

Association between the Interleukin-10 -1082 G/A polymorphism and risk of hepatocellular carcinoma

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Abstract

Background: Inconsistent results have been reported from studies investigating the relationship of the interleukin-10 (IL-10) -1082 G/A polymorphism and the susceptibility of hepatocellular carcinoma (HCC). Therefore, a thorough literature review of related studies was performed in this meta-analysis to examine the association of the interleukin-10 (IL-10) -1082 G/A polymorphism with HCC susceptibility.

Methods: Electronic databases were searched for literature on the relationship between interleukin-10 (IL-10) -1082 G/A polymorphism and the risk of HCC in accordance with the inclusion and exclusion criteria. The selected studies were analyzed using the Stata 12.0 software. Finally, the strength of the associations was evaluated using the odds ratio (OR) and 95% confidence intervals (95% CI).

Results: A total of six case-control studies were enrolled into the current meta-analysis, which included a total of 911 patients and 1889 control subjects. Our data revealed no association between the IL-10 -1082 G/A polymorphism and the risk of HCC (GG vs AA: OR=0.84, 95%CI=0.57-1.25; AG vs AA: OR=0.85, 95%CI=0.70-1.05; Dominant model: OR=0.85, 95%CI=0.70-1.03; and Recessive model: OR=0.92, 95%CI = 0.64-1.32). Similarly, no association was found in sub-group analysis based on ethnicity.

Conclusion: The results of our study suggest no association between IL-10 -1082 G/A polymorphism and the risk of HCC.

Keywords: Hepatocellular carcinoma, IL-10 polymorphism, risk analysis.

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Introduction

As a global health problem, hepatocellular carcinoma (HCC) presents a tremendous economic burden on both patients and society. HCC is the fifth most commonly diagnosed cancer, and is the second-highest cause of cancer-related deaths worldwide¹. China has an average of about 695,000 primary liver cancer-induced deaths annually, accounting for 45% of the mortality worldwide. Typically, early detection of HCC is of crucial significance, since more advanced HCC cases typically are associated with poor prognosis. HCC is mainly caused by infection

with chronic hepatitis B virus and hepatitis C virus². There are other well-recognized risk factors, such as smoking, drinking, and exposure to aflatoxin³. Furthermore, recent studies examining genetic changes during HCC genesis and development suggest potential genetic factors that can also contribute to the development of cancer⁴. Specifically, single nucleotide polymorphism (SNP) changes are extensively investigated genetic variations that may contribute to the risk of disease development.

Recent studies have shown that cytokines including transforming growth factor, interleukin-6 (IL-6), IL-8, and IL-10, play critical roles in cancer etiologies⁸. Of these factors, IL-10 is an anti-inflammatory cytokine, which shows immune suppression⁹. An increasing amount of evidence indicates that IL-10 may inhibit carcinogenesis, angiogenesis, and tumor metastasis¹⁰. In contrast, a deficiency in IL-10 will promote pro-inflammatory cytokines production, restrain anti-cancer immunity, and facilitate tumor growth¹¹.

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The human IL-10 gene, which is located on chromosome 1 (1q31-q32), encodes an acid-sensitive homodimeric protein encoded by five exons and four introns. There are several SNPs in the promoter region of the IL-10 gene, including -1082 G/A, -819 T/C, and -592 A/C, which can alter the transcription start site to influence IL-10 mRNA transcription¹². Polymorphism in the promoter region of the IL-10 gene may be correlated with changes in IL-10 expression, which may thereby give affect tumorigenesis¹³.

The association of the IL-10 -1082 G/A(NCBI ID:rs1800896) polymorphism with the risk of incidence of HCC was recently examined, but the findings have been inconsistent. A single study with a relatively small sample size may not be sufficient to detect a very small effect of the polymorphism on HCC. For this reason, the current meta-analysis was conducted to comprehensively assess the association of the IL-10 -1082 G/A polymorphism with HCC susceptibility.

