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Association between transforming growth factor-β1 -509 C>T variants and hepatocellular carcinoma susceptibility: a meta-analysis

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The transcriptional activity of transforming growth factor-β (TGF-β) is increased in subjects with hepatocellular carcinoma (HCC). Recent studies have indicated that the -509C genotype in hepatitis B virus (HBV)-infected subjects and the -509T genotype in hepatitis C virus (HCV)-infected subjects can increase the transcriptional activity of the TGF-β1 gene. We conducted a meta-analysis to clarify whether these two hepatitis viruses affect the association between TGF-β1 C-509T variants and HCC susceptibility. Using data derived from 8 case-control studies available in the PubMed database (5 with Asian and 3 with Caucasian populations), including 1,427 cases and 3,735 controls [1,610 patients with chronic liver disease and 2,125 healthy controls], we calculated pooled odds ratios with corresponding 95% confidence intervals. We used dominant (TT + CT vs. CC), recessive (TT vs. CC + CT), and co-dominant (TT vs. CC and CT vs. CC) genetic models. An overall analysis showed no association between the TGF-β1 C-509T variants and HCC susceptibility for all models. In contrast, a subgroup analysis, based on the infecting hepatitis viruses, provided the following results. Among the cases and controls with chronic liver disease, the TGF-β1 C-509T variants were significantly associated with decreased HCC susceptibility for two models with HBV-infected subjects, whereas the variants were significantly associated with increased HCC susceptibility for one model with HCV-infected subjects. Among the cases and healthy controls, there was a significant association between the TGF-β1 C-509T variants and increased HCC susceptibility for two models involving HCV-infected subjects. Among the cases and the entire control group, the same results were obtained for all genetic models with HCV-infected subjects. Although further data accumulation is required, our results suggest that these two hepatitis viruses affect the association between TGF-β1 C-509T variants and HCC susceptibility in opposite manners.

Key words: transforming growth factor-β1, gene variants, hepatocellular carcinoma, hepatitis B virus, hepatitis C virus

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related deaths worldwide [1]. The incidence of HCC has increased primarily because of an increased number of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections [1]. However, the same viral infection does not necessarily lead to HCC with the same level of probability among individuals. Therefore, it is important to investigate and understand the factors that contribute to HCC susceptibility. Genetic epidemiological analyses have shown that host genetic factors can influence disease susceptibility. In this context, the association between genetic variants and HCC susceptibility has been investigated [2, 3].

Experimental and clinical investigations have suggested that transforming growth factor-β (TGF-β) plays a pleiotropic role in the hepatocarcinogenic process because it suppresses the proliferation of hepatocytes during hepatic regeneration, and it promotes HCC cell invasion by inducing the epithelial–mesenchymal transition [4, 5]. TGF-β has 3 isoforms (TGF-β1–3), among which TGF-β1 is the most common. Recent studies have found that TGF-β1 is overexpressed in the sera of HCC patients [6-8] and that its overexpression is associated with poor HCC prognosis [9, 10]. Some studies have also described TGF-β1 gene variants in codons 10 and 25 of exon 1 and at the promoter region positions -800 and -509 [11, 12]. Among these variants, TGF-β1 -509 C>T variants (rs1800469) have been most frequently examined as a possible genetic factor contributing to HCC susceptibility [13-21]. However, these studies have yielded conflicting results.

Recent studies have found that TGF-β1 -509 C>T variants are closely associated with transcriptional activity of the TGF-β1 gene [12]. Moreover, it has been shown that the type of hepatitis virus infection influences this association [22, 23]. A study of HBV-related cirrhosis cases reported that serum TGF-β1 levels were higher in patients with the -509C geno-

type than those with the -509T genotype [23]. This study also demonstrated that the -509C genotype was associated with greater transcriptional activity of the TGF-β1 gene. In contrast, in a study of HCV infection, an in vitro promoter assay showed that compared with the -509T genotype, the -509C genotype was associated with lower transcriptional activity of the TGF-β1 gene under co-expression of the HCV core protein [22]. Therefore, these studies indicate that in opposite manners, these two hepatitis viruses influence the association between the TGF-β1 -509 C>T variants and the transcriptional activity of the TGF-β1 gene.

Given these findings, we hypothesized that combined patterns of the TGF-β1 -509 C>T variants and infecting hepatitis viruses may affect HCC susceptibility. To evaluate this hypothesis, we conducted a meta-analysis of related studies.

Materials and methods

Literature search. We searched the PubMed database to identify studies involving the relationship between TGF-β1 -509 C>T variants and HCC susceptibility. The following keywords were used: (hepatocellular carcinoma or HCC or hepatoma or liver cancer or liver carcinoma or liver tumor or hepatic tumor) and (transforming growth factor or TGF) and (polymorphism or genotype or variation or variant or alteration or mutation). Our search was restricted to English-language studies published online until January 31, 2016. Original, case-control studies were selected if they included data sufficient for our meta-analysis.

