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META-ANALYSIS

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Interferon-γ +874A/T Polymorphism and Hepatocellular Carcinoma Risk: A Meta-Analysis

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCDE Huan Zhou
CDF Lizhou Wang
BC Xing Li
BCD Jie Song
C Tianpeng Jiang
C Xiaoping Wu
ABCDEF Shi Zhou

Department of Radiology, Affiliated Hospital of Guiyang Medical College, Guiyang, Guizhou, China

Corresponding Author: Shi Zhou, e-mail: zhoushiguiyang@126.com
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Background: Studies have evaluated the association between interferon-γ (IFN-γ) +874A/T polymorphism and hepatocellular carcinoma (HCC) risk, but the results are controversial. We performed this meta-analysis to further investigate this association.

Material/Methods: Relevant studies were searched by using the PubMed, Web of Science, and Embase databases. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of the association. Subgroup analysis and sensitivity analysis were conducted.

Results: Seven case-control studies (859 HCC patients and 1482 healthy controls) were identified to assess the association between IFN-γ +874A/T polymorphism and risk of HCC. IFN-γ +874A/T polymorphism was significantly associated with an increased risk of HCC (OR=1.38; 95% CI 1.12–1.70; *P*=0.002). In the subgroup analysis by ethnicity, IFN-γ +874A/T polymorphism was significantly associated with HCC risk in Asians (OR=1.42; 95% CI 1.08–1.87; *P*=0.01), but no significant association was found in Caucasians (OR=1.21; 95% CI 0.86–1.70; *P*=0.28). IFN-γ +874A/T polymorphism also increased HBV-induced HCC risk (OR=1.42; 95% CI 1.08–1.87; *P*=0.01). In the subgroup analysis by control source, IFN-γ +874A/T polymorphism was associated with HCC risk in hospital-based studies (OR=1.45; 95% CI 1.09–1.53; *P*=0.01). A marginal association was found in population-based studies (OR=1.33; 95% CI 0.97–1.83; *P*=0.08).

Conclusions: This meta-analysis indicates that the IFN-γ +874A/T polymorphism might contribute to HCC risk.

MeSH Keywords: Carcinoma, Hepatocellular • Interleukins • Meta-Analysis • Polymorphism, Genetic

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Background

Hepatocellular carcinoma (HCC) is among the most malignant cancers worldwide. Annually, there are approximately 700 000 newly-diagnosed HCC cases, about half of which were found in China [1]. Despite advances in surveillance, chemotherapy for advanced patients, and surgical intervention for patients with early-stage disease, the prognosis of patients with HCC remains poor. Therefore, it is urgent to seek new effective strategies to identify high-risk individuals.

IFN-γ is a product of Th1 cells; it exerts inhibitory effects on Th2 cell differentiation [2]. A significant correlation was found between IFN-γ expression and stage of fibrosis or progressive liver injury in individuals with chronic hepatitis C [3]. Falasca et al. reported that HBV-infected patients showed higher plasma IFN-γ levels than the control group [4]. Recently, Lee et al. found that serum IFN-γ level was correlated with tumor stage and tumor size in HCC patients [5].

The human IFN-γ gene is located on chromosome 12. It has been established that the T-to-A polymorphism at position874 of the first intron of IFN-γ gene could directly influence IFN-γ production level [6]. The +874A/T polymorphism is located within a putative nuclear factor-κB (NF-κB) binding site, and T allele might be important in the induction of higher IFN-γ production [6]. Recently, many studies have assessed the association between IFN-γ +874A/T polymorphism and the risk of HCC [7–13], but results were conflicting. We conducted this meta-analysis to investigate the association between IFN-γ +874A/T polymorphism and the risk of HCC.

Material and Methods

Publication search

Relevant studies were searched by using the PubMed, Web of Science, and Embase databases (the last retrieval date was Oct 21, 2014, using the search terms: "Hepatocellular carcinoma or liver cancer or liver tumor" and "interferon-γ or interferon or IFN-γ"). All searched studies were retrieved and only published studies with full-text articles were included. For publications with duplicate samples, only the newest study was used in this research.

Inclusion and exclusion criteria

Studies that were included in the meta-analysis met all of the following criteria: (1) evaluated the IFN-γ +874A/T polymorphism and HCC risk, (2) used a case-control design, and (3) had sufficient data for estimating an odds ratio (OR) with 95% confidence interval (CI). Studies were excluded if any of the following criteria were present: (1) not relevant to IFN-γ or HCC risk, (2) animal study, (3) genotype frequencies or numbers were not reported, and (4) reviews or abstracts.

Data extraction

Based on the selection criteria, 2 reviewers extracted and sorted the data independently. The extracted data included: author, year, country, ethnicity, hepatitis virus type, sample size, and source of controls. Authors were contacted by email if further study details were needed.

