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Review Article

Intercellular Adhesion Molecule-1 (ICAM-1) Polymorphisms and Cancer Risk: A Meta- Analysis

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Abstract

Background: Intercellular adhesion molecule-1 (ICAM-1) Lys469Glu (K469E) polymorphism and Gly 241Arg (G241R) polymorphism might play important roles in cancer development and progression. However, the results of previous studies are inconsistent. The aim of this study was to evaluate the association between ICAM-1 K469E and G241R polymorphisms and the risk of cancer by meta-analysis.

Methods: A comprehensive literature search (last search updated in November 2013) was conducted to identify case-control studies that investigated the association between ICAM-1 K469E and G241R polymorphisms and cancer risk.

Results: A total of 18 case-control studies for ICAM-1 polymorphisms were included in the meta-analysis, including 4,844 cancer cases and 5,618 healthy controls. For K469E polymorphism, no significant association was found between K469E polymorphism and cancer risk. However, subgroup analysis by ethnicity revealed one genetic comparison (GG vs. AA) presented the relationship with cancer risk in Asian subgroup, and two genetic models (GG+GA vs. AA and GA vs. AA) in European subgroup, respectively. For G241R polymorphism, G241R polymorphism was significantly association with cancer risk in overall analysis. The subgroup analysis by ethnicity showed that G241R polymorphism was significantly associated with cancer risk in European subgroup.

Conclusion: ICAM-1 G241R polymorphism might be associated with cancer risk, especially in European populations, but the results doesn't support ICAM-1 K469E polymorphism as a risk factor for cancer.

Keywords: Intercellular adhesion molecule-1, Polymorphism, Cancer, Meta-analysis

Introduction

The term "adhesion molecules" refers to those cell surface structures that allow cells to adhere to each other and the extracellular matrix. Cell adhesion molecules (CAMs) enable cancer-related biological processes like survival, detachment, migration, extravasation, and metastasis, and thus play a crucial role in tumorigenesis, tumor progression, and metastasis (1, 2). Apart from regulating cell-cell and cell-matrix interactions, CAMs also influence cell motility, signalling, and differentiation, apoptosis, and gene transcription (3). Five families of cell adhesion molecules (CAMs) have been identified, which include cadherins, integrins, immunoglobulin superfamily, selectins, and CD44 (4). To date, reduced, absent, or disorganized expression of CAMs has been observed in a variety of human tumor, including breast, lung, gastric, bladder, prostate, head and neck, and colorectal cancer (5, 6).

ICAM-1 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily of CAMs (7). ICAM-1 is normally expressed on the surface of various types of cells: leukocytes, endothelial cells, and fibroblasts (8, 9). There is mounting evi-

dence demonstrating that ICAM-1 is also expressed on the surface of many cancer cell types (10-13). It has also been proposed that ICAM-1 may be involved in the process of cancer metastases, facilitating the spread of metastatic cancer cells to secondary sites (9). Moreover, increased ICAM-1 expression enhances tumor growth, while altered ICAM-1 expression could be caused by genetic variation (14).

The *ICAM-1* gene, located in chromosome 19p13, has at least two functional biallelic polymorphisms. These two single nucleotide polymorphisms (SNPs), previously described in *ICAM-1* gene at codons 241(glycine to arginine substitution; G to A; rs1799969) in exon 4 and 469 (a lysine to glutamic acid substitution; A to G; rs5498) in exon 6, were also shown to modulate the susceptibility for several types of cancers including prostate (15), colorectal (16) and breast cancers (17). Recent genome-wide association study has demonstrated a strong correlation between K469E polymorphism and ICAM-1 levels (18). ICAM-1 G241R polymorphism has been demonstrated to be of importance in binding to the Mac-1 form of leucocyte integrin (19), and therefore affect the adhesive function of ICAM-1.

A growing number of studies have studied the relationship between *ICAM-1* gene polymorphisms and tumor susceptibility, but their results remain inconsistent. This lack of consistency might be attributable to the presence of genetic heterogeneity across ethnic populations, small sample size limitations, and publication bias.

