

IL-1 α -889 C/T polymorphism and cancer susceptibility: a meta-analysis

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Abstract: The -889 C/T polymorphism in the *interleukin-1 α* (*IL-1 α*) gene has been implicated in the risk of cancer, but the results are inconclusive. The present meta-analysis aimed to investigate the association between the -889 C/T polymorphism and cancer risk. A literature search in PubMed, EmbaseTM, Web of ScienceTM, Science Direct[®], SpringerLink, EBSCO, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) databases was carried out to identify studies investigating the association between *IL-1 α* -889 C/T polymorphism and cancer risk. The odds ratio (OR) with 95% confidence interval (CI) were used to assess the strength of association. A total of 20 publications, involving 6,782 cases and 7,767 controls, were included in this meta-analysis. Combined analysis revealed a significant association between -889 C/T polymorphism and cancer risk under an allele model (OR =1.12, 95% CI =1.02–1.24, $P=0.02$), recessive model (OR =1.34, 95% CI =1.06–1.68, $P=0.01$), and homozygous comparison (OR =1.38, 95% CI =1.10–1.74, $P<0.01$). Subgroup analysis by ethnicity showed there was significant association between cancer risk and *IL-1 α* -889 C/T polymorphism in Asian populations under a recessive model (OR =2.57, 95% CI =1.11–5.98, $P=0.03$) and homozygous comparison (OR =2.60, 95% CI =1.12–6.04, $P=0.03$). Moreover, a subgroup analysis was conducted by source of control, and a statistically increased cancer risk was found in the hospital-based group, under a recessive model (OR =1.62, 95% CI =1.03–2.56, $P=0.04$) and homozygous comparison (OR =1.67, 95% CI =1.04–2.68, $P=0.03$). This meta-analysis suggests that *IL-1 α* -889 C/T polymorphism contributes to cancer susceptibility. Further large and well-designed studies are needed to confirm this association.

Keywords: neoplasma, biomarker, cytokine, systematic review

Introduction

In recent years, the role for inflammation in tumorigenesis has become more evident. Chronic inflammation, not only facilitates the progression of normal cells to malignancy but also, supports survival of many malignancies through production of proinflammatory cytokines.^{1,2} Through activation of various downstream effectors, cytokines control the immune and inflammatory milieu to either favor antitumor immunity or enhance tumor progression, and also, have direct effects on cancer cell growth and survival.^{3,4}

Interleukin-1 (IL-1) is a pleiotrophic cytokine that primarily affects inflammatory responses, immune reactivity, and hematopoiesis.^{5,6} Accumulating evidence has shown that IL-1 is involved in all phases of the malignant process, such as tumorigenesis, tumor invasiveness and progression, as well as activation/suppression of antitumor immunity. The IL-1 cytokine family consists of three members, IL-1 α , IL-1 β , and IL-1 receptor

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(IL-1R) antagonist.⁷ In particular, IL-1 α has been suggested to regulate cancer cell invasion and metastasis, inducing invasiveness-promoting factors (ie, matrix metalloproteinases) and adhesion molecules.^{8,9} In animal models, mice solely deficient in IL-1 α exhibit dramatically impaired tumor development and blood vessel growth.¹⁰ IL-1 α expression has also been found in pancreatic adenocarcinoma,¹¹ colon cancer,¹² gastric carcinoma,¹³ thyroid carcinoma,¹⁴ ovarian carcinoma,¹⁵ lung carcinoma,¹⁶ and adult T-cell leukemia.¹⁷ Wolf et al reported that IL-1 α contributes to the transcriptional activation of nuclear factor kappaB (NF- κ B) and activator protein 1 (AP-1), and promotes cell survival and growth in the head and neck squamous cell carcinoma cell line.¹⁸ Xu et al revealed that autocrine IL-1 α and paracrine hepatocyte growth factor (HGF) coenhance the metastatic potential of pancreatic cancer cells via both IL-1 α and HGF signaling pathways.¹⁹ Therefore, IL-1 α may be involved in tumor progression.

The gene encoding IL-1 α is located in chromosome 2q13-21, and there is a single nucleotide polymorphism (SNP) at position -889. *IL-1 α -889 C/T* polymorphism has been reported to be associated with an increased cytokine production.^{21,22} To date, many studies have been published to assess the association between *IL-1 α -889 C/T* polymorphism and cancer susceptibility, but they reported controversial results. A single case-control study may fail to completely demonstrate the complicated genetic relationship because of the small sample size.²³ In order to provide strong evidence of the effects of *IL-1 α -889 C/T* polymorphism on cancer susceptibility, we performed a meta-analysis by combining data from numerous published studies.

