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CXCL12 G801A POLYMORPHISM CONTRIBUTES TO CANCER SUSCEPTIBILITY: A META-ANALYSIS

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Abstract

CXCL12 is an important alpha-chemokine that regulates many essential biological processes including tumor development and metastasis. The CXCL12 G801A polymorphism is associated with multiple kinds of malignant cancer, but the associations are inconsistent. To derive a more precise estimation of the relationship, we conducted a meta-analysis of 16 publications with 2,888 cases and 3,611 controls. We used the odds ratio (OR) corresponding to 95% confidence interval (CI) to estimate the strength of association. The increased risk of overall cancer was found in the homozygote comparison (AA vs. GG, OR=1.43, 95%CI=1.07-1.91), the recessive model (AA vs. GG+GA, OR=1.26, 95%CI=1.03-1.54), and the dominant model (GA+AA vs. GG, OR=1.35, 95%CI=1.15-1.58). In the stratified analyses, the associations were significant in breast cancer, Asians and hospital-based controls. In conclusion, this meta-analysis suggests that the CXCL12 G801A polymorphism may be a risk factor of cancer, especially in the subgroups of breast cancer, Asians and hospital-based controls.

Key words: CXCL12, polymorphism, cancer, meta-analysis.

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INTRODUCTION

Chemokines are a large family of polypeptide signaling molecules that bind to specific seven-transmembrane receptors linked to G proteins (30, 33), which can lead to signal transduction events, including the generation of inositol triphosphate, the activation of protein kinases and proteins of the ras and rho families, and the release of intracellular calcium (26). Chemokines have recently been implicated in tumor progression and metastasis (33).

CXCL12, also known as stromal cell-derived factor-1 (SDF-1), is located on chromosome 10q11.1 (41). It is an important alpha-chemokine expressed in various organs (32). CXCL12 primarily binds to the CXC receptor 4 (CXCR4, CD184), and can also bind to CXC receptor 7(CXCR7, RDC1) (42). It regulates many essential biological processes, including mobilizing hematopoietic stem cells (18), facilitating the development of cardiac, neuronal, vascular, and craniofacial systems during embryogenesis (29), participating in immunity and inflammation processes (3), and participating in HIV infection (2). It has also been reported that CXCL12 is involved in tumor development and metastasis (4).

The CXCL12 gene has a guanine to adenine (G→A) mutation at position 801 in its 3'-untranslated region, resulting in a CXCL12 gene single nucleotide polymorphism (SNP) (rs1801157) (31, 35) with a significant regulatory function. The polymorphism is associated with multiple kinds of malignant cancer, such as breast cancer (25), colorectal cancer (14, 19), and bladder cancer (46). However, the associations of these studies are inconsistent. A single study may not be able to detect the real associations between gene polymorphism and cancer risk, especially when the sample size is relatively small. Thus, we conducted a meta-analysis to evaluate the association of CXCL12 G801A polymorphism with cancer risks.

MATERIALS AND METHODS

Publication search and selection criteria

We carried out a search in PubMed and Chinese National Knowledge Infrastructure (CNKI) databases to identify all relevant papers published to date on the association between the CXCL12 G801A polymorphism with cancer risks, with the subject terms: ''CXCL12'' or ''SDF-1'', ''polymorphism'', and ''cancer'' or ''carcinoma'' or ''neoplasm'' (the last search update was May, 2011). The references cited in the original studies or review articles were retrieved on this topic by manual search. Studies included in the meta-analysis had to meet the following criteria: (a) use an unrelated case-control design, (b) evaluate the association of the CXCL12 G801A polymorphism and cancer risks, (c) the genotype frequencies for both patients and control populations should be available, (d) the genotype of the control population must be in Hardy-Weinberg equilibrium. When a study reported results on several tumor types, we treated each tumor type as a distinct comparison.

Data extraction

Data was extracted by two investigators from the studies independently, and an agreement was reached after a discussion. The following information was collected from the studies: first author, year of publication, ethnicity, cancer type, control source, total number of cases and controls,

and genotype frequency for cases and controls. Different ethnicity descents were classified as Caucasian, Asian, and Mixed.

Statistical methods

We used the odds ratio (OR) corresponding to 95% confidence interval (CI) to estimate the strength of association between CXCL12 polymorphism and cancer. The significance of the pooled OR was determined by the Z-test, and $P<0.05$ was considered as statistically significant. In meta-analysis, we investigated the associations using homozygote comparison (AA vs. GG), the recessive model (AA vs. GG+GA), and the dominant model (GA+AA vs. GG). Subgroup analysis was performed by cancer type, ethnicity, and study design.