Therefore, to confirm the role of the *ICAM-1 K469E and G241R* polymorphisms in tumorigenesis, we conducted a comprehensive meta-analysis on eligible case-control studies published to date. To the best of our knowledge, this is the most comprehensive meta-analysis regarding the *ICAM-1 K469E and G241R* polymorphisms and their association with cancer risk.

Materials and Methods

Search Strategy

A comprehensive literature search of PubMed, Embase, Web of Science, Science Direct, SpringerLink, EBSCO, Wanfang, and Chinese National Knowledge Infrastructure databases (last search updated in November 2013) was conducted to identify case-control studies that investigated the association between *ICAM-1 K469E and G241R* polymorphisms and cancer risk. The search terms were as follows: "cancer or carcinoma or neoplasm or tumor" in combination with "ICAM-1 or CD54" in combination with "polymorphism or variant or mutation." There was no restriction on period, sample size, population, language, or type of report for minimizing potential publication bias. We evaluated potentially relevant genetic association studies by examining their titles and abstracts, and all published studies matching with the eligible criteria were retrieved.

Inclusion and exclusion criteria

Studies included in the meta-analysis were required to meet the following criteria: 1) Case-control studies which evaluated the association between *ICAM-1 K469E and/or G241R* polymorphisms and cancer risk; 2) study design: either retrospective or nested case-control design; 3) any diagnoses of patients with cancer had to be confirmed by pathological examinations; and 4) independent variables: the genotype and/or allele counts of *ICAM-1 K469E* polymorphism or G241R polymorphism. The exclusion criteria of the meta-analysis were: 1) case-control studies not focusing on the correlation between *ICAM-1 K469E and G241R* polymorphisms and cancer risk; 2) studies with duplicate data; 3) studies based on incomplete data; and 4) meta-analyses, letters, reviews and editorial articles. When an individual author published several articles obtained from the same patient population, only the newest or most complete article was included in the analysis.

Data extraction

The data from the published studies were extracted independently by two reviewers (D Cheng and B Liang). The following information was collected from each study: first author's name, year of publication, country of origin, ethnicity, cancer type, genotyping method, source of controls,

number of cases and controls, genotype frequency in cases and controls, and Hardy-Winberg equilibrium (HWE). In case of discrepancies, a consensus on each item was reached among the authors.

Statistical analysis

Crude odds ratios (ORs) together with their corresponding 95% CIs were used to assess the strength of association between *ICAM-1 K469E or G241R* polymorphisms and the risk of cancer. Allele model (mutation (M) allele versus wild (W) allele), dominant model (WM+MM versus WW), recessive model (MM versus WM+WW), homozygote comparison (MM versus WW), and heterozygote comparison (WM versus WW) were evaluated, respectively. Subgroup analyses were done by ethnicity (Asian, European, and America).

Between-study heterogeneity was assessed by calculating Q-statistic (Heterogeneity was considered statistically significant if $P < 0.10$)(20) and quantified using the I^2 value (I^2< 25% represents no heterogeneity, I^2= 25–50% represents moderate heterogeneity, I^2= 50–75% represents large heterogeneity, and I^2 >75% represents extreme heterogeneity) (21). If results were not heterogeneous, the pooled ORs were calculated by a fixed-effect model; otherwise, a random-effect model was used. The significance of the combined ORs was determined by the Z-test, in which P<0.05 was considered significant. Moreover, relative influence of each study on the pooled estimate was assessed by excluding a single study each time for sensitivity analysis. Begg's funnel plots (22) and Egger's linear regression test (23) were used to evaluate publication bias. All statistical analyses were performed using STATA version 12.0 (STATA Corporation, College Station, TX).

Results

Characteristics of Eligible Studies

The flow chart that displays the study selection process was shown in Fig. 1. In accordance with the inclusion criteria, 16 articles containing 18 case-control studies were included in the meta-analysis, including 4,844 cancer cases and 5,618 healthy controls. There were 18 case-control studies concerning ICAM-1 K469E polymorphism (15-17, 24-35), and 6 case-control studies concerning ICAM-1 G241R (24, 27-30, 33). For ICAM-1 K469E polymorphism, seven studies were conducted in European populations, six in Asian populations, four in America populations, and one in Oceania populations. Moreover, there were four studies of European populations (28-30, 33), one study of Asian populations (24), and one study of America populations (27) for ICAM-1 G241R polymorphism. The genotype distributions among the controls of all studies were in agreement with HWE except for two studies for K469E (27, 31) and one study for G241R (33). The detailed characteristics of the eligible studies included in this meta-analysis were shown in Table 1.