Statistical analysis

Statistical analysis was all conducted using Stata software 11.0 (StataCorp, College Station, Texas, USA). Hardy-Weinberg equilibrium (HWE) test in healthy control group was conducted using χ^2 test. Odds ratio (OR) with a 95% confidence interval (CI) was calculated, and the significance level was 0.05. *Q*-statistic and I^2-statistic were used to measure statistical heterogeneity and the significance level was 0.10. Effect model selection was on the basis of heterogeneity test. The fixed-effects model was selected when there was no significant heterogeneity; otherwise, the random-effects model was used. A funnel plot was employed to evaluate publication bias. A $P<0.05$ was considered statistically significant.

Results

Study characteristics

Seven case-control studies were identified to assess the association between IFN-γ +874A/T polymorphism and risk of HCC. A total of 859 HCC patients and 1482 healthy controls were included in this meta-analysis. The characteristics of the included studies are shown in Table 1. There were 4 studies in Asians, 2 studies in Caucasians, and 1 study in Africans. Four studies included HBV-positive HCC patients.

Meta-analysis result

As shown in Figure 1, IFN-γ +874A/T polymorphism was significantly associated with an increased risk of HCC (OR=1.38; 95% CI 1.12–1.70; *P*=0.002). In the subgroup analysis by ethnicity, IFN-γ +874A/T polymorphism was significantly associated with HCC risk in Asians (OR=1.42; 95% CI 1.08–1.87; *P*=0.01), but no significant association was found in Caucasians (OR=1.21; 95% CI 0.86–1.70; *P*=0.28). IFN-γ +874A/T polymorphism also increased HBV-induced HCC risk (OR=1.42; 95% CI 1.08–1.87; *P*=0.01). In the subgroup analysis by control source, IFN-γ +874A/T polymorphism was associated with HCC risk in hospital-based studies (OR=1.45; 95% CI 1.09–1.53; *P*=0.01).

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

Author	Year	Country	Ethnicity	Cases/ controls (n)	Hepatitis virus status	Control source
Migita	2005	Japan	Asian	48/188	HBV	Hospital
Nieters	2005	China	Asian	250/250	HBV	Hospital
Bouzgarrou	2009	Tunisia	African	100/103	HCV	Population
Ognjanovic	2009	USA	Caucasian	120/230	NA	Population
Kim	2013	Korea	Asian	170/171	HBV	Hospital
Teixeira	2013	Brazil	Caucasian	112/202	Mixed	Population
Saxena	2014	India	Asian	59/338	HBV	Hospital

NA – not available.

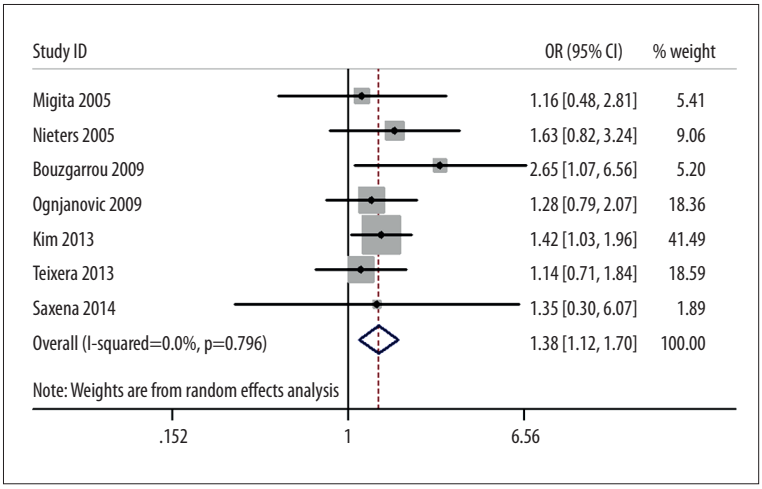

Figure 1. Association between IFN-γ +874A/T polymorphism and risk of HCC.

Table 2. Meta-analysis results and subgroup analyses.

	$P_{heterogeneity}$	Test of association		
		Model	OR (95% CI)	*P* value
Overall	0.80	F	1.38 (1.12–1.70)	0.002
Asian	0.95	F	1.42 (1.08–1.87)	0.01
Caucasian	0.74	F	1.21 (0.86–1.70)	0.28
HBV	0.95	F	1.42 (1.08–1.87)	0.01
Hospital	0.93	F	1.45 (1.09–1.93)	0.01
Population	0.27	F	1.33 (0.97–1.83)	0.08

F – fixed-effects model.

A marginal association was found in population-based studies (OR=1.33; 95% CI 0.97–1.83; *P*=0.08). Table 2 shows the results of the meta-analysis.