Hardy-Weinberg equilibrium (HWE) was tested by the chi-square test among controls, and $P<0.05$ was considered departure from HWE. Heterogeneity between studies was tested by the chi-square-based Q-test. If $P<0.05$ (13), indicating there was a heterogeneity among the studies, the random-effects model was used (the DerSimonian and Laird method) (12). Otherwise, the fixed-effects model was more appropriate (the Mantel-Haenszel method) (28).

Sensitivity analyses were performed to assess the stability of the results where a single study in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled ORs. Funnel plots were used to access publication bias by the method of Egger's linear regression test, and $P<0.05$ was used as an indication for possible publication bias (16). All analyses were done with Stata 11.0 (StataCorpLP, College Station, TX). *P* values were two-sided.

RESULTS

Study characteristics

This study focused on the association between CXCL12 G801A polymorphism and cancer risk. A total of 42 candidate publications were retrived from PubMed and CNKI, of which 26 publications were eligible for further evaluation. Then, three studies were excluded because of departure from HWE (*P* value<0.05) (5, 43, 44), three were excluded because they were not case-control studies (6, 17, 38), and four publications were deleted for the lack of genotype frequency (7, 15, 27, 34). Two publications (11, 49), involving three different cancers, were defined as three studies in the analysis stratification by tumor type. In one publication, controls were shared by different cancers, therefore it was defined as one study in the subgroup analyses of ethnicity and control-source. Overall, a total of 2,888 cancer patients and 3,611 controls available from 16 publications including 20 data sets were investigated; the details were listed in Table 1. There were 6 studies of breast cancer, the remaining was defined as other cancers. Ten studies were Caucasians, six studies were Asians and one was Mixed. The controls were mainly healthy populations and matched for sex and age.

Meta-analysis results

Overall, as shown in Table 2, the CXCL12 G801A polymorphism was associated with increased risk of cancer in the homozygote comparison (AA vs. GG, OR=1.43, 95%CI=1.07-1.91) (Fig. 1), the recessive model (AA vs. GG+GA, OR=1.26, 95%CI=1.03-1.54), and the dominant model (GA+AA vs. GG, OR=1.35, 95%CI=1.15-1.58).