Data collection. Three researchers (Y. M., T. M., and N.H.) independently performed the literature search and data extraction. The collected data included the first author's name, publication year, study design, subject ethnicities, number of cases and controls, HCC causes, and number of cases and controls with TGF-β1 C-509T variants. Discrepancies were resolved through discussions between the researchers.

Statistical analysis. We used four genetic models for the analysis: dominant (TT + CT vs. CC), recessive (TT vs. CC + CT), and co-dominant (TT vs. CC and CT vs. CC) [24]. First, we performed an overall analysis for each model, and then we performed a subgroup analysis based on the subjects' ethnicities and infecting hepatitis viruses. Ethnicity was categorized as Asian or Caucasian. For these analyses, we used the following control groups: individuals with chronic liver disease (CLD), healthy controls, and a group that included healthy controls and CLD patients. Using a chi-squared test, Hardy-Weinberg equilibrium was tested in the controls. We determined pooled odds ratios, with corresponding 95% confidence intervals, to assess the relationship between the TGF-β1 C-509T variants and HCC susceptibility. Cochran's Q test was used to determine heterogeneity between studies [25]. If study heterogeneity was found (Q, $P \leq 0.1$), the DerSimonian and Laird random effects model was adopted [26]; otherwise, the Mantel-Haenszel fixed effects model was adopted [27]. Sensitivity analyses were performed by omitting one study at a time to assess the influence of single studies. Egger's test was used to test for publication bias. All analyses were performed using STATA ver. 13.1 (STATA Corp., College Station, TX, USA), and a P-value of <0.05 was considered to be statistically significant.

Results

A total of 143 publications were identified as being possibly relevant. Fourteen of the studies examined the association between the TGF-β1 C-509T variants and HCC susceptibility.

Table 1. Studies of the relationship between TGF β1 C-509T variants and HCC susceptibility.

Author	Year	Ethnicity	Etiology of CLD or HCC	Cases	CLD controls (A)	Healthy controls (B)	(A) + (B)	TGF-β1 C-509T variant												*P*-value of HWE in (A)	*P*-value of HWE in (B)	*P*-value of HWE in (A) + (B)
								Cases			(A)			(B)			(A) + (B)					
								CC	CT	TT	CC	CT	TT	CC	CT	TT	CC	CT	TT			
Kim	2003	Asian	HBV	228	773	0	773	76	152		187	586					187	586				
Falleti	2008	Caucasian	Various*	54	134	140	274	14	23	17	36	62	36	57	61	22	93	123	58	0.39	0.40	0.15
Qi	2009	Asian	HBV	379	196	299	495	89	198	92	31	101	64	50	156	93	81	257	157	0.40	0.26	0.16
Radwan	2012	Caucasian	HCV	128	152	160	312	24	64	40	34	74	44	62	68	30	96	142	74	0.79	0.15	0.13
Xin	2012	Asian	HBV	347	0	881	881	82	177	88				212	432	237	212	432	237		0.58	0.58
Shi	2012	Asian	NA	73	0	117	117	24	40	8				55	53	9	55	53	9		0.44	0.44
Saxena	2014	Caucasian	HBV	59	121	153	274	9	39	11	16	85	20	44	94	15	60	179	35	< 0.0001	0.007	< 0.0001
Ma	2015	Asian	HCV	159	234	375	609	50	67	42	91	101	42	143	161	71	234	262	113	0.14	0.036	0.010

TGF-β transforming growth factor-β, *HCC* hepatocellular carcinoma, *CLD* chronic liver disease, *HWE* Hardy-Weinberg equilibrium, *HBV* hepatitis B virus, *HCV* hepatitis C virus, *NA* not available

* The etiologies were HBV in 9 cases, HCV in 25 cases, and others in 20 cases; HBV in 14 CLD controls, HCV in 62 CLD controls, and others in 58 CLD controls.

Of these 14 studies, 1 family study of liver disease and 5 review articles were excluded. Eventually, 8 studies were selected.

Overall analysis. Table 1 provides the details of the 8 studies (Asian populations, n=5; Caucasian populations, n=3) included in our analysis. There were 1,427 HCC cases and 3,735 controls, and all studies were hospital-based. In studies by Falleti et al. [14], Qi et al. [15], Radwan et al. [16], Xin et al. [17], and Shi et al. [18], the control genotype distributions were in Hardy-Weinberg equilibrium, but they were not in the studies by Saxena et al. [19] and Ma et al. [20]. In the Kim et al. study [13], it could not be determined whether the genotype distribution of the controls was in Hardy-Weinberg equilibrium because the TT and CT genotypes were counted as a single group.