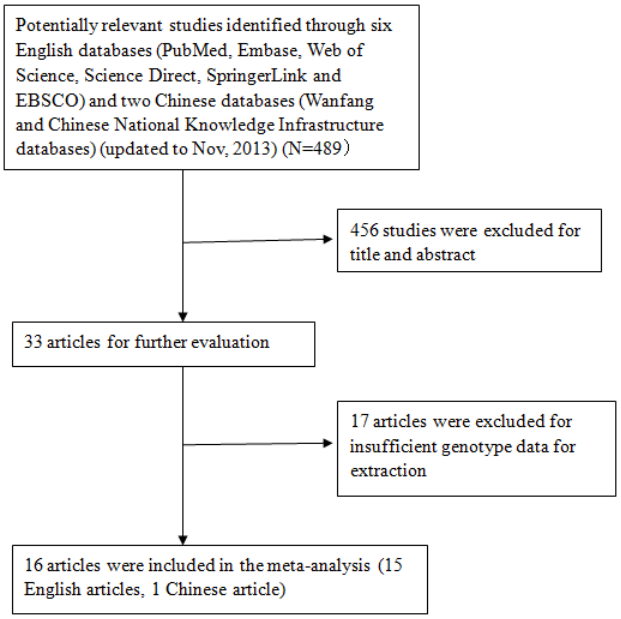

Fig. 1: Flow chart showing study selection procedure

Quantitative data synthesis

Results of this meta-analysis were shown in Table 2.

ICAM-1 K469E polymorphism

In the overall analysis, we did not find any significant association between ICAM-1 K469E polymorphism and the risk of cancers in all

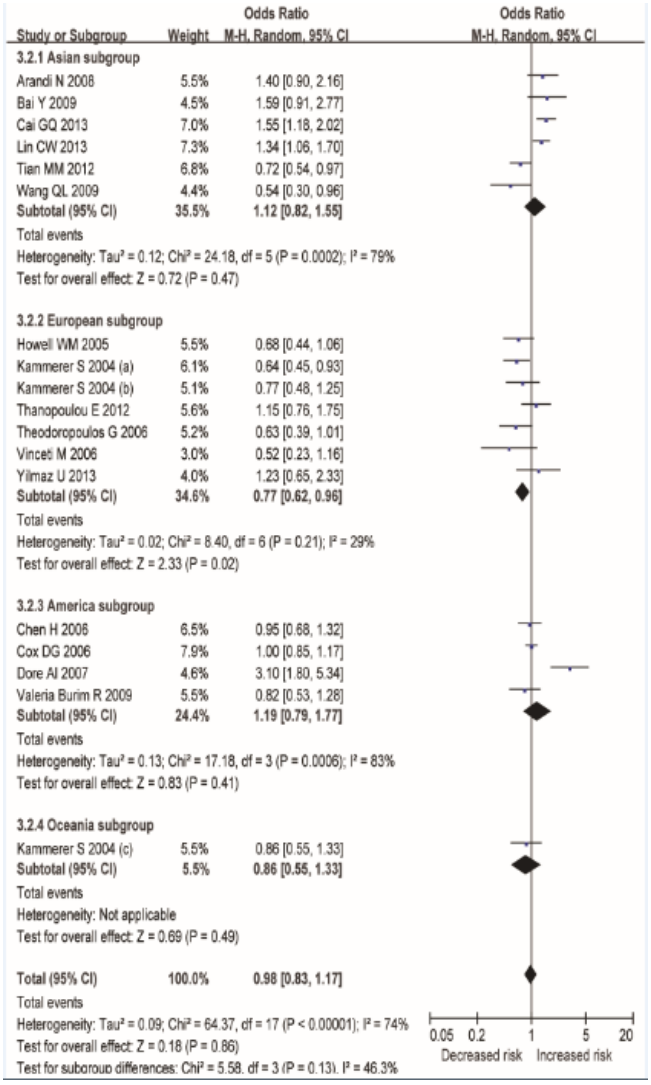

Fig. 2: Meta-analysis with a random-effects model for the association between the risk of cancer and ICAM-1 K469E polymorphism (dominant model: GG + GA vs. AA)