Methods

Literature Search

We searched for relevant studies in the PubMed and CNKI electronic databases using the terms “liver cancer” or “hepatocellular carcinoma” “interleukin-10” or “IL-10” and “polymorphism”. Studies published by the same

authors were checked for overlapping participant groups. In the case of partially overlapping studies, the most recent article was used.

Inclusion and exclusion criteria

For inclusion in this meta-analysis, the studies must have met the following criteria: 1) a case-control design including HCC cases and healthy controls; 2) reporting the association between the -1082 G/A polymorphism and susceptibility to HCC; and 3) the inclusion of sufficient genotype data for extraction. The exclusion criteria were: 1) non-case-control studies evaluating the association between the -1082 G/A polymorphism and HCC risk; 2) case reports, letters, reviews, and editorial articles; and 3) studies with incomplete raw data or without usable data reported.

Quality score assessment

The quality of the included studies was assessed based on a set of predetermined criteria (Table 1), and include the representativeness of cases, source of controls, certainty of HCC diagnosis, total sample size, quality control of genotyping methods, and evidence of Hardy-Weinberg equilibrium (HWE) in the control population. Different opinions were resolved by discussion to reach consensus¹⁴. Papers scoring <10 were classified as “low quality” and those scoring ≥10 were classified as “high quality.”

Table 1. Scale for quality assessment

Criteria	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathological archives, but without a description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Specimens obtained from patients to determine genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Totalsample size	
≥ 1000	3
≥ 500 but < 1000	2
≥ 200 but < 500	1
> 0 but < 200	0

Data extraction

Information was independently extracted carefully from all eligible publications by two authors, based on the inclusion criteria above. Disagreements were resolved by discussion between the two authors. The following data were collected from each article: first author, publication date, country where study was performed, number of cases and controls, genotype frequencies of case and control groups, quality score, and evidence of HWE in the control group.

Statistical analysis

Statistical analysis was performed using the Stata software package, version 12.0 (StataCorp LP, College Station, TX, USA), and P-values less than 0.05 were considered statistically significant. The association between the IL-10 -1082 G/A polymorphism and HCC risk were estimated

by pooled ORs with 95% CI for homozygote comparison (GG vs. AA), heterozygote comparison (AG vs. AA), dominant model (GG +AG vs. AA) and the recessive model (GG vs. AG+ AA). Heterogeneity was investigated and measured using the I² statistic, where I²>50% indicated evidence of heterogeneity. When heterogeneity was present, the random effects model was used to calculate the pooled OR, otherwise the fixed effects model was used. One-way sensitivity analyses were performed to determine the stability of the results, where each individual study in the meta-analysis was individually omitted to reflect the influence of each individual dataset on the pooled OR¹⁵. Publication bias was evaluated using the funnel plot with Egger's test. Power analysis was performed using the statistical program PS: Power and Sample Size Calculation (<http://biostat.mc.vanderbilt.edu/wiki/Main/PowerSampleSize>).

Results

Study characteristics

A flow diagram of the study selection process is shown in Figure 1. A total of 181 potentially relevant studies were identified from the database searches. Of these, 170 studies were excluded based on the title or abstract. In addition, one study was excluded because the full text was not available, two were excluded because they were not case-control studies, and two were excluded because they lacked the necessary data. After exclusion, six studies remained and were included in this meta-analysis¹⁶⁻²¹.

The characteristics of the included studies are presented in Table 2. There were four studies conducted in Asian populations, and two in mixed populations. Together, the studies included a total of 911 cases and 1889 controls. The genotype distributions in the control groups in all studies were consistent with HWE. All publications were written in English. All included studies were of high quality, with quality score assessments higher than or equal to 10 points. The statistical powers of included studies ranged from 52.6% to 72.3%. None of the studies had a statistical power exceeding 80%.

