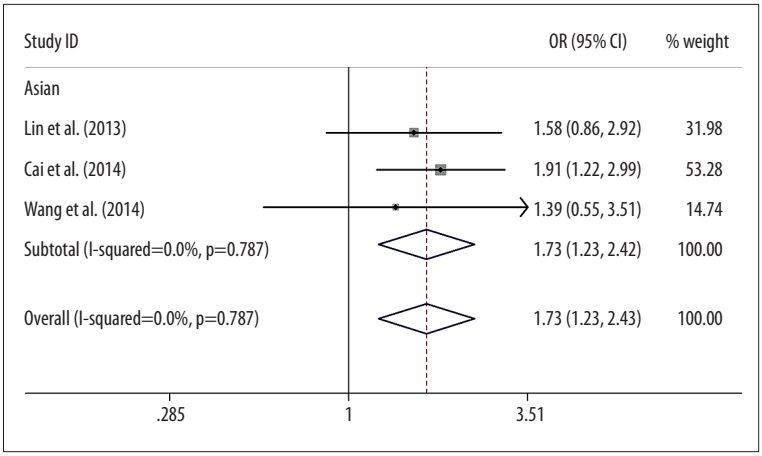

Figure 3. OR estimates with the corresponding 95% CI for the association of *ICAM-1* polymorphism rs3093030 with overall cancer risk (CC *vs.* TC+TT) in the Asian subgroup analysis by ethnicity. The sizes of the squares represent the weighting of included studies; OR – odds ratio; CI – confidence interval.