comparison models (G allele vs. A allele: OR= 1.03, 95% CI=0.89-1.19, *P*=0.66; GG+GA vs. AA: OR= 0.98, 95% CI= 0.83-1.17, *P*=0.86; GG vs. GA+AA: OR= 1.09, 95% CI=0.87-1.37, *P*=0.44; GG vs. AA: OR= 1.15, 95% CI=0.84-1.56, *P*=0.38; GA vs. AA: OR= 0.95, 95% CI=0.82-1.11, *P*=0.53) (Fig.2). The results suggested that the ICAM-1 K469E polymorphism may be not associated with overall cancer risk.

As shown in Table 2, in the subgroup analysis by ethnicity, we found a significant association under homozygous comparison (GG vs. AA: OR=1.53, 95 % CI=1.03-2.27, *P*=0.03) in Asian subgroup. Moreover, there was significant association under dominant model (GG+GA vs. AA: OR=0.77, 95 % CI=0.62-0.96, *P*=0.02) and heterozygous comparison (GA vs. AA: OR=0.77, 95 % CI=0.64-0.93, *P*<0.01) in European subgroup. No significant associations were found in the other models in Asian subgroup and European subgroup. There was no significant association between ICAM-1 K469E polymorphism and cancer risk under all models in America subgroup (all *P*>0.05). In addition, there was a tendency that the GG genotype was associated with a higher risk for cancer in Asian subgroup and America subgroup (OR>1.0 under all comparison models); however, G-containing genotypes, GG/GA, were associated with decreased risk for cancer in European subgroup (OR<1.0 under all comparison models).

ICAM-1 G241R polymorphism

A total of 921 cases and 955 controls from 6 case-control studies on the correlation of ICAM-1 G241R polymorphism and cancer risk were included for data synthesis. In general, the overall analysis revealed ICAM-1 G241R polymorphism seemed to be associated with cancer risk (A allele vs. G allele: OR= 2.21, 95% CI=1.31-3.74, *P*<0.01; AA+AG vs. GG: OR= 2.16, 95% CI= 1.37-3.43, *P*<0.01; AA vs. GG: OR= 2.45, 95% CI=1.12-5.35, *P*=0.02; AG vs. GG: OR= 2.03, 95% CI=1.54-2.67, *P*<0.01) (Fig. 3).

Subgroup analysis by ethnicity showed that ICAM-1 G241R polymorphism was associated with the risk of cancer in European populations (A allele vs. G allele: OR= 2.46, 95% CI=1.06-5.69, *P*=0.04; AA+GA vs. GG: OR= 2.38, 95% CI= 1.12-5.08, *P*=0.02; GA vs. GG: OR= 1.95, 95% CI=1.41-2.70, *P*<0.01).

Sensitivity analysis

In order to assess the stability of the results of the meta-analysis, sensitivity analysis was performed by sequentially excluding each study. Statistically similar results were obtained after sequentially excluding each study, suggesting the stability of this meta-analysis.

Table 1: Baseline characteristics of the 18 eligible studies for the analysis of ICAM-1 K469E and G241R polymorphisms

