Association Between *TGF-β1* Polymorphisms and Hepatocellular Carcinoma Risk: A Meta-Analysis

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Background: Associations between transforming growth factor (*TGF*)- $\beta 1$ polymorphisms and hepatocellular carcinoma (HCC) risk remained controversial. Therefore, we performed this meta-analysis to investigate these associations. **Methods:** We searched Pubmed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases for studies before March 2013. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to calculate the strength of association. **Results:** A total of 14 studies were included in this meta-analysis. *TGF-β1* +869C/T polymorphism was significantly associated with HCC risk (OR=1.74, 95% CI: 1.22–2.47, $p=0.002$). In addition, a significant association between –509C/T polymorphism and HCC risk was observed (OR=1.40, 95% CI: 1.15–1.70, $p=0.0007$). Furthermore, significant associations between these polymorphisms and HCC risk were found in Asians and population-based studies. **Conclusions:** Our meta-analysis suggested that the *TGF-β1* +869C/T and –509C/T polymorphisms may be risk factors for developing HCC.

Introduction

HEPATOCELLULAR CARCINOMA (HCC) is a primary cancer of the liver; it ranks as the fifth most common malignant cancer and the third leading cause of cancer-related death worldwide. Chronic hepatitis B virus (HBV) and/or hepatitis C virus (HCV) infections resulting in hepatic fibrosis and cirrhosis are the major risk factors for HCC (Yuen *et al.*, 2009). However, only a part of the people exposed to HBV or HCV eventually develop HCC, indicating that host genetic factors might play an important role in the tumorigenesis of HCC (Han, 2012).

Transforming growth factor (*TGF*)- β is a multiplicity factor mediating cellular processes, including cell growth, cell differentiation, apoptosis, and cellular homeostasis (Epstein *et al.*, 2000; Verrecchia and Mauviel, 2002). Morris *et al.* (2012) reported that *TGF-β* signaling promoted the formation of liver tumors that arose in the setting of p53 inactivation. *TGF-β1* is one of *TGF-β* isoforms. *TGF-β1* promotes the epithelial-to-mesenchymal transformation in HCC cells *in vitro* in combination with Laminin-5 (Giannelli *et al.*, 2002). In addition, previous studies have shown upregulated expression of *TGF-β1* in tumor cells, including HCC. Furthermore, the overexpression of hepatic *TGF-β1* was found in HCC tissues and correlated with carcinogenesis, progression, and prognosis of HCC (Teicher, 2001; Okumoto *et al.*, 2004). Therefore, these results indicated that *TGF-β1* may have a critical role in the pathogenesis of HCC.

The human *TGF-β1* gene is located on chromosome 19q13.1–13.39. Five polymorphisms have been identified: two in the promoter region at positions –800 and –509, one at position +72 in a nontranslated region, and two in the signal sequence at positions +869 and +915. Some studies have investigated the associations between the *TGF-β1* polymorphisms and susceptibility of HCC (Ben-Ari *et al.*, 2003; Kwon *et al.*, 2003; Migita *et al.*, 2005; Falletti *et al.*, 2008; Zhang, 2008; Qin, 2009, 2012; Okamoto *et al.*, 2010; Miki *et al.*, 2011; Yang, 2011; Radwan *et al.*, 2012; Shi *et al.*, 2012; Xin *et al.*, 2012; Wei *et al.*, 2012). Most of the studies focused on two polymorphisms: +869C/T (rs1800470) and –509C/T (rs1800469). However, the associations observed between two polymorphisms and the risk for HCC were controversial and inconclusive. This meta-analysis aimed to comprehensively explore the associations between the *TGF-β1* polymorphisms and risk of HCC.

Materials and Methods

Publication search

PubMed, EMBASE, Chinese National Knowledge Infrastructure (CNKI), and Wanfang databases were searched for genetic association studies published before April 2013 that evaluated the *TGF-β1* polymorphisms and HCC in humans. We used combinations of the following terms: (hepatocellular carcinoma or liver cancer or hepatoma or liver tumor) and (transforming growth factor beta or transforming growth

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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	Polymorphisms
Ben-Ari	2003	Israel	Caucasian	10/48	No	Population	+869C/T
Kwon	2003	Korea	Asian	49/35	No	Population	+869C/T
Migita	2005	Japan	Asian	48/188	HBV	Hospital	+869C/T, +915C/G
Falleti	2008	Italy	Caucasian	54/140	No	Population	+869C/T, -509C/T -800A/G, +915C/G
Zhang	2008	China	Asian	78/101	No	Population	+869C/T, +915C/G
Qin	2009	China	Asian	434/480	No	Population	-509C/T
Okamoto	2010	Japan	Asian	92/83	HCV	Hospital	+869C/T
Miki	2011	Japan	Asian	212/765	HCV	NA	-509C/T
Yang	2011	China	Asian	608/612	No	Population	-509C/T
Radwan	2012	Egypt	African	128/160	Mixed	Mixed	-509C/T
Xin	2012	China	Asian	347/881	No	Population	-509C/T
Qin L.	2012	China	Asian	114/114	Mixed	Population	-509C/T
Wei	2012	China	Asian	102/110	No	Population	-509C/T, -800A/G