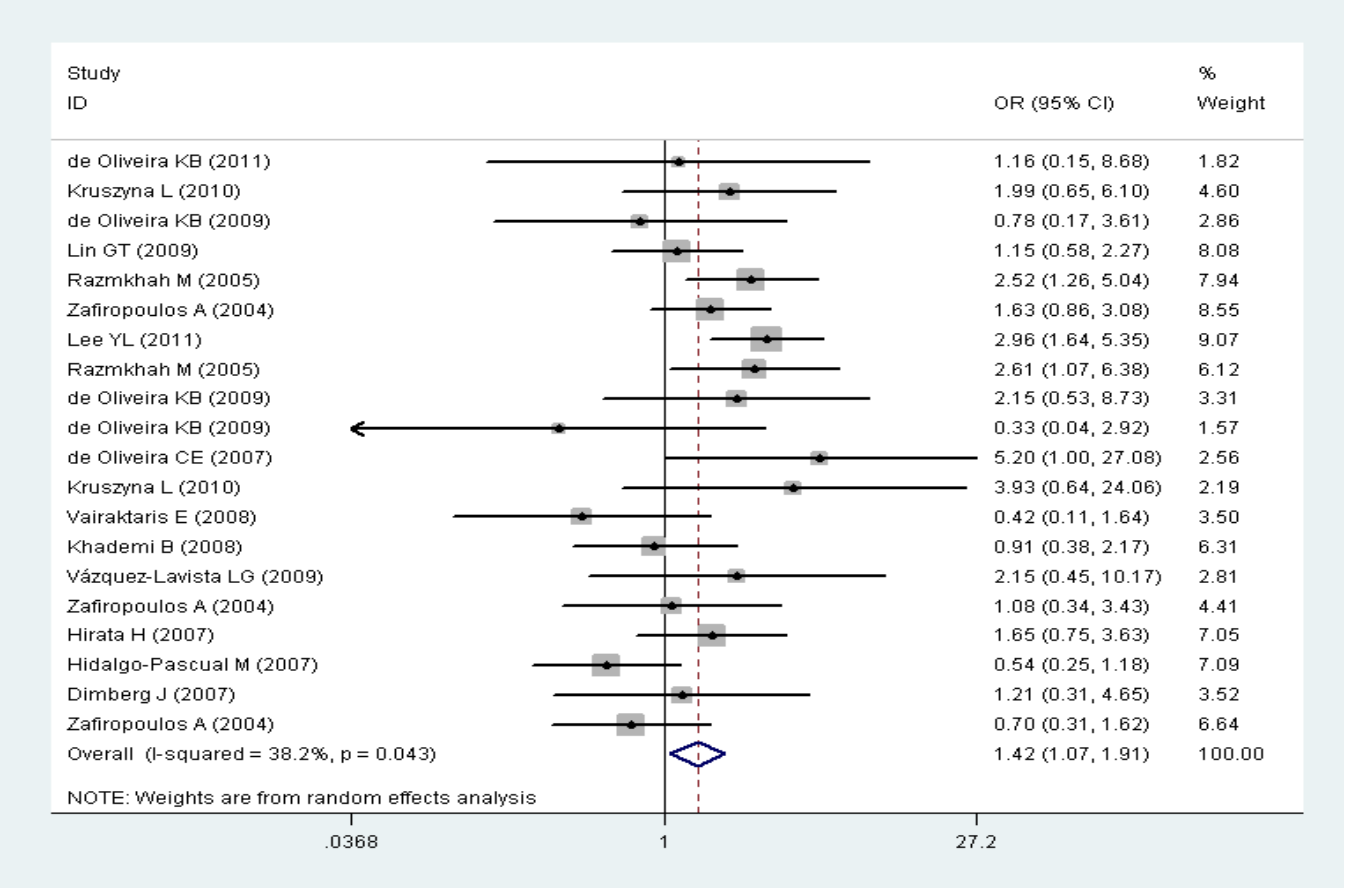

Figure 1. Forest plot of cancer risk associated with CXCL12 G801A polymorphism (AA vs. GG). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the pooled OR and 95% CI.

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

Author	Year	Ethnicity	Control source	Cancer type	Case/control	Case			Control			HWE
						G/G	G/A	A/A	G/G	G/A	A/A	
de Oliveira (10)	2011	Caucasian	Hospital-based	Breast	55/54	58.2	38.2	3.6	68.5	27.8	3.7	0.758
Lee (24)	2011	Asian	Hospital-based	NSCLC	247/328	40.0	45.0	15.0	52.0	42.0	6.0	0.379
Kruszyna (22)	2010	Caucasian	Population-based	Breast	193/199	63.7	31.6	4.7	68.3	29.1	2.5	0.686
de Oliveira (11)	2009	Caucasian	Hospital-based	Breast	103/97	57.3	39.8	2.9	62.9	33.0	4.1	0.939
de Oliveira (11)	2009	Caucasian	Hospital-based	HL	36/90	51.4	47.1	1.4	65.6	28.9	5.6	0.356
de Oliveira (11)	2009	Caucasian	Hospital-based	NHL	70/90	61.1	27.8	11.1	65.6	28.9	5.6	0.356
Kruszyna (23)	2010	Caucasian	Population-based	Laryngeal	118/250	58.0	39.0	3.0	72.0	67.0	1.0	0.114
Vázquez-Lavista (46)	2009	Mixed	Population-based	Bladder	47/126	61.7	31.9	6.4	65.9	31.0	3.2	0.822
Lin (25)	2009	Asian	Hospital-based	Breast	220/334	48.2	44.5	7.3	52.4	40.7	6.9	0.621
Khademi (21)	2008	Asian	Hospital-based	Head,Neck	156/262	41.0	53.8	5.2	55.3	37.0	7.7	0.504
Vairaktaris (45)	2008	Caucasian	Population-based	Oral	159/101	65.4	32.0	2.5	54.5	40.6	5.0	0.448
Hidalgo-Pascual (19)	2007	Caucasian	Population-based	Colorectal	349/596	60.7	36.7	2.6	61.8	33.3	4.8	0.770
Hirata (20)	2007	Asian	Hospital-based	Prostate	167/167	43.0	47.0	10.0	54.0	38.0	8.0	0.651
de Oliveira (9)	2007	Caucasian	Hospital-based	CML	25/60	0.4	0.4	0.2	0.7	0.3	0.1	0.628
Dimberg (14)	2007	Caucasian	Hospital-based	Colorectal	151/141	55.6	41.1	3.3	57.5	39.7	2.8	0.117
Razmkhah (37)	2005	Asian	Hospital-based	Breast	278/181	37.8	50.0	12.2	55.8	37.0	7.2	0.682
Razmkhah (36)	2005	Asian	Hospital-based	Lung	72/262	34.7	52.8	12.5	55.3	37.0	7.7	0.504
Zafiropoulos (49)	2004	Caucasian	Population-based	Breast	264/212	37.1	51.5	11.3	47.6	43.3	9.0	0.764
Zafiropoulos (49)	2004	Caucasian	Population-based	Skin	110/363	58.1	34.5	7.2	46.5	45.2	8.3	0.262
Zafiropoulos (49)	2004	Caucasian	Population-based	Bladder	68/148	45.5	47.1	7.4	45.3	48.0	9.7	0.124