Methods

Search strategy

A literature search in PubMed, EmbaseTM, Web of ScienceTM, Science Direct[®], SpringerLink, EBSCO, Wanfang, and Chinese National Knowledge Infrastructure (CNKI) databases was carried out to identify studies investigating the association between cancer risk and *IL-1 α -889 C/T* polymorphism, without language, time period, or sample size limitations, and covering all papers published up to May 2014. The sets of search terms were as follows: “IL-1, or IL-1 α , or IL-1alpha, or interleukin-1A, or IL-1A” and “cancer, or carcinoma, or tumor, or neoplasma” and “polymorphism, or variant, or SNP”.

Inclusion and exclusion criteria

The selection criteria of the retrieved articles in our meta-analysis were as follows: a) case-control studies or cohort

studies; b) studies evaluating the association between *IL-1 α -889 C/T* polymorphism and cancer risk; c) identification of cancer patients was confirmed histologically or pathologically; and d) sufficient data available to calculate an odds ratio (OR) with 95% confidence interval (CI). The exclusion criteria of the meta-analysis were: a) case-only studies; b) studies with incomplete data; and c) meta-analyses, letters, reviews, and editorial articles. If more than one study was published by the same author using the same patient population or overlapping case series, the study with the largest size of samples was included.

Data extraction

The following data from included studies were extracted independently by two authors (Cheng and Hao). The following data were collected: name of first author; year of publication; country; ethnicity; cancer types; sources of control; number of cases and controls, and genotype frequency in cases and controls; genotyping methods; *P* value for Hardy-Weinberg equilibrium; and minor allele frequency. Any disagreement was resolved through discussions by these two authors until consensus was reached.

Sensitivity analysis

Sensitivity analysis was performed by excluding each investigation individually and recalculating the pooled estimates and their corresponding 95% CIs to determine the effect of each study on the summary estimate.

Statistical analysis

The strength of the association between *IL-1 α -889 C/T* polymorphism and cancer risk was estimated by calculating ORs with 95% CIs, based on the genotype frequencies in cases and controls. The pooled ORs were calculated for five models: allele model (T allele vs C allele), dominant model (TT+TC vs CC), recessive model (TT vs TC+CC), homozygous comparison (TT vs CC), and heterozygous comparison (TC vs CC). The chi square-based *Q* statistic test was employed to test between-study heterogeneity, and heterogeneity was considered significant when *P*<0.1 for the *Q* statistic. The fixed effect model was chosen when studies were homogeneous (with *P*>0.10 for the *Q* test); otherwise, a random effects model was adopted. The significance of the pooled OR was determined by *Z* test, and *P*-value less than 0.05 was considered as statistically significant. Subgroup analyses were carried out to explore the source of heterogeneity among variables, including ethnicity and source of control, respectively. Publication bias was both examined

with Begg's funnel plot²⁴ and Egger's regression method²⁵ ($P < 0.05$ was considered representative of statistically significant publication bias). All statistics were conducted by using Stata Statistical Software: Release 11.0 (StataCorp, College Station, TX, USA).

Results

Characteristic of eligible studies

The detailed screening process is shown in Figure 1. A total of 311 publications from all databases were reviewed. After a review of titles, abstracts, and articles, 20 studies, with 6,782 cases and 7,767 controls, were included in this meta-analysis.^{20–22,26–42} Table 1 lists the studies identified and their main characteristics. There were six studies conducted in Asian populations, ten studies in Caucasian populations, and four studies in mixed populations. Population-based controls were performed in eleven studies, and hospital-based controls in nine studies. The genotype distribution of IL-1 α -889 C/T polymorphism in the controls was in compliance with Hardy–Weinberg equilibrium, except for in three studies.^{22,26,33}

Meta-analysis results

The main results of the meta-analysis of the association between IL-1 α -889 C/T polymorphism and cancer risk are shown in Table 2. In the overall analysis, there was significant association between IL-1 α -889 C/T polymorphism and cancer risk under an allele model (OR = 1.12, 95% CI = 1.02–1.24, $P = 0.02$), recessive model

(OR = 1.34, 95% CI = 1.06–1.68, $P = 0.01$), and homozygous comparison (OR = 1.38, 95% CI = 1.10–1.74, $P < 0.01$), but no significant association was found under other models.