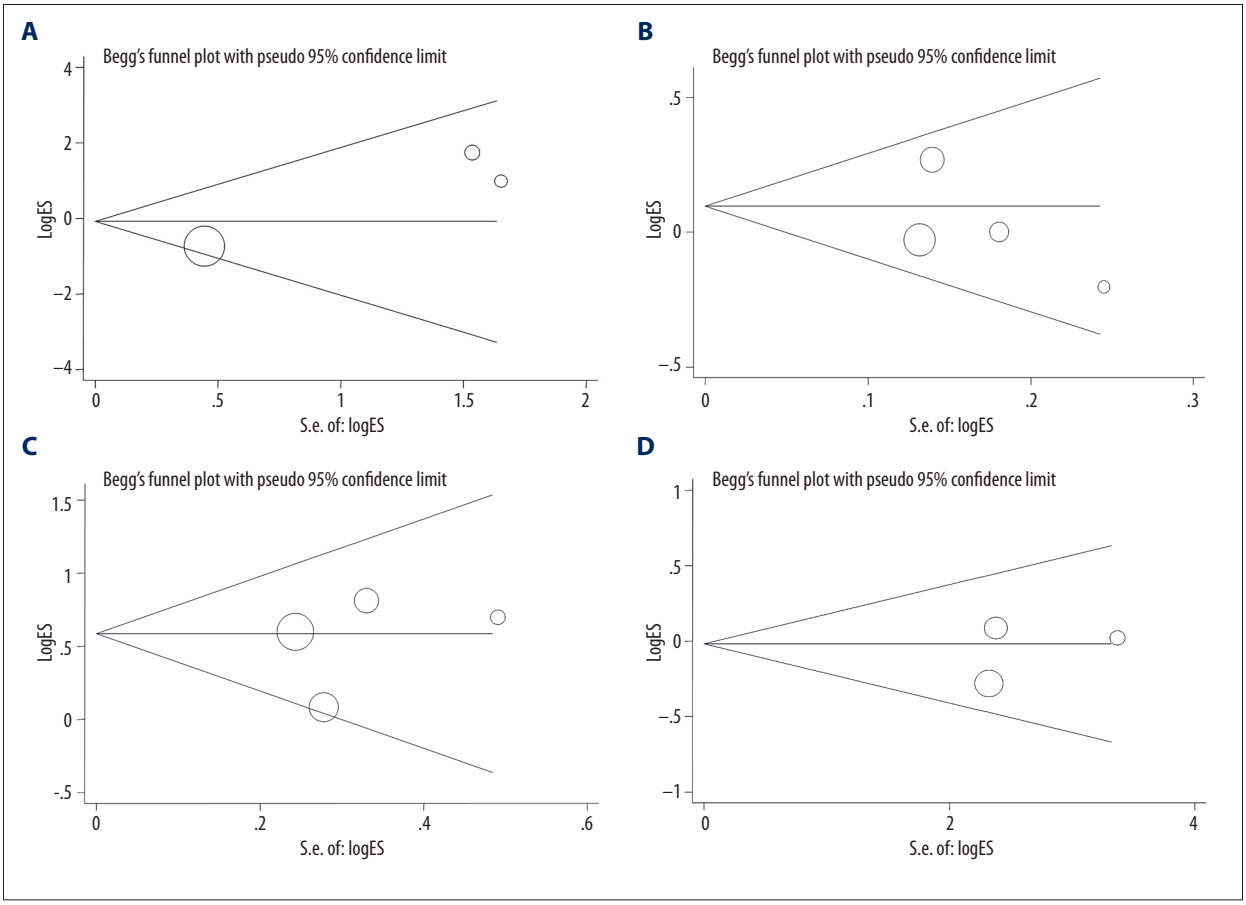

Figure 4. (**A**) Publication bias in studies of the association between the *ICAM-1* rs5491 polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test. Log (OR) – the natural logarithm of the odds ratio. (**B**) Publication bias in studies of the association between the *ICAM-1* rs3093030 polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test. Log (OR) – the natural logarithm of the odds ratio. (**C**) Publication bias in studies of the association between the *ICAM-1* rs1799969 polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test. Log (OR) – the natural logarithm of the odds ratio. (**D**) Publication bias in studies of the association between the *ICAM-1* rs281432 polymorphism and cancer susceptibility assessed by Begg's funnel plot and Egger's test. Log (OR) – the natural logarithm of the odds ratio.

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Table 3. Methodological quality of the included studies according to the Newcastle-Ottawa Scale.

	Author	Ethnicity	Adequacy of case definition	Representativeness of the Cases	Selection of controls	Definition of controls	Comparability cases/controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate
rs5491	Lin et al.	Asian	*	*	*	*	**	*	*	*
	Wang et al.	Asian	*	*	NA	*	**	*	*	*
	Chen et al.	African	*	*	NA	*	**	*	*	*
rs3093030	Cai et al.	Asian	*	*	*	*	**	*	*	*
	Lin et al.	Asian	*	*	*	*	**	*	*	*
	Han et al.	white	*	*	*	*	**	*	*	*
	Wang et al.	Asian	*	*	NA	*	**	*	*	*
rs281432	Cai et al.	Asian	*	*	*	*	**	*	*	*
	Lin et al.	Asian	*	*	*	*	**	*	*	*
	Wang et al.	Asian	*	*	NA	*	**	*	*	*
rs1799969	Theodoropoulos et al.	white	*	*	*	*	**	*	*	*
	Arandi et al.	white	*	*	*	*	**	*	*	*
	Dore et al.	white	*	*	*	*	**	*	*	*
	Howell et al.	white	*	*	NA	*	**	*	*	*

This table identifies 'high' quality choices with a 'star'. A study can be awarded a maximum of 1 star for each numbered item within the Selection and Exposure categories. A maximum of 2 stars can be given for Comparability. *, Yes; NA, not applicable. (*http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm*).

respectively [10,12,15]. In addition, several publications (case-control studies) indicated that *ICAM-1* polymorphisms (rs5491, rs3093030, and rs281432) were also involved in tumorigenesis and tumor progression. However, the conclusions were inconclusive because of the limited number of relevant published reports. Therefore, we performed the present meta-analysis.

We aimed to comprehensively define the association between *ICAM-1* polymorphisms (rs5491, rs3093030, rs281432, and rs1799969) and cancer susceptibility in a total of 9 publications, including 14 case-control studies with 4608 cases and 4913 controls. We demonstrated that polymorphism rs1799969 of *ICAM-1* was significantly associated with cancer susceptibility. Moreover, in the stratified analysis, significant cancer susceptibility in population-based and Asian groups was identified for rs1799969 and rs3093030, respectively. It was well-established that hospital-based studies may have selection bias; the controls may only represent a poorly-defined reference population rather than the general population or the population of interest, especially when the genotypes examined are relevant to disease-related factors that the hospital-based controls may have been exposed to. The selection of appropriate and representative controls is of great importance in reducing biases in polymorphism association studies. Therefore, we conducted subgroup analysis by source of control and found that the source of control did not influence our conclusions.

Although we conducted a comprehensive retrieval of all eligible studies, several limitations of this meta-analysis should be acknowledged. Firstly, the number of currently available case-control studies enrolled in our study was small and we could not achieve definitive results. Secondly, lack of detailed data on individuals limited the precision of our analysis of adjusted estimates involving other factors such as age and sex. Thirdly, only 1 study discussed the genetic predisposition of every *ICAM-1* polymorphism to each cancer, and we could not evaluate the effects of a single polymorphism of *ICAM-1* on a specific cancer because eligible case-control studies were insufficient for pooled analysis. Finally, the effect of *ICAM-1* polymorphisms on cancer susceptibility might be affected by complex factors, such as histological types of cancer and matching criteria.

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Conclusions

Results of our meta-analysis show that *ICAM-1* polymorphism rs1799969 is significantly associated with increased susceptibility to cancer. Future well-designed studies are warranted to further explore the relationship between *ICAM-1* polymorphisms and cancer susceptibility.

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