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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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=0.0141; 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 leukemia (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 χ2-based Q statistic test to assess the heterogeneity within the case-control studies [21]. When there was homogeneity (P>0.10, I²≤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 χ2 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.
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].

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 | Cancer type | P (HWE) | Y or N |
|---------|----------------|------|-----------|-------------------|-------------------|-------------|-------|----------|-------------|---------|--------|
| rs5491  | Lin et al.     | 2013 | Asian     | TaqMan            | PB                | OC          | 537   | 55      | 3 514       | 47      | 0.300  |
|         | Wang et al.    | 2014 | Asian     | PCR               | HB                | UCC         | 253   | 25      | 1 250       | 29      | 0.360  |
|         | Chen et al.    | 2006 | African   | PCR               | PC                | UCC         | 167   | 107     | 12 246      | 124     | 0.037  |
|         | Cai et al.     | 2014 | Asian     | PCR               | PB                | OVC         | 183   | 172     | 51 271      | 207     | 0.678  |
|         | Lin et al.     | 2013 | Asian     | TaqMan            | PB                | OC          | 382   | 183     | 28 365      | 179     | 0.377  |
|         | Han et al.     | 2010 | white     | PCR               | PB                | BC          | 59    | 54      | 4 75        | 65      | 0.117  |
|         | Wang et al.    | 2014 | Asian     | PCR               | UCC               | 176          | 92    | 111     | 178 93      | 8       | 0.314  |
| rs3093030 | Cai et al.   | 2014 | Asian     | PCR               | PB                | OVC         | 215   | 153     | 37 259      | 202     | 0.068  |
|         | Lin et al.     | 2013 | Asian     | TaqMan            | PB                | OC          | 332   | 218     | 45 324      | 200     | 0.418  |
|         | Wang et al.    | 2014 | Asian     | PCR               | UCC               | 136          | 123   | 20      | 146 114     | 19      | 0.607  |
| rs281432 | Theodoropoulos et al. | 2006 | white | PCR               | PB                | CRC         | 144   | 74      | 4 158       | 40      | 0.762  |
|         | Arandi et al.  | 2008 | white     | PCR-RFLP          | PB                | BC          | 237   | 39      | 0 220       | 15      | 0.613  |
|         | Dore et al.    | 2007 | white     | PCR               | PB                | APL         | 96    | 12      | 2 100       | 7       | 0.726  |
|         | Howell et al.  | 2005 | white     | TaqMan            | HB                | CMM         | 134   | 28      | 2 222       | 35      | 0.001  |

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

| Variables (rs5491)         | Case/ control | C vs. T | OR (95% CI) | P^a | I^2 (%) | CC vs. TT | OR (95% CI) | P^a | I^2 (%) | CT vs. TT | OR (95% CI) | P^a | I^2 (%) |
|---------------------------|---------------|---------|-------------|-----|---------|-----------|-------------|-----|---------|-----------|-------------|-----|---------|
|                           |               |         |             |     |         |           |             |     |         |           |             |     |         |
| 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 | OR (95% CI) | P^a | I^2 (%) | CC vs. CT+TT | 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     |
Table 2B. Results of meta-analysis for polymorphism rs3093030 in ICAM-1 and cancer susceptibility.

| Variables (rs3093030) | OR (95% CI) | P | I² (%) | OR (95% CI) | P | I² (%) | OR (95% CI) | P | I² (%) |
|------------------------|-------------|---|--------|-------------|---|--------|-------------|---|--------|
| Total                  | 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                     | 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                    | 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                  | 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 | I² (%) | OR (95% CI) | P | I² (%) |
|------------------------|--------------|--------------|-------------|-------------|---|--------|-------------|---|--------|
| Total                  | 1.102 (0.949–1.279) | 0.225 | 9.8 | 1.079 (0.496–2.345) | 0.003 | 62.1 |
| Source of control      |             |     |        |             |     |        |             |     |        |
| PB                     | 1.119 (0.948–1.320) | 0.123 | 27.4 | 0.965 (0.346–2.693) | 0.001 | 73.8 |
| Genotyping method      |             |     |        |             |     |        |             |     |        |
| PCR                    | 1.153 (0.953–1.395) | 0.151 | 22.2 | 0.880 (0.257–3.014) | 0.001 | 73.6 |
| Ethnicity              |             |     |        |             |     |        |             |     |        |
| Asian                  | 1.137 (0.971–1.331) | 0.243 | 8.6 | 1.728 (1.234–2.421)* | 0.787 | 0.0 |

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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.