Subgroup analysis by ethnicity and source of controls was performed in order to determine the source of heterogeneity among the studies and to assess the effect of ethnicity and source of controls on the association between IL-1 α -889 C/T polymorphism and cancer risk. Then, stratified analysis by ethnicity showed that a statistically increased cancer risk was found in the Asian population under a recessive model (OR = 2.57, 95% CI = 1.11–5.98, $P = 0.03$) and homozygous comparison (OR = 2.60, 95% CI = 1.12–6.04, $P = 0.03$), but there was no significant association between cancer risk and IL-1 α -889 C/T in either the Caucasian or mixed population (Table 2, Figure 2). Moreover, a subgroup analysis was conducted by source of control, and a statistically increased cancer risk was found in the hospital-based group, under a recessive model (OR = 1.62, 95% CI = 1.03–2.56, $P = 0.04$) and homozygous comparison (OR = 1.67, 95% CI = 1.04–2.68, $P = 0.03$) (Table 2, Figure 3).

Sensitivity analysis

Sensitivity analysis was performed to evaluate the stability of the meta-analysis. Statistically similar data were obtained after sequentially excluding each study, indicating that our results were statistically reliable.

Publication bias

Begg's funnel plot and Egger's test were performed to assess the publication bias of studies. The shape of Begg's funnel plot was symmetrical (Figure 4). The statistical results still did not show publication bias by Egger's test ($P = 0.923$).

Discussion

Cytokines might contribute to tumor development by enhancing angiogenesis and tumor cell adhesions or by interfering with the antitumoral mechanisms of the immune system.⁴³ In recent years, studies have demonstrated that carcinogenesis is associated with altered levels of inflammatory cytokines, which have a substantial impact on numerous biological activities. Common variation in cytokine genes could lead to variation in protein structure, thus affecting the quantity and activity of cytokines.^{20,44} Knowledge of the genetic variations that influence cancer development is important for assessing cancer risk and identifying preventive strategies.

IL-1 α , an important proinflammatory cytokine, plays an important role in tumorigenesis and development.⁴⁵

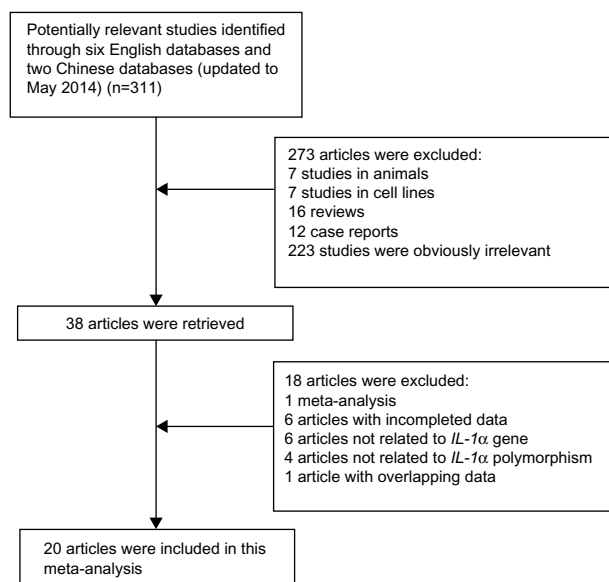


Figure 1 Flow diagram of the study selection process.
Abbreviation: IL, interleukin.