Reference	Year	Country	Ethnicity	Cancer type	Source of controls	Sample size	SNP studied	Genotyping method	HWE
(24)	2008	Iran	Asian	Breast	HB	276/235	K469E G241R	PCR-RFLP	0.556 0.613
(25)	2013	China	Asian	Ovarian	HB	408/520	K469E	MassARRAY	0.651
(15)	2006	USA	America	Prostate	HB	286/391	K469E	PCR-RFLP	0.290
(26)	2006	USA	America	Breast	HB	104/102	K469E	PCR-sequencing	0.978
(27)	2007	Brazil	America	Leukemia	HB	127/249	K469E G241R	Nested-PCR	0.002 0.726
(16)	2009	China	Asian	Colorectal	HB	87/102	K469E	PCR-SSP	0.499
(28)	2006	Greece	European	Colorectal	HB	222/200	K469E G241R	PCR-sequecing	0.261 0.762
(29)	2013	Turkey	European	Brain	HB	92/92	K469E G241R	PCR-RFLP	0.246 0.958
(30)	2006	Italy	European	Melanoma	PB	59/59	K469E G241R	PCR-RFLP	0.068 0.838
(17)	2004	German	European	Breast	HB	242/265	K469E	MassEXTEND	0.822
(17)	2004	German	European	Breast	HB	178/142	K469E	MassEXTEND	0.511
(17)	2004	Australia	Oceania	Breast	PB	167/170	K469E	MassEXTEND	0.234
(31)	2009	Brazil	America	Astrocytomas	HB	158/162	K469E	PCR-RFLP	0.010
(32)	2012	Greece	European	Lung	HB	203/175	K469E	PCR-RFLP	0.854
(33)	2005	UK	European	Melanoma	PB	151/224	K469E G241R	PCR-sequencing	0.768 <0.001
(34)	2013	Taiwan	Asian	Oral	HB	595/561	K469E	PCR-sequencing	0.403
(35)	2012	China	Asian	Gastric	HB	332/380	K469E	PCR-sequencing	0.079
(36)	2009	China	Asian	Oral	HB	112/98	K469E	PCR-RFLP	0.602

PB, population-based controls, HB, hospital-based controls. HWE, Hardy–Weinberg equilibrium. PCR, polymerase chain reaction; SSP, sequence-specific primers; RFLP, restriction fragment length polymorphism

Table 2: ICAM-1 K469E and G241R polymorphisms and cancer risk

	Allele model		Dominant model		Recessive model		Homozygous comparison		Heterozygous comparison	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
K469E	**G allele vs. A allele**		**GG+GA vs. AA**		**GG vs. AA+GA**		**GG vs. AA**		**GA vs. AA**	
Overall	1.03 (0.89-1.19)	0.66	0.98 (0.83-1.17)	0.86	1.09 (0.87-1.37)	0.44	1.15 (0.84-1.56)	0.38	0.95 (0.82-1.11)	0.53
Asian	1.16 (0.91-1.47)	0.22	1.12 (0.82-1.55)	0.47	1.20 (0.92-1.57)	0.18	1.53 (1.03-2.27)	0.03	1.04 (0.76-1.42)	0.81
European	0.87 (0.73-1.03)	0.11	0.77 (0.62-0.96)	0.02	0.91 (0.70-1.18)	0.49	0.79 (0.56-1.12)	0.19	0.77 (0.64-0.93)	<0.01
America	1.19 (0.78-1.81)	0.41	1.19 (0.79-1.77)	0.41	1.38 (0.51-3.78)	0.53	1.52 (0.47-4.90)	0.49	1.09 (0.82-1.44)	0.55
G241R	**A allele vs. G allele**		**AA+AG vs. GG**		**AA vs. GG+AG**		**AA vs. GG**		**AG vs. GG**	
Overall	2.21 (1.31-3.74)	<0.01	2.16 (1.37-3.43)	<0.01	2.22 (1.02-4.86)	0.05	2.45 (1.12-5.35)	0.02	2.03 (1.54-2.67)	<0.01
European	2.46 (1.06-5.69)	0.04	2.38 (1.12-5.08)	0.02	2.06 (0.91-4.65)	0.08	2.28 (1.01-5.15)	0.05	1.95 (1.41-2.70)	<0.01