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

| Variables (rs1799969)       | C vs. T | CC vs. TT | CT vs. TT |
|-----------------------------|---------|-----------|-----------|
| Total                       | 1.662   | 1.208     | 1.860     |
|                            | (1.288–2.143)* | (0.462–3.161) | (1.398–2.474)* |
|                            | 0.141   | 0.261     | 0.507     |
|                            | 20.3    | 6.6       | 0.0       |

| Genotyping method           |         |           |           |
|-----------------------------|---------|-----------|-----------|
| PCR                         | 1.905   | 2.812     | 1.985     |
|                            | (1.327–2.735)* | (0.646–12.251) | (1.323–2.977)* |
|                            | 0.641   | 0.626     | 0.815     |
|                            | 0.0     | 0.0       | 0.0       |
|                            | 62.1%   | 62.1%     | 0%        |

| Source of control           |         |           |           |
|-----------------------------|---------|-----------|-----------|
| PB                          | 2.007   | 2.812     | 2.110     |
|                            | (1.471–2.737)* | (0.646–12.251) | (1.502–2.962)* |
|                            | 0.778   | 0.626     | 0.852     |
|                            | 0.0     | 0.0       | 0.0       |
|                            | 4.4     | 0.0       | 0.0       |

| Case/ control               | CC+CT vs. TT | CC vs. CT+TT |
|-----------------------------|--------------|--------------|
| Total                       | 1.812        | 1.095        |
|                            | (1.373–2.391)* | (0.417–2.875) |
|                            | 0.284        | 0.291        |
|                            | 4.4          | 3.6          |

| Genotyping method           |            |             |             |
|-----------------------------|------------|-------------|-------------|
| PCR                         | 2.046      | 2.423       | 0.571       |
|                            | (1.375–3.045)* | (0.560–10.478) | 0.0         |
|                            | 0.967      | 0.571       | 0.0         |
|                            | 0.0        | 0.0         | 0.0         |

| Source of control           |            |             |             |
|-----------------------------|------------|-------------|-------------|
| PB                          | 2.151      | 2.423       | 0.571       |
|                            | (1.539–3.006)* | (0.560–10.478) | 0.0         |
|                            | 0.907      | 0.571       | 0.0         |
|                            | 0.0        | 0.0         | 0.0         |
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,

| Variables (rs281432) | Case/control | C vs. T | OR (95% CI) | P | I² (%) | CC vs. TT | OR (95% CI) | P | I² (%) | CT vs. TT | OR (95% CI) | P | I² (%) |
|-----------------------|--------------|---------|-------------|---|--------|-----------|-------------|---|--------|-----------|-------------|---|--------|
| 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   |

| Variables (rs281432) | Case/control | CC+CT vs. TT | OR (95% CI) | P | I² (%) | CC vs. TC+TT | OR (95% CI) | P | I² (%) |
|-----------------------|--------------|--------------|-------------|---|--------|--------------|-------------|---|--------|
| 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   |

I² = 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 – P value of Q test for heterogeneity test; * means statistically significant (P<0.05).
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.
respectively [10,12,15]. In addition, several publications (casecontrol 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, and rs281432) 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.

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 of cases/controls | Ascertainment of exposure | Same method of ascertainment | Non-response rate |
|-------------------|-----------|----------------------------|---------------------------------|------------------------|------------------------|-------------------------------|--------------------------|---------------------------|-------------------|
| rs5491 Lin et al. | Asian     | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs3093030 Wang et al. | Asian | *                          | *                               | *                      | NA                     | *                             | *                        | *                        |                   |
| Chen et al. | African | *                          | NA                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs3093030 Cai et al. | Asian | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs3093030 Lin et al. | Asian | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs3093030 Han et al. | white   | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs3093030 Wang et al. | Asian | *                          | NA                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs281432 Cai et al. | Asian | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs281432 Lin et al. | Asian | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs281432 Wang et al. | Asian | *                          | NA                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs1799969 Theodoropoulos et al. | white | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs1799969 Arandi et al. | white | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs1799969 Dore et al. | white | *                          | *                               | *                      | **                     | *                             | *                        | *                        |                   |
| rs1799969 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).
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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