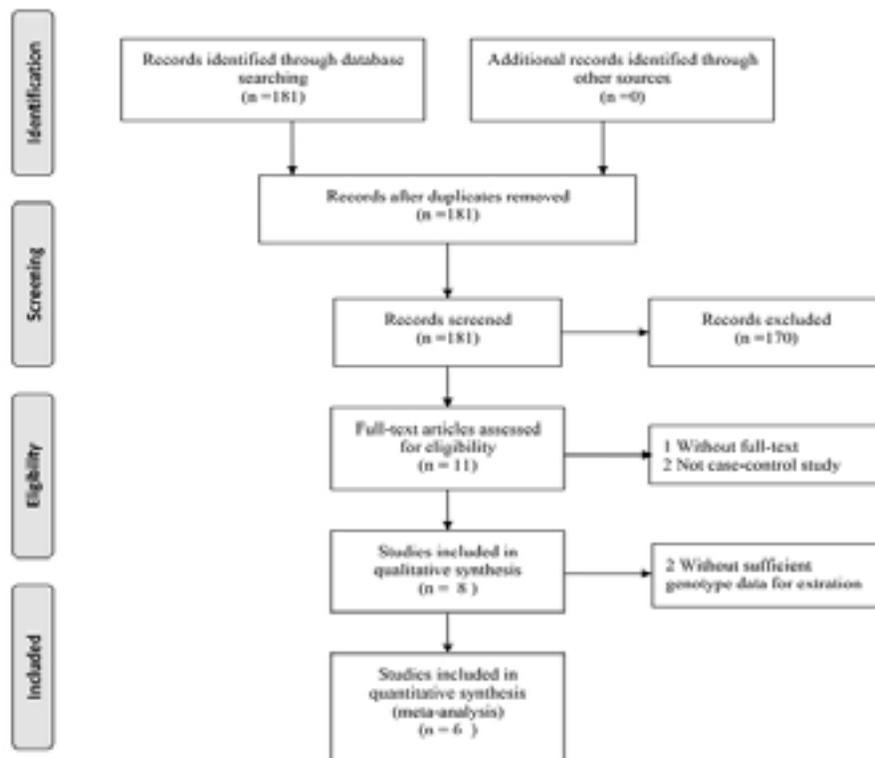


Figure 1. Study selection and inclusion process

Table 2. Characteristics of studies included in the meta-analysis

Study included	Area	Cases/ Controls	Genotypes for cases			Genotypes for controls			HWE test	Quality scores
			AA	AG	GG	AA	AG	GG		
Shin 2003	Korea	230/792	201	28	1	675	112	5	0.88	12
Heneghan 2003	China	98/175	86	12	0	160	15	0	0.55	10
Nieters 2005	China	249/250	130	99	20	115	109	26	0.98	10
Bouzgarrou 2009	Tunisia	58/103	24	24	10	42	49	12	0.69	10
Ognjanovic 2009	USA	118/214	39	57	22	67	106	41	0.94	12
Li 2011	China	158/355	132	25	1	278	72	5	0.89	13

Meta-analysis results

As no statistically significant heterogeneity was observed in our meta-analysis, all pooled OR were derived from the fixed-effects models. Table 3 lists the main results of the meta-analysis of IL-10 -1082 G/A polymorphism and HCC risk in all of the four models (Figure 2, GG vs AA:OR=0.84, 95%CI=0.57-1.25; AG vs AA:OR=0.85, 95%CI=0.70-1.05; Dominant model: OR=0.85, 95%CI=0.70-1.03; Recessive model: OR=0.92, 95%CI = 0.64-1.32). Sub-group analysis was next stratified by ethnicity. The meta-analysis included four studies (735 cases and 1572 controls) in Asian populations and two studies (176 cases and 317 controls) in mixed populations. No significant association was detected in all genetic models of stratified sub-group analysis by race.

95%CI=0.70-1.05; Dominant model: OR=0.85, 95%CI=0.70-1.03; Recessive model: OR=0.92, 95%CI = 0.64-1.32). Sub-group analysis was next stratified by ethnicity. The meta-analysis included four studies (735 cases and 1572 controls) in Asian populations and two studies (176 cases and 317 controls) in mixed populations. No significant association was detected in all genetic models of stratified sub-group analysis by race.