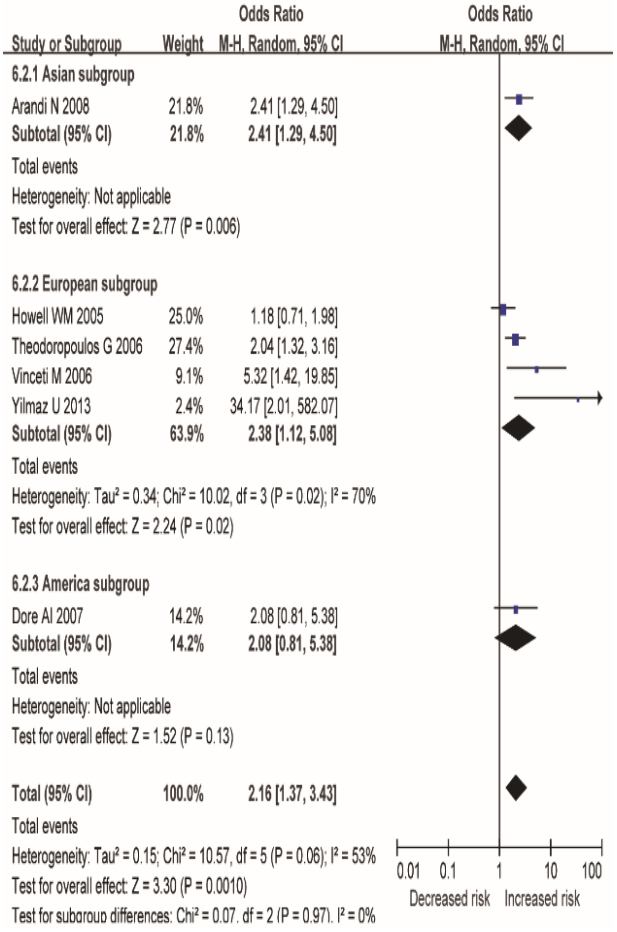

Fig.3: Meta-analysis with a random-effects model for the association between the risk of cancer and ICAM-1 G241R polymorphism (dominant model: AA + AG vs. GG)

Publication bias

In this meta-analysis, we performed Begg's funnel plot and Egger's test to access the publication bias. The shape of the funnel plots did not reveal any evidence of obvious asymmetry under all contrast models for ICAM-1 K469E and G241R (Fig.4). In addition, the *P* value of Egger's test was 0.633 for ICAM-1 K469E polymorphism, and 0.704 for ICAM-1 G241R polymorphism under the allele model, respectively, providing statistical evidence of funnel plot's symmetry. Therefore, the results revealed that publication bias was not significant in this meta-analysis.

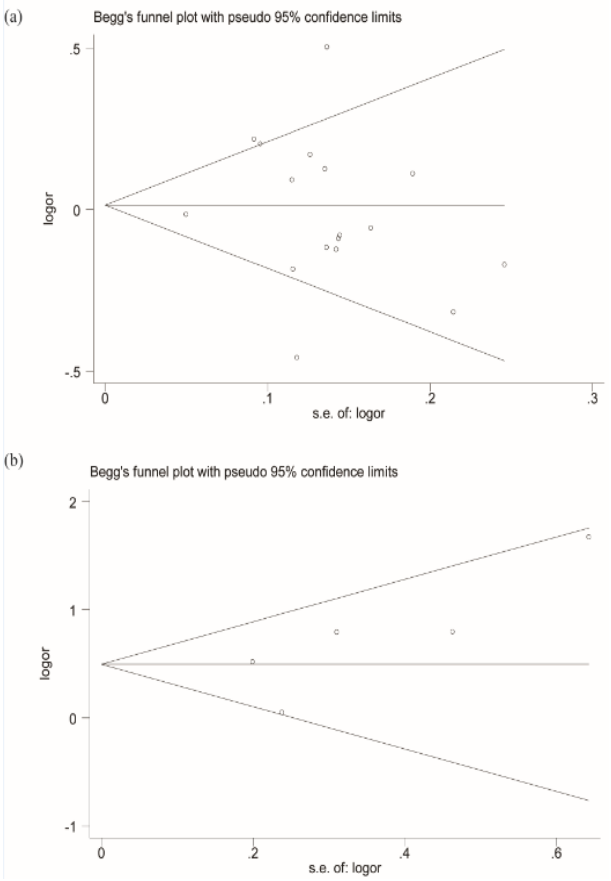

Fig. 4: Begg's funnel plot for publication bias test. Each point represents an independent study for the indicated association under the allele model. (a) ICAM-1 K469E polymorphism, (b) ICAM-1 G241R polymorphism

Discussion

To the best of our knowledge, our meta-analysis represents the most comprehensive investigation on the association between ICAM-1 K469E and G241R polymorphisms and cancer risk. The results suggested that ICAM-1 K469E polymorphism was not associated with cancer susceptibility. Since demographic characteristics influence genotype frequencies, different races have different gene-environment interaction models. Therefore, we conducted a subgroup analysis according to ethnic differences, and the results indicated that there was a significant association between K469E polymorphism and decreased cancer risk in Euro-

pean populations, while there were not significant associations in Asian populations and America population. Moreover, ICAM-1 G241R polymorphism displayed significant association with cancer risk, especially in European populations.