NA, not available; HBV, hepatitis B virus; HCV, hepatitis C virus.

factor- β 1 or TGF β 1 or TGF) and (polymorphism or mutation or variant). All eligible articles were retrieved, and their references were checked for other relevant studies. We also contacted the authors of the genome-wide association studies (GWAS) to get more data by E-mail.

Study selection

The inclusion criteria were (1) evaluation of TGF- β 1 polymorphisms and HCC risk, (2) case-control studies, and (3) with sufficient available data to estimate an odds ratio (OR) with its 95% confidence interval (95% CI). The included studies should meet all of these above-mentioned criteria. Any study with wrong data or inconsistent data was excluded.

Data extraction

The following variables were extracted from each study if available: first author's name, year of publication, original country, ethnicity, sample size, hepatitis virus status of the controls, source of controls (hospital based or population based), TGF- β 1 polymorphisms, and genotype number in cases and controls. Information was carefully extracted from all the eligible publications, independently by two of the authors.

Statistical analysis

When the data from at least three similar studies were available, the meta-analysis was performed. Because there were no +915CG and +915CC carriers in the study by Migita *et al.* (2005), thus only two studies can be used. Therefore, we did not carry out the meta-analysis for +915C/G polymorphism.

The strength of the associations between the TGF- β 1 polymorphisms and HCC risk was measured by ORs and 95% CIs. OR1, OR2, and OR3 were calculated for the genotypes: TT versus CC (OR1), CT versus CC (OR2), and TT versus CT (OR3) for the +869C/T and -509C/T polymorphisms. These pairwise differences were used to indicate the most appropriate genetic model (Thakkinstian *et al.*, 2005). Once the best genetic model was identified, this model was used to collapse the three genotypes into two groups (except in the case of a codominant model) and to pool the results.

Hardy-Weinberg equilibrium (HWE) was evaluated using the Chi-square test. $p < 0.05$ was considered representative of a departure from HWE. Heterogeneity assumption was checked by the Q-test and a p -value greater than 0.10 indicates a lack of heterogeneity among studies. The random-effects model was used. Subgroup analyses were performed by stratifying on ethnicity and controls of source. We performed influence analysis by omitting each study to assess the stability of results; we also performed sensitivity analysis by excluding the HWE-violating studies to check the robustness of the result. Possible publication bias was tested by funnel plots. All statistical tests were performed by STATA 11.0 software (Stata Corporation,

TABLE 2. DISTRIBUTION OF TGF- β 1 GENOTYPE AMONG PATIENTS AND CONTROLS

	Patients			Controls			
Study	CC	CT	TT	CC	CT	TT	HWE
+ 869C/T							
Ben-Ari	0	2	8	3	10	35	Yes
Kwon	10	21	18	12	14	9	Yes
Migita	7	30	11	60	93	35	Yes
Falleti	8	26	20	29	62	49	Yes
Zhang	17	28	33	34	44	23	Yes
Okamoto	20	47	22	22	32	29	No
- 509C/T							
Falleti	14	23	17	57	61	22	Yes
Qin	48	197	147	61	212	101	Yes
Miki	46	107	59	192	379	194	Yes
Yang	236	285	87	251	277	84	Yes
Radwan	24	64	40	96	142	74	Yes
Shi	24	40	8	55	53	9	Yes
Xin	82	177	88	212	423	237	Yes
Qin L.	11	49	54	18	45	51	Yes
Wei	19	57	26	41	53	16	Yes
	CC	CG	GG	CC	CG	GG	
+ 915C/G							
Migita	0	0	48	0	0	188	NA
Falleti	0	7	47	0	13	127	Yes
Zhang	0	16	62	0	15	86	Yes

HWE, Hardy-Weinberg equilibrium; TGF- β 1, transforming growth factor beta 1.