Table 3. Summary of different comparative results.

Variables	N	Cases/ controls	GG vs AA		AG vs AA		Dominant model		Recessive model	
			OR(95%CI)	I ²						
Total	6	911/1889	0.84(0.57-1.25)	0.0%	0.85(0.70-1.05)	0.0%	0.85(0.70-1.03)	0.0%	0.92(0.64-1.32)	0.0%
Ethnicity										
Asian	4	735/1572	0.65(0.36-1.17)	0.0%	0.84(0.66-1.06)	0.0%	0.82(0.65-1.03)	0.0%	0.72(0.41-1.26)	0.0%
Mixed	2	176/317	1.06(0.62-1.82)	0.0%	0.90(0.60-1.36)	0.0%	0.94(0.64-1.39)	0.0%	1.11(0.68-1.80)	0.0%

N: number; I²: Inconsistency index; CI: confidence interval; OR: odds ratio

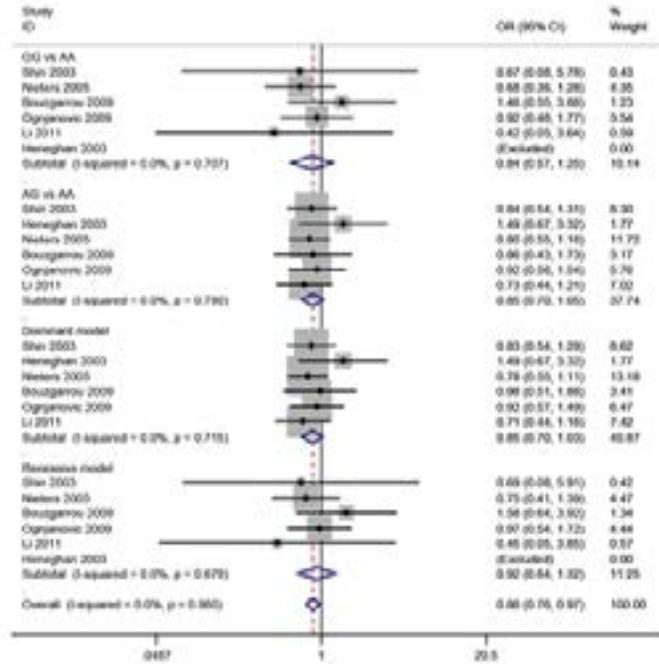


Figure 2. Forest plots of the association between IL-10 -1082 G/A polymorphism and HCC risk

Sensitivity analysis

Sensitivity analysis was performed to assess the influence of each individual article on the pooled OR by deleting each study individually. No single article influenced the pooled ORs, suggesting stable results (Figure 3).

Publication bias

The Egger's test was performed to assess the publication bias. There was no evidence of publication bias visually from the funnel plot (Figure 4), indicating low publication bias of our meta-analysis.