NSCLC: non-small cell lung cancer. HL: Hodgkin's lymphoma. NHL: Non-Hodgkin's lymphoma. CML: chronic myelogenous leukemia.

Table 2. Stratified analysis of the *CXCL12* G801A polymorphism on cancer risk.

Subgroup	N[a]	Cases/controls	AA vs GG		GA/AA vs GG		AA vs GA/GG	
			OR(95% CI)	P*h*[b]	OR(95% CI)	P*h*[b]	OR(95% CI)	P*h*[b]
All	20	2888/3611	1.43(1.07-1.91)	0.04	1.35(1.15-1.58)	0	1.26(1.03-1.54)	0.17
Cancer type								
Breast cancer	6	1113/1077	1.63(1.15-2.30)	0.6	1.48(1.22-1.72)	0.33	1.35(0.96-1.88)	0.79
Others	14	1775/2746	1.35(0.89-2.05)	0.01	1.31(1.05-1.63)	0	1.21(0.94-1.56)	0.05
Ethnicity								
Asian	6	1140/1534	1.87(1.41-2.53)	0.14	1.65(1.41-1.94)	0.24	1.50(1.13-1.98)	0.14
European	10	1748/2077	0.98(0.68-1.41)	0.14	1.13(0.88-1.45)	0.01	0.98(0.68-1.42)	0.29
Control source								
Hospital-based	11	1580/1976	1.83(1.40-2.40)	0.31	1.56(1.36-1.80)	0.28	1.49(1.15-1.93)	0.35
Population-based	6	1308/1635	0.86(0.56-1.32)	0.12	1.02(0.74-1.40)	0.01	0.89(0.59-1.36)	0.19

[a]number of studies.

[b]*P*-value of Q-test for heterogeneity test.

In the subgroup analysis by cancer type, a significant increased risk was found in breast cancer (OR=1.63, 95%CI=1.15-2.30 for AA vs. GG), the association was found in the dominant model (GA+AA vs. GG, OR=1.31, 95%CI=1.05-1.63) in other cancers. In the stratified analysis based on ethnicity, there was increased risk in Asians, but not Caucasians. When stratifying for study design, the polymorphism had an increased risk in the hospital-based controls (OR=1.56, 95%CI=1.36-1.80 for GA+AA vs. GG; OR=1.49, 95%CI=1.15-1.93 for AA vs. GG+GA), but a difference was not found in the population-based source.

Sensitivity analysis

Sensitivity analysis was performed to reflect the influence of each single study on the final results. The corresponding pooled ORs were not materially altered (data not shown), suggesting that the results of this meta-analysis were consistent.

Publication bias

Begg's funnel plot and Egger's test were performed to assess publication bias. The shapes of the funnel plots were symmetrical in all comparison (Fig. 2). Then we used Egger's test to provide statistical evidence for the funnel plot symmetry. There was no publication bias (P =0.507 for AA vs. GG; P =0.621 for GA+AA vs. GG; P =0.528 for AA vs. GG+GA) in our meta-analysis.