TABLE 3. DETERMINATION OF THE GENETIC EFFECT OF *TGF- β 1* POLYMORPHISMS AND SUBGROUP ANALYSES

Contrast	Comparison	Sample size		P _{heterogeneity}	Test of association		
		Case	Control		Model	OR (95% CI)	p-Value
+869C/T							
TT vs. CC	Overall	174	340	0.34	R	1.80 (1.15–2.80)	0.009
CT vs. CC	Overall	216	415	0.87	R	1.68 (1.15–2.46)	0.007
TT vs. CT	Overall	266	435	0.13	R	1.07 (0.68–1.68)	0.77
TT + CT vs. CC	Overall	328	595	0.82	R	1.74 (1.22–2.47)	0.002
TT+CT vs. CC	Asian	264	407	0.56	R	1.79 (1.21–2.64)	0.003
TT+CT vs. CC	Population	191	324	0.97	R	1.76 (1.11–2.79)	0.02
TT+CT vs. CC	HWE	239	512	0.90	R	1.94 (1.29–2.92)	0.001
–509C/T							
TT vs. CC	Overall	1030	1771	0.02	R	1.61 (1.21–2.14)	0.001
CT vs. CC	Overall	1503	2628	0.32	R	1.28 (1.09–1.50)	0.003
TT vs. CT	Overall	1525	2433	0.26	R	1.15 (0.97–1.36)	0.10
TT+CT vs. CC	Overall	2030	3416	0.08	R	1.40 (1.15–1.70)	0.0007
TT+CT vs. CC	Asian	1848	2964	0.13	R	1.30 (1.07–1.58)	0.009
TT+CT vs. CC	Population	1690	2339	0.07	R	1.40 (1.10–1.77)	0.006

R, random-effects model; OR, odds ratio; CI, confidence interval.

College Station, TX) and Revman 5.1 software (Nordic Cochrane Center, Copenhagen, Denmark).

Results

Study characteristics

Fourteen association studies relating to the *TGF- β 1* polymorphisms with susceptibility to HCC met the inclusion requirements for the meta-analysis (Ben-Ari *et al.*, 2003; Kwon

et al., 2003; Migita *et al.*, 2005; Falletti *et al.*, 2008; Zhang, 2008; Qin, 2009, 2012; Okamoto *et al.*, 2010; Miki *et al.*, 2011; Yang, 2011; Radwan *et al.*, 2012; Shi *et al.*, 2012; Xin *et al.*, 2012; Wei *et al.*, 2012). There were six studies on +869C/T polymorphism, nine studies on –509C/T polymorphism, and three studies on +915C/G polymorphism. There were 11 studies performed using Asians, 2 studies using Caucasians, and 1 study using Africans. Table 1 lists the main characteristics of studies for meta-analysis. Genotype numbers and HWE examination results are listed in Table 2. Genotype distributions

FIG. 1. Meta-analysis for the association between hepatocellular carcinoma (HCC) risk and the transforming growth factor (*TGF*)- β 1 +869C/T polymorphism.

FIG. 2. One-way sensitivity analysis for the *TGF- β 1* +869C/T polymorphism with HCC risk.

in the controls of all studies were in agreement with HWE except for one study (Okamoto *et al.*, 2010).

Quantitative data synthesis

***TGF- β 1* +869C/T polymorphism.** Six studies determined the association between +869C/T polymorphism and HCC risk. The sample sizes for case and control groups were 328 and 595, respectively. The estimated OR1, OR2, and OR3 were 1.80 ($p=0.009$), 1.68 ($p=0.007$), and 1.07 ($p=0.77$) (Table 3). These estimates suggested a dominant genetic model; therefore, TT and CT were combined and compared with CC. The pooled OR was 1.74 (95% CI: 1.22–2.47, $p=0.002$) (Fig. 1). In the stratified analysis by ethnicity, a statistically significant association was found for studies with Asians (OR = 1.79, 95% CI: 1.21–2.64, $p=0.003$). In the subgroup analysis by source of controls, the *TGF- β 1* +869C/T polymorphism was significantly associated with the risk of HCC in population-based studies (OR = 1.76, 95% CI: 1.11–2.79, $p=0.02$).

We performed sensitivity analysis to evaluate the stability of the meta-analysis. As shown in Figure 2, the statistical significance of the result was not altered when a single study

was omitted. In addition, sensitivity analysis by excluding the studies departure from HWE did not materially alter the result (Table 3). The funnel plot did not reveal evidence of obvious asymmetry (Fig. 3).

***TGF- β 1* –509C/T polymorphism.** Eight studies identified the association between *TGF- β 1* –509C/T polymorphism and HCC risk. A total of 2030 cases and 3416 controls were included in this meta-analysis. The estimated OR1, OR2, and OR3 were 1.61 ($p=0.001$), 1.28 ($p=0.003$), and 1.15 ($p=0.10$), respectively (Table 3). Thus, these estimates suggested a dominant genetic model; therefore, TT and CT were combined and compared with CC. The pooled OR was 1.40 (95% CI: 1.15–1.70, $p=0.0007$) (Fig. 4). Subgroup analysis was performed by ethnicity. A statistically significant finding was found in Asians (OR = 1.30, 95% CI: 1.07–1.58, $p=0.009$). In the stratified analysis by the control source, statistically significantly increased HCC risk was found in population-based studies (OR = 1.40, 95% CI: 1.10–1.77, $p=0.006$).