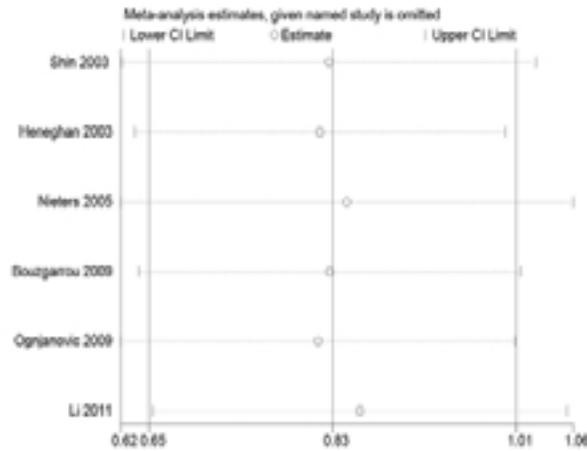


Figure 3. Sensitivity analysis of the IL-10 -1082 G/A polymorphism with HCC risk

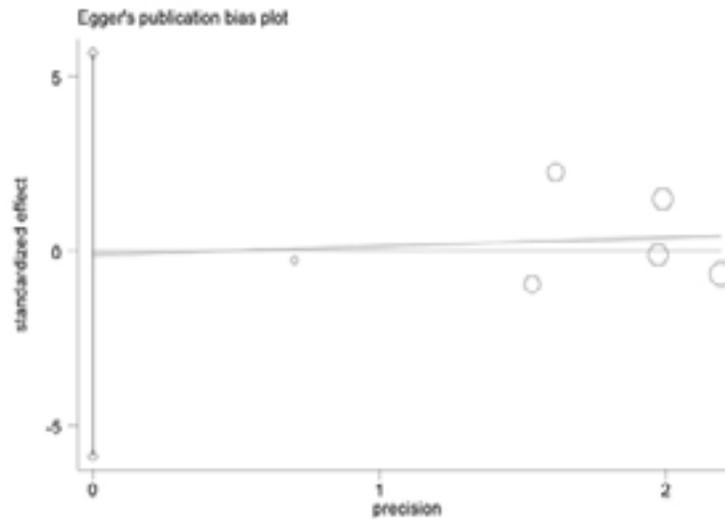


Figure 4. Egger's funnel plot test

Discussion

HCC is a common malignant tumor caused by complex interactions between environmental and genetic factors. With increased attention to genetic susceptibility to carcinogenesis, more and more studies are devoted to investigation of genetic variants and HCC risk. IL-10 plays a key role in anti-inflammation and can block tumor im-

mune surveillance to inhibit T-cell immunity²². A previous study suggested that the secretion of IL-10 is determined largely (74%) by heritable factors²³. Several studies have found an association between the IL-10 -1082 G/A polymorphism and oral cancer, head and neck cancer^{24,25}. Because meta-analysis is a suitable method to evaluate small effects in genetic association studies, we designed

this study to systematically evaluate the association of the IL-10 -1082 G/A polymorphism with HCC risk.

This is the first meta-analysis of the relationship between the IL-10 -1082 G/A polymorphism and HCC risk. After literature search and screening, six studies were selected for analysis, with a total of 2800 subjects. Although data from individual studies suggested a relationship, the overall result of our meta-analysis argued against an association of IL-10 -1082G/A polymorphism with HCC risk in all genetic models. Ethnicity-related subgroup analyses also did not reveal a significant association between IL-10 -1082G/A and HCC risk in any of the comparisons. Green tea has been found to have anti-inflammatory, anti-oxidative and anti-carcinogenic properties²⁶. Li et al. found that the IL-10 -1082 G/A polymorphism was associated with increased risk of cancer for non-drinkers of green tea, but decreased risk among green tea drinkers²¹. In addition, a previous study demonstrated that haplotypes(-1082 G/A, -819 T/C, and -592 A/C) of the IL-10 gene may synergistically increase the risk of HCC¹⁶. Only two articles have studied gene-gene and gene-environment interactions, we can not do further subgroup study. One possibility is that the IL-10 -1082G/A polymorphism itself may not contribute to the risk of HCC, or have only limited effect on HCC that depends on neighboring variants or environmental factor.

There are several limitations of this meta-analysis. First, we did not have the original data for included studies to adjust estimates and analyze for differences due to gender, age, drinking, smoking, lifestyle, body mass index, or other characteristics. Second, our study only included articles published in English, which might have limited the results of the meta-analysis. Third, gene-gene and gene-environment interactions have not been evaluated due to the absence of original data. Therefore, additional studies are needed to obtain more reliable results. Fourth, The statistical powers of included articles were relatively low, further well-designed and large-scale studies should be performed to further evaluate this association. Finally, the inclusion criteria for cases and controls were not clearly defined in all the included articles, which may have influenced the findings.

In summary, the results of this meta-analysis indicated that there is no association between the -1082G/A polymorphism of IL-10 and HCC susceptibility. Further

studies estimating the effect of gene-gene and gene-environment interactions may ultimately provide more comprehensive understanding of the association.

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Conflict of interest

None declared.

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