According to the respective combinations of the cases and controls, we performed meta-analyses using each genetic model (Tables 2, 3, and 4). For the abovementioned reason, we only incorporated data from the Kim et al. study [13] into a dominant model. For all genetic models used, there was no significant association between the TGF-β1 C-509T variants and HCC susceptibility. A sensitivity analysis found no alterations in the pooled odds ratios for most of the models (data not shown). Egger's test ruled out the presence of publication bias, except for a recessive model using healthy controls.

Subgroup analysis based on ethnicity and infecting hepatitis viruses. First, we performed a subgroup analysis based on ethnicity. Among the cases and controls with CLD, there was no significant association between the TGF-β1 C-509T variants and HCC susceptibility for all genetic models (Table 2). In contrast, among the cases and healthy controls/entire control group, there was a significant association between the TGF-β1 C-509T variants and increased HCC susceptibility for all genetic models in Caucasians (Tables 3 and 4).

Table 2. Association between TGF-β1 C-509T variants and HCC susceptibility (cases and CLD controls).

Category	No. of studies	Dominant TT + CT vs. CC				Recessive TT vs. CC + CT				Homogeneous co-dominant TT vs. CC				Heterogeneous co-dominant CT vs. CC			
		OR (95% CI)	P^a	I^2,%	P^b	OR (95% CI)	P^a	I^2,%	P^b	OR (95% CI)	P^a	I^2,%	P^b	OR (95% CI)	P^a	I^2,%	P^b
Overall	5*	0.90 (0.65–1.24)	0.51	59	0.033	1.09 (0.75–1.57)	0.69	57	0.055	1.06 (0.62–1.82)	0.83	67	0.016	0.96 (0.74–1.24)	0.73	0	0.46
Ethnicity																	
Asian	2*	0.81 (0.49–1.34)	0.41	79	0.008	1.03 (0.42–2.51)	0.95	88	0.004	0.95 (0.27–3.37)	0.94	91	0.001	0.91 (0.52–1.59)	0.74	65	0.092
Caucasian	3	1.09 (0.73–1.64)	0.67	0	0.77	1.16 (0.80–1.68)	0.43	0	0.97	1.20 (0.75–1.93)	0.45	0	0.92	1.04 (0.68–1.59)	0.86	0	0.74
Viral causes																	
HBV	2*	0.64 (0.50–0.83)	0.001	0	0.81	0.73 (0.52–1.03)	0.077	33	0.22	0.57 (0.36–0.90)	0.016	14	0.28	0.71 (0.47–1.08)	0.11	0	0.73
HCV	2	1.34 (0.95–1.89)	0.098	0	0.78	1.37 (0.96–1.94)	0.083	13	0.28	1.58 (1.04–2.43)	0.034	0	0.44	1.21 (0.84–1.76)	0.31	0	0.97

TGF-β transforming growth factor-β, *HCC* hepatocellular carcinoma, *CLD* chronic liver disease, *HBV* hepatitis B virus, *HCV* hepatitis C virus
P^a P-value for association, P^b P-value for heterogeneity
*The data from the Kim et al. study were included only when an analysis using a dominant model was performed because the TT and CT genotypes were counted as a single group in that study.

Table 3. Association between TGF-β1 C-509T variants and HCC susceptibility (cases and healthy controls).

Category	No. of studies	Dominant TT + CT vs. CC				Recessive TT vs. CC + CT				Homogeneous co-dominant TT vs. CC				Heterogeneous co-dominant CT vs. CC			
		OR (95% CI)	P^a	I^2,%	P^b	OR (95% CI)	P^a	I^2,%	P^b	OR (95% CI)	P^a	I^2,%	P^b	OR (95% CI)	P^a	I^2,%	P^b
Overall	7	1.44 (0.99–2.10)	0.058	77	< 0.0001	1.36 (0.94–1.97)	0.098	72	0.001	1.70 (0.98–2.95)	0.059	82	< 0.0001	1.32 (0.96–1.82)	0.083	62	0.014
Ethnicity																	
Asian	4	1.08 (0.75–1.56)	0.68	70	0.018	1.02 (0.71–1.46)	0.92	64	0.040	1.07 (0.63–1.82)	0.80	76	0.006	1.06 (0.78–1.44)	0.70	52	0.10
Caucasian	3	2.37 (1.62–3.46)	< 0.0001	0	0.75	2.12 (1.44–3.13)	< 0.0001	0	0.89	3.38 (2.11–5.42)	< 0.0001	0	0.98	2.05 (1.37–3.05)	< 0.0001	0	0.64
Viral causes																	
HBV	3	1.04 (0.61–1.75)	0.90	76	0.015	0.95 (0.63–1.44)	0.82	65	0.056	1.06 (0.51–2.19)	0.88	82	0.004	1.04 (0.66–1.63)	0.87	65	0.057
HCV	2	1.87 (0.93–3.76)	0.078	77	0.038	1.70 (1.21–2.38)	0.002	0	0.49	2.33 (1.16–4.66)	0.017	64	0.095	1.65 (0.82–3.32)	0.16	73	0.053