In the sensitivity analysis, we found that there was no substantial modification of our estimates after exclusion of

FIG. 3. Funnel plot for HCC risk and the *TGF- β 1* +869C/T polymorphism.

FIG. 4. Meta-analysis for the association between HCC risk and the *TGF-β1* -509C/T polymorphism.

individual studies (Fig. 5). The shape of the funnel plot seemed a little asymmetrical (Fig. 6).

Discussion

Ito *et al.* (1991) found that both mRNA and protein concentrations of *TGF-β1* levels were increased in patients with HCC. Higher levels of *TGF-β1* were present in patients with aggressive and metastatic HCC as compared to patients with non-metastatic HCC (Giannelli *et al.*, 2002). In addition to plasma levels, urinary *TGF-β1* levels were also found to have a prog-

nostic value, determining poor survival in HCC patients (Van Zijl *et al.*, 2009). Furthermore, *TGF-β1* levels decreased in patients who underwent effective therapy for HCC, suggesting its potential use as a marker of the antitumoral effect (Shirai *et al.*, 1994). Thus, *TGF-β1* appeared to play a unique role in the molecular pathogenesis of HCC. *TGF-β1* +869C/T and -509C/T polymorphisms have been identified. These allelic variants resulted in significant differences with regard to *TGF-β1* expression and plasma concentration (Grainger *et al.*, 1999). Therefore, it is possible that *TGF-β1* +869C/T and -509C/T polymorphisms could influence the risk of HCC.

FIG. 5. One-way sensitivity analysis for the *TGF-β1* -509C/T polymorphism with HCC risk.

FIG. 6. Funnel plot for HCC risk and the TGF- β 1 -509C/T polymorphism.

The present meta-analysis, including 13 studies evaluated the association between two functional polymorphisms in the TGF- β 1 gene and HCC risk. For TGF- β 1 +869C/T polymorphism, we found that individuals with the +869T allele (TT or CT) showed an increased risk of HCC in the overall population. For TGF- β 1 -509C/T polymorphism, a significant association was also found. The result indicated that -509T allele carriers had a 40% increased HCC risk than CC carriers. These results suggested that TGF- β 1 +869C/T and -509C/T polymorphisms may be risk factors of HCC.

Population stratification is an area of concern and can lead to spurious evidence for the association between the marker and disease, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they live in (Hirschhorn *et al.*, 2002). Thus, we carried out stratified analysis by ethnicity. In the stratified analyses by ethnicity, the significant associations were observed in Asians for two polymorphisms. However, in our studies, only two studies for Caucasians and one study for Africans were included in this meta-analysis. Thus, the positive associations between these polymorphisms and HCC could not be ruled out in Caucasians and Africans. More studies using Caucasians and Africans are needed in the future. Different control sources may be a confounding factor that may impact the conclusion of our study because of case-control studies. In this meta-analysis, some studies used a healthy population as the reference group, whereas others selected chronic hepatitis virus carriers without HCC as the reference group. To eliminate interference from the confounding factor, we performed stratified analysis by the source of controls. We found that TGF- β 1 polymorphisms exhibited increased HCC risk in the population-based studies. Our findings suggested that TGF- β 1 polymorphisms were genetic susceptibility factors for HCC in the background of healthy individuals. Whether chronic HBV/HCV infection could mediate the ability of genetic factors to contribute to HCC is still unknown. More studies should be designed to analyze the association between hepatitis virus infection-TGF- β 1 interactions and HCC risk.

Some limitations should be pointed out. First, the numbers of published studies using Caucasians and Africans were limited. In addition, the numbers of studies for +869C/T and

other polymorphisms (e.g., -800A/G and +915C/G) were small. Second, these results were based on unadjusted estimates that lack the original data from the eligible studies, which limited the evaluation of the effect of the gene-gene interaction during HCC development. Third, we were unable to adjust the meta-analysis to correct for common HCC risk factors (e.g., alcohol or smoking) as these were not uniformly reported in the independent investigations and could not be easily obtained.

In conclusion, this meta-analysis found significant associations between TGF- β 1 +869C/T and -509C/T polymorphisms and HCC risk. To better understand the potential mechanism for HCC in humans, large well-designed cohort studies are needed to confirm these associations. Further researches should be carried out to explore the effect of genetic networks and environmental factors in different ethnic populations.

Acknowledgments

We thank Dr. Hidenori Ochi and Dr. Kazuaki Chayama (Laboratory for Digestive Diseases, Center for Genomic Medicine, RIKEN, Hiroshima, Japan) for providing relevant information. This work is supported by Grant 81171365 from the National Natural Science Foundation of China.

Author Disclosure Statement

The authors have declared that no competing interests exist.

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