Table 1 Characteristics of the eligible studies included in the meta-analysis

Studies	Year	Country	Ethnicity	Cancer type	Source of controls	Sample size	Genotyping method	HWE (controls)	MAF (controls)
Abazis-Stambouliet al ²⁶	2007	Greece	Caucasian	Myeloma	PB	74/160	PCR-RFLP	<0.01	0.213
Ioana Braicu ²⁰	2007	Germany	Caucasian	Ovarian	HB	147/129	Pyrosequencing	0.565	0.283
Bushley et al ²⁷	2004	USA	Mixed	Ovarian	PB	178/216	PCR-sequencing	0.687	0.169
Foster et al ²⁸	2000	USA	Mixed	Sarcoma	HB	111/123	PCR-sequencing	0.393	0.272
Ennas et al ²⁹	2008	Italy	Caucasian	Leukemia	PB	40/111	Taqman®	0.835	0.261
Eshghyar et al ³⁰	2012	Iran	Asian	KCOT	PB	30/145	PCR-SSP	0.541	0.317
Grimm et al ²²	2004	Austria	Caucasian	Vulvar	HB	68/228	Pyrosequencing	0.008	0.307
Grimm et al ³¹	2011	Austria	Caucasian	Cervical	HB	131/204	Pyrosequencing	0.532	0.314
Wang ³²	2005	People's Republic of China	Asian	Cervical	PB	50/50	PCR	0.408	0.300
Hefler et al ³³	2005	Germany	Caucasian	Breast	PB	269/227	Pyrosequencing	0.012	0.304
Hoelt et al ³⁴	2008	Germany	Caucasian	Lymphoma	PB	650/659	PCR-RFLP	0.557	0.284
Hou et al ³⁵	2007	Poland	Caucasian	Gastric	PB	304/417	PCR-sequencing	0.090	0.350
Rothman et al ³⁶	2006	Mixed	Mixed	NHL	PB	3053/3457	N/A	0.524	0.289
Saenz-Lopez et al ³⁷	2008	Spain	Caucasian	Prostate	PB	297/311	PCR-sequencing	0.533	0.297
Senguen and Oygur ²¹	2011	Turkey	Caucasian	KCOT	HB	74/30	PCR-RFLP	0.258	0.300
Snoussi et al ³⁸	2005	Tunisia	Mixed	Breast	PB	305/200	PCR-RFLP	0.066	0.380
Yang et al ³⁹	2011	People's Republic of China	Asian	Nasopharyngeal	HB	248/296	PCR-RFLP	0.401	0.265
Zheng et al ⁴⁰	2013	People's Republic of China	Asian	Esophageal	HB	366/370	SNPlex® genotyping	0.579	0.104
Bai et al ⁴¹	2013	People's Republic of China	Asian	Lung	HB	193/211	Taqman	0.117	0.097
Qu et al ⁴²	2014	People's Republic of China	Asian	Nasopharyngeal	HB	194/231	Taqman	0.961	0.113

Abbreviations: HB, hospital-based controls; HWE, Hardy–Weinberg equilibrium; KCOT, keratocystic odontogenic tumor; MAF, minor allele frequency; N/A, not available; NHL, non-Hodgkin's lymphoma; PB, population-based controls; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSP, sequence-specific primers.

IL-1 α has been reported to be produced by cancer cell lines derived from carcinomas of the pancreas, lung, ovary, colon, and stomach.¹⁹ Of note, some data suggest that IL-1 α is less important in carcinogenesis and tumor

invasion than IL-1 β . Membrane-associated IL-1 α seems to increase antitumor immunity and subsequently might contribute to tumor cell eradication.⁴⁶ Cancer is considered to be a complex and multistep disease that results from

Table 2 Overall and subgroup estimates of the associations of *IL-1 α -899 C/T* polymorphism with cancer risk under all models.

	T allele vs C allele Allele model		TT+TC vs CC Dominant model		TT vs TC+CC Recessive model		TT vs CC Homozygous comparison		TC vs CC Heterozygous comparison	
	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
Overall	1.12 (1.02–1.24)	0.02	1.12 (0.98–1.27)	0.10	1.34 (1.06–1.68)	0.01	1.38 (1.10–1.74)	<0.01	1.07 (0.92–1.24)	0.41
Ethnicity										
Caucasian	1.07 (0.98–1.17)	0.15	1.19 (0.95–1.50)	0.14	1.10 (0.90–1.34)	0.37	1.14 (0.92–1.41)	0.22	1.21 (0.90–1.60)	0.20
Asian	1.34 (0.95–1.90)	0.10	1.12 (0.86–1.48)	0.40	2.57 (1.11–5.98)	0.03	2.60 (1.12–6.04)	0.03	0.93 (0.76–1.15)	0.51
Mixed	1.04 (0.97–1.11)	0.32	1.02 (0.80–1.29)	0.87	1.04 (0.88–1.22)	0.67	1.07 (0.90–1.26)	0.44	1.01 (0.78–1.31)	0.96
Source of control										
PB	1.09 (0.97–1.22)	0.14	1.15 (0.95–1.40)	0.15	1.17 (0.92–1.50)	0.20	1.10 (0.96–1.27)	0.15	1.14 (0.90–1.44)	0.28
HB	1.16 (0.97–1.39)	0.11	1.09 (0.94–1.27)	0.27	1.62 (1.03–2.56)	0.04	1.67 (1.04–2.68)	0.03	0.99 (0.84–1.17)	0.95

Abbreviations: CI, confidence interval; HB, hospital-based control; IL, interleukin; PB, population-based control; OR, odds ratio; vs, versus.