We performed a sensitivity analysis to assess the stability of the meta-analysis. No single study changed the pooled OR, suggesting that results of this meta-analysis are robust (Figure 2).

The shape of the funnel plot was symmetrical (Figure 3) and no significant publication bias was detected by Begg's test (*P*=0.564).

Discussion

This meta-analysis, with 859 HCC patients and 1482 healthy controls, investigated the association between IFN-γ +874A/T

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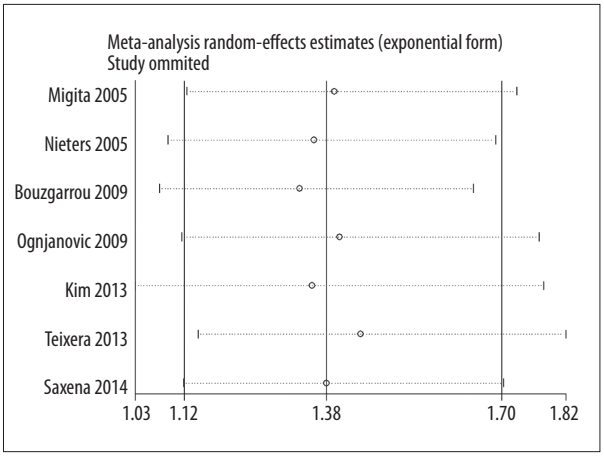

Figure 2. Sensitivity analysis for the association between IFN-γ +874A/T polymorphism and risk of HCC.

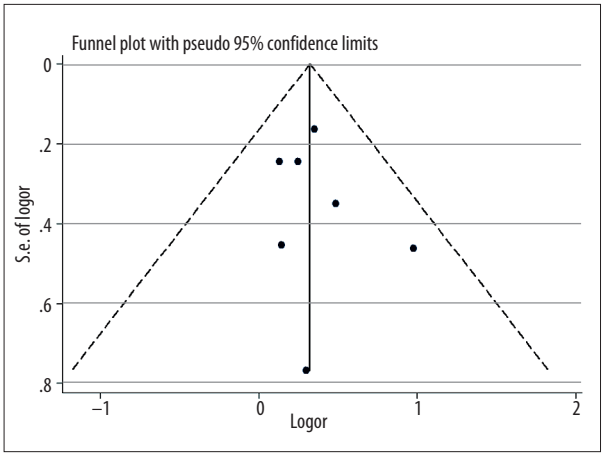

Figure 3. Funnel plot for the association between IFN-γ +874A/T polymorphism and risk of HCC.

polymorphism and HCC risk. Results of this study revealed that individuals with IFN-γ +874A/T polymorphism might have increased HCC risk. Furthermore, Asians, but not Caucasians, with IFN-γ +874A/T polymorphism showed increased HCC risk in the subgroup analysis. Different environments and lifestyles might account for this result. In the HBV patients, IFN-γ +874A/T polymorphism was also significantly associated with HCC risk. There was only 1 study using HCV patients included in this meta-analysis, thus more studies with HCV patients are needed to test this result. In the subgroup analysis by control source, we found a positive association in hospital-based studies, but only a marginal result was observed in the population-based studies. Therefore, more population-based studies are needed to validate this result.

Lee et al. reported that pretreatment serum IFN-γ level not only correlated with the baseline tumor stage and size, but also correlated with tumor recurrence after curative treatment in early-stage HCC patients [5]. In addition, Xiao et al. found that the combination of intratumoral iNKT cells and IFN-γ was an independent predictor for recurrence and survival in HCC patients [14]. The imbalance of Th1 and Th2 cytokines in the microenvironment might play a critical role in modulating HCC progression and metastasis [15]. Saxena et al. found that IFN-γ level was higher in HCC patients [13]. In addition, a previous study suggested that IFN-γ +874A/T polymorphism could influence the production of IFN-γ level [6,16]. Therefore, IFN-γ +874A/T polymorphism might impact the risk of HCC.

To the best of our knowledge, this is the first meta-analysis to assess the association between IFN-γ +874A/T polymorphism and risk of HCC. There was no significant heterogeneity or publication bias in this meta-analysis. Furthermore, sensitivity analysis indicated that the results were stable. However, there were some limitations. First, the number of included case-control studies was small; thus, more studies should be designed to investigate the association between IFN-γ +874A/T polymorphism and risk of HCC. Second, there was only 1 study in Africans and 2 studies in Caucasians in this meta-analysis; therefore, further studies are needed to validate the results in these races. Third, we did not perform other subgroup analyses due to limited data. Forth, we did not assess the interactions between IFN-γ +874A/T polymorphism and other risk factors of HCC, such as smoking.

Conclusions

Results of this study suggest that IFN-γ +874A/T polymorphism is associated with HCC risk.

Conflict of interest

The authors declare that no competing interests exist.

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