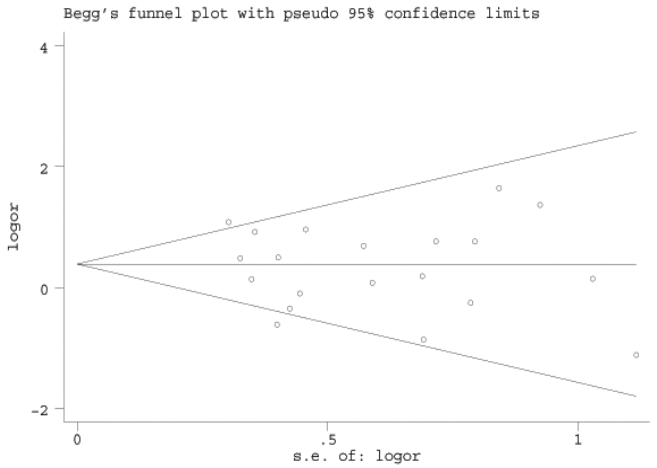

Figure 2. Begg's funnel plot for publication bias test. Each point represents a separate study for the indicated association. Log[OR], natural logarithm of OR. Horizontal line, mean effect size.

DISCUSSION

The present meta-analysis, including 2,888 cases and 3,611 controls from 16 published studies, explored the association between CXCL12 G801A polymorphism and cancer risk. We found this polymorphism was associated with the risk of cancer. Furthermore, in the subgroup analyses of breast cancer, Asian population, and hospital-based controls, the association was significant.

CXCL12 contains a common guanine to adenine mutation (G→A) at position 801 in its 3'-untranslated region which may serve as a target for cis-acting factors up-regulating the expression of the CXCL12 protein (47). It has been suggested that individuals with genotypes AA or GA could affect the expression of CXCL12 (39, 48), and the genotypes could change the amount of CXCL12 available to bind to the receptor CXCR4 (1). In fibroblast cells, the expression of CXCL12 was higher in GA/AA fibroblasts than in GG fibroblasts (6). In prostate cancer, the CXCL12 expression was also significantly higher among AA or GA genotypes carriers than those with GG genotype (20). Furthermore, the AA or GA genotypes are associated with a poorer prognosis, distant metastasis, and also with lower overall survival of cancer patients (6, 8, 17). Our results showed that individuals carrying AA or GA genotypes had a high cancer risk compared with individuals with GG genotype, which was consistent with the biological and functional studies mentioned above.

In the subgroup analysis, our results indicated that the association between the polymorphism and cancer risk was more significant in breast cancer than other cancer types. In another meta-analysis, Shen et al. showed that CXCL12 G801A polymorphism may be a low risk factor for developing breast cancer with five published case–control studies (40). Our study had 6 eligible publications for breast cancer, and the result had the same tendency. The "other" group was composed of multiple cancer types, whereby each kind of cancer had a small sample size. Different pathways participate in the cancer generation process for different cancers, and there may be other factors that interact with the CXCL12 chemokine. Therefore, the same genotype may play different roles in the carcinogenesis for different cancers.

The results from stratification analysis indicated the association was more significant among Asians, but not among Caucasians. Cancer is a complicated multi-genetic disease and can be affected by the environment. Different groups of people have differences in genetics backgrounds, environmental conditions, and life styles; these factors may all contribute to the development of cancer. In Europeans, the influence of the CXCL12 G801A allele might be masked by the presence of other genes involved in cancer development.

In the stratified analysis based on study design, an increased risk in AA or GA genotypes carriers was found in the hospital-based controls, but not in population-based controls. Most of the hospital-based controls were ill-defined reference population, and may not be a true representative of the general population. Therefore, using a proper and representative population based study is very important to reduce biases in such genetic association studies.

Our meta-analysis had some limitations. First, the results of this meta-analysis were based on unadjusted estimates, while a more precise analysis needs to be conducted if individual data were available, which would allow for the adjustment by other covariants such as age, sex, smoking and alcohol consumption usage, environmental factors, and other lifestyle habits. Second, in the subgroup analysis by cancer type, each kind of cancer had a small sample size except for breast cancer, so we need further studies with larger number of participants to confirm the association between CXCL12 G801A polymorphism and other cancer types. Nevertheless, the current meta-analysis also had some advantages. First, this meta-analysis significantly increased statistical power by pooling data from different studies. Second, according to our inclusion criteria, the quality of studies included in this meta-analysis was satisfactory. Third, there was no publication bias

in our meta-analysis, suggesting the results of this meta-analysis are valid.

In conclusion, this meta-analysis suggests that the CXCL12 G801A polymorphism may be a risk factor of cancer, especially in the subgroups of breast cancer, Asians and hospital-based controls. Due to the limitations of meta-analysis, larger well-designed studies with standardized unbiased methods and well-matched controls are needed. Moreover, gene-gene and gene-environment interactions should be considered to better assess the association between the CXCL12 G801A polymorphism and cancer risk.

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