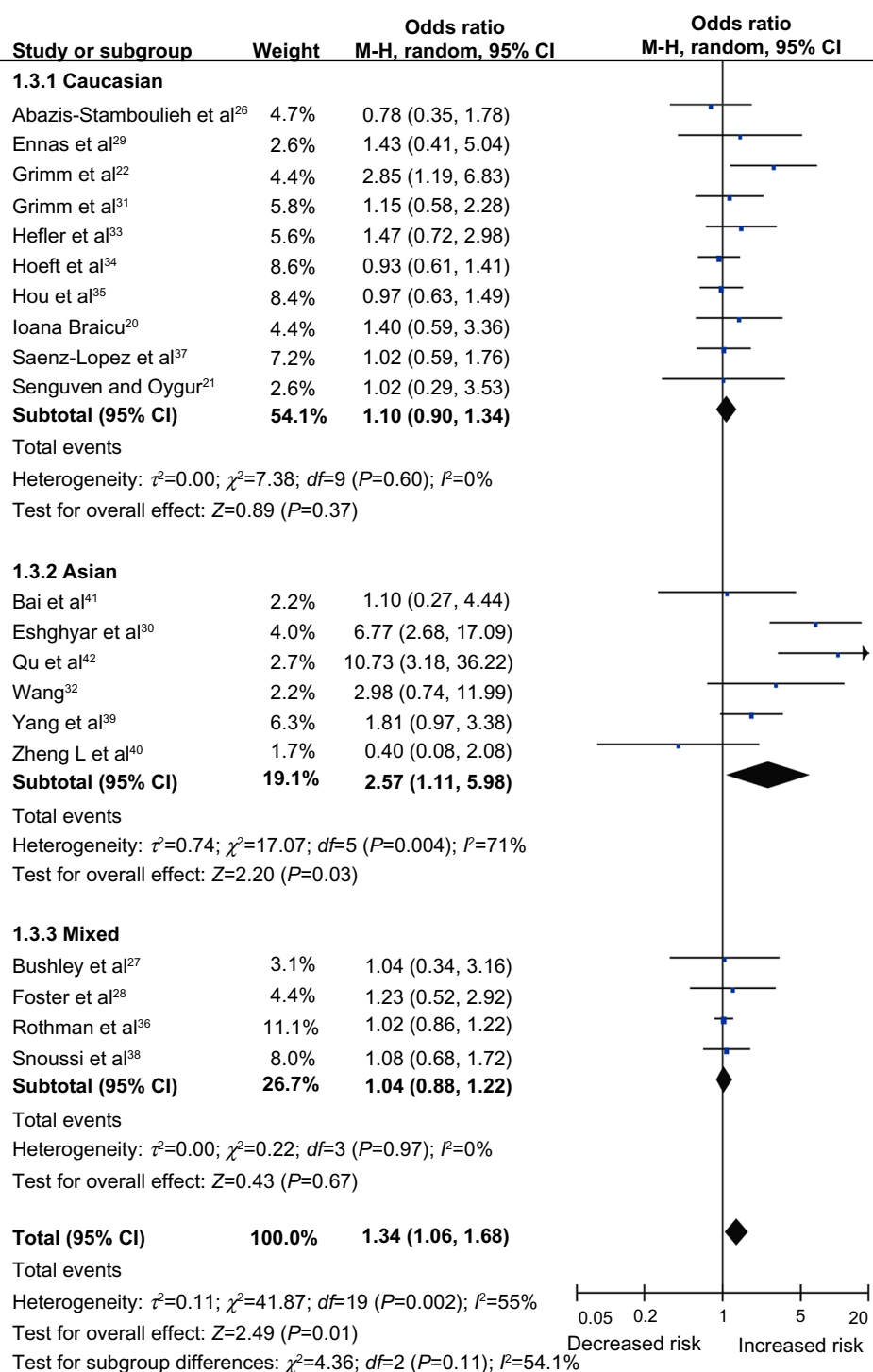


Figure 2 Meta-analysis for IL-1 α -889 C/T polymorphism and cancer susceptibility, based on ethnicity under a recessive model (TT vs TC+CC).