Recent studies demonstrated that ICAM-1 possibly contributes to tumorigenesis and metastasis (12, 36, 37). The potential involvement of ICAM-1 expression in cancer invasion and metastasis was reported in melanomas, pancreatic, lung, and oral cancers (34). Conversely, some studies indicated that increased ICAM-1 expression was correlated with a more favorable prognosis in gastric, breast, and colorectal cancers under the influence of the host immunosurveillance system (38-40). The progression of most cancers is resulted from the interaction of environmental and genetic factors. It is well known that genetic variants in the pathway of the pathogenesis of cancer may alter protein function and individual's susceptibility to cancer. Thus, polymorphism within the ICAM-1 gene likely played a significant role in the susceptibility to and development of cancer. While several genetic polymorphisms have been indentified in ICAM-1, the frequently investigated two polymorphisms in several types of cancer involve the K469E and G242R polymorphisms, due to their functional implications in the ICAM-1 protein. ICAM-1 K469E polymorphism is located three bases upstream of ICAM-1 mRNA splicing site that influence RNA splicing patterns (31). This region seems to be particularly important for the dimerization of ICAM-1. Compared to ICAM-1 monomers, ICAM-1 dimers exhibit enhanced binding to lymphocyte function-associated protein-1 Therefore, the amino acid exchange might diminish ICAM-1 dimerization and in turn lead to decreased integrin receptor binding, thus affecting ICAM-1 function (41). G241R polymorphism is located in exon 4, which has been shown to be of importance in binding to the Mac-1 form of the leukocyte integrin. The interaction between Mac-1 and ICAM-1 makes an important contribution to leukocyte adhesion in the execution of immunological and inflammatory functions and may play a role in regulating localization of leukocytes (42). G241R polymorphism can modify the functional activity of the ICAM-1 molecule leading to a different recruitment and activation of the inflammatory cells (43). In our study, ICAM-1 G241R polymorphism, but not K469E, was significantly associated with cancer risk. Given the difference, it is reasonable to speculate that the substitution (G to A) in G241R site could have functional significance in the progression of cancer by affecting the adhesive function of ICAM-1.

The result in the subgroup analysis demonstrated that ICAM-1 G241R polymorphism was associated with cancer risk in European populations. As for ICAM-1 K469E, the results indicated that GG genotype was associated with a higher risk of cancer in Asian subgroup; however, G-containing genotypes, GG/GA, were associated with decreased risk for cancer in European subgroup. The differences may be explained by genetic diversities, different risk factors in life styles, and the exposure to different environmental factors (44). The identification of susceptibility genes in cancer patients of different ethnicities provides an opportunity to explore new mechanisms of disease that are specific in different populations.

On the other hand, limitation of this meta-analysis should also be noted. First, heterogeneity can interfere with the interpretation of the results of a meta-analysis, which was unavoidable when combing many studies. Variation in the environmental and genetic background of study participants may contribute to the heterogeneity. Second, small number of included studies may decrease statistical power and even may produce a fluctuated risk estimate. Therefore, this relationship needs to be further confirmed in larger size, well-designed prospective studies. Third, the interaction of different susceptibility genes and environment factors leaded to the disease, but our study could not assess gene-gene and gene-environment interactions due to the limited information of included studies. Forth, only studies published were included in the meta-analysis, and non-significant or negative findings may be unpublished. Hence, some inevitable publication biases might exist in the results.

Conclusion

This meta-analysis suggested that ICAM-1 G241R polymorphism might be a genetic risk factor for the development of cancer, especially in European populations. In addition, ICAM-1 K469E polymorphism might not act as a cancer risk factor among all subjects. However, subgroup analysis revealed one genetic model (GG vs. AA) presented the relationship with cancer risk in Asian subgroup, and two genetic models (GG+GA vs. AA and GA vs. AA) in European subgroup, respectively. Further studies with large sample size, standardized unbiased genotyping methods, homogeneous cancer patients, well-matched controls and multiethnic groups would be warranted.

Ethical considerations

Ethical issues (Including plagiarism, informed consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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