Abbreviations: IL, interleukin; M-H, Mantel-Haenszel method.

interactions between environmental and genetic factors,⁴⁷ and SNPs are associated with intersubject variation and diversity, and have been recently considered as important genetic factors involved in the development of cancer. Several polymorphisms have been described in IL-1 α genes, which probably modulate IL-1 α protein production

and have been related with the development and severity of cancer.^{26,48} The most common polymorphism, -889 C/T polymorphism, has been associated with high production of IL-1 α .^{22,49} To date, many studies have investigated the role of the IL-1 α -889 C/T polymorphism in different types of cancer. However, the results of these studies remain

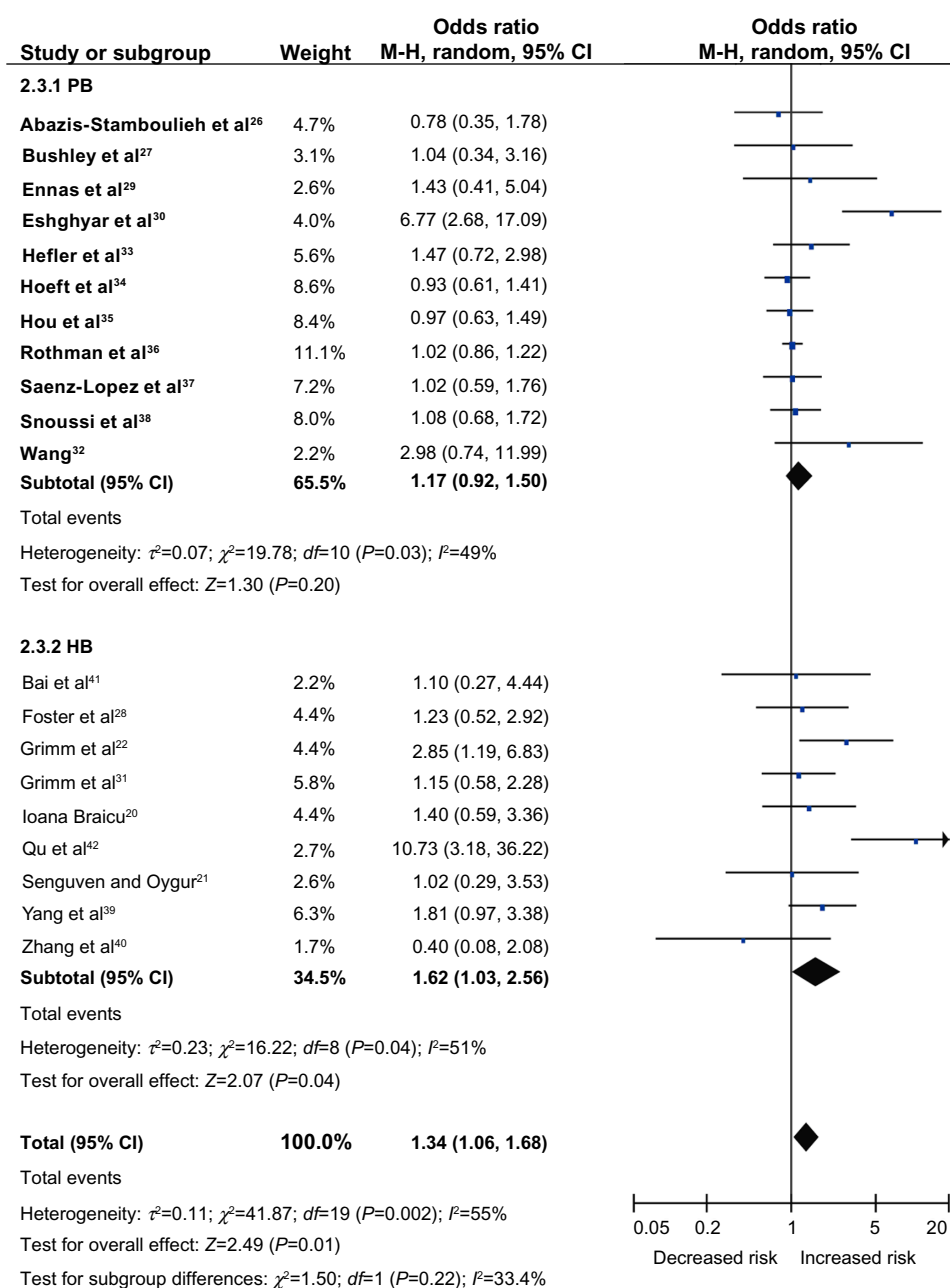


Figure 3 Meta-analysis for *IL-1α* -889C/T polymorphism and cancer susceptibility, based on source of control under a recessive model (TT vs TC+CC).

Abbreviations: CI, confidence interval; HB, hospital-based controls; IL, interleukin; PB, population-based controls; vs, versus; M-H, Mantel-Haenszel method.

inconclusive. We, therefore, performed a meta-analysis by pooling 20 eligible studies, including 6,782 cases and 7,767 controls, to clarify this inconsistency and to achieve a more precise estimation of the relationship between *IL-1α* -889 C/T polymorphism and cancer risk. Our results demonstrated that *IL-1α* -889 C/T polymorphism was significantly associated with increased overall cancer risk under an allele model ($P=0.02$), recessive model ($P=0.01$), and homozygous comparison ($P<0.01$).

In order to explore a potential source of heterogeneity, we also performed subgroup analysis based on ethnicity.

We found the significant association of *IL-1α* -889 C/T polymorphism with cancer risk only in the Asian population, under a recessive model ($P=0.03$) and homozygous comparison ($P=0.03$). Our results also revealed that no statistically significant risk was observed in Caucasian and mixed populations, under all genetic models. Moreover, in the subgroup analysis by source of control, we found a statistically increased cancer risk in the hospital-based group, under a recessive model ($P=0.04$) and homozygous comparison ($P=0.03$), but not in the population-based group. Hospital-based controls were randomly selected cancer-free

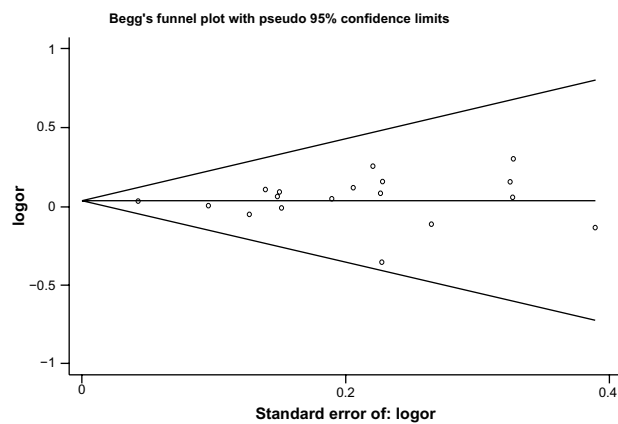


Figure 4 Funnel plots for publication bias of IL-1 α -889 C/T polymorphism and cancer risk in the overall populations under a dominant model.

Abbreviation: IL, interleukin.

patients from the same hospital as the cancer patients during the same period, and they might be from a related disease population and not the general population. Selection bias could not be avoided.

The findings in this meta-analysis should be interpreted with caution because of several limitations. First, in the subgroup analysis by ethnicity, the included studies were mainly in Asians and Caucasians, and future study should evaluate the association between IL-1 α -889 C/T polymorphism and cancer risk in different ethnicities, especially in Africans. Second, the meta-analysis was limited by a relatively small number of available studies. It is difficult to perform subgroup analysis for every type of cancer. Third, only published studies in the selected databases were included in this meta-analysis. It is possible that some studies that were not included in these databases or some unpublished studies with null results were not identified, and this may have biased our results. Fourth, gene-gene and gene-environment interactions may play important roles in the function of IL-1 α -889C/T polymorphism, but the effect was not addressed in our meta-analysis, due to unavailable data.

Conclusion

To the best of our knowledge, this is the first meta-analysis to assess the relationship between IL-1 α -889 C/T polymorphism and cancer risk. Our results demonstrated that IL-1 α -889 C/T polymorphism was associated with increased risk of cancer. Further stratification by ethnicity or source of control indicated that the association between IL-1 α -889 C/T polymorphism and cancer was restricted to the Asian population and the hospital-based group. More studies with large sample size are needed to further assess the associations described above.

Disclosure

The authors report no conflicts of interest in this work.

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