TGF-β transforming growth factor-β, *HCC* hepatocellular carcinoma, *CLD* chronic liver disease, *HBV* hepatitis B virus, *HCV* hepatitis C virus
P^a P-value for association, P^b P-value for heterogeneity

Table 4. Association between TGF-β1 C-509T variants and HCC susceptibility (cases and CLD and healthy controls).

Category	No. of studies	Dominant TT + CT vs. CC				Recessive TT vs. CC + CT				Homogeneous co-dominant TT vs. CC				Heterogeneous co-dominant CT vs. CC			
		OR (95% CI)	P^a	I^2, %	P^b	OR (95% CI)	P^a	I^2, %	P^b	OR (95% CI)	P^a	I^2, %	P^b	OR (95% CI)	P^a	I^2, %	P^b
Overall	7*	1.14 (0.83–1.56)	0.42	76	< 0.0001	1.12 (0.88–1.63)	0.24	67	0.007	1.38 (0.87–2.19)	0.17	78	< 0.0001	1.18 (0.91–1.53)	0.22	51	0.056
Ethnicity																	
Asian	4*	0.96 (0.68–1.37)	0.82	79	0.001	1.03 (0.70–1.52)	0.90	73	0.011	1.07 (0.60–1.90)	0.82	82	0.001	1.05 (0.76–1.45)	0.75	61	0.054
Caucasian	3	1.70 (1.19–2.43)	0.003	0	0.79	1.54 (1.11–2.15)	0.011	0	0.93	2.09 (1.37–3.18)	0.001	0	0.98	1.55 (1.06–2.26)	0.022	0	0.71
Viral causes																	
HBV	3*	0.87 (0.70–1.08)	0.20	64	0.038	0.89 (0.63–1.25)	0.50	58	0.094	0.90 (0.49–1.65)	0.74	77	0.012	0.95 (0.66–1.36)	0.77	54	0.112
HCV	2	1.54 (1.15–2.08)	0.004	15	0.28	1.52 (1.12–2.06)	0.007	0	0.81	1.90 (1.32–2.73)	0.001	0	0.57	1.40 (1.01–1.93)	0.043	30	0.23

TGF-β transforming growth factor-β, *HCC* hepatocellular carcinoma, *CLD* chronic liver disease, *HBV* hepatitis B virus, *HCV* hepatitis C virus
P^a P-value for association, P^b P-value for heterogeneity
*The data from the Kim et al. study were included only when an analysis using a dominant model was performed because the TT and CT genotypes were counted as a single group in that study.

Second, we performed a subgroup analysis based on the infecting hepatitis viruses. Among the cases and controls with CLD, the TGF-β1 C-509T variants were significantly associated with decreased HCC susceptibility for two models in the HBV-infected subjects, whereas the variants were significantly associated with increased HCC susceptibility for one model in the HCV-infected subjects (Table 2). Among the cases and healthy controls, there was a significant association between TGF-β1 C-509T variants and increased HCC susceptibility for two models involving HCV-infected subjects (Table 3); among the cases and the entire control group, the same results were obtained for all models involving HCV-infected subjects (Table 4).

Discussion

In the present study, our overall analysis showed no association between the TGF-β1 C-509T variants and HCC susceptibility. Previous meta-analyses on this topic have yielded conflicting results [28-32]. The results of meta-analyses by Xiang et al. [28], Liu et al. [30], and Li et al. [31] were similar to ours. However, a meta-analysis by Zhang et al. [29] reported a significant association between TGF-β1 C-509T variants and decreased HCC susceptibility, and another meta-analysis by Guo et al. [32] demonstrated a close association between TGF-β1 C-509T variants and increased HCC susceptibility.

Our meta-analysis suggested, for the first time, that infecting hepatitis viruses may affect the association between the TGF-β1 C-509T variants and HCC susceptibility. Although most previous meta-analyses have reported negative results for this association, the results of primary studies seem to suggest some tendencies, in terms of the infecting hepatitis virus. Of the four studies including HBV-infected subjects, three indicated a significant association between TGF-β1 C-509T variants and decreased HCC susceptibility [13, 15, 17, 19]. However, two studies using HCV-infected subjects suggested a significant association between TGF-β1 C-509T variants and increased HCC susceptibility [16, 20]. Thus, it is possible that an overall meta-analysis using integrated data that include subjects with HBV-related CLD and those with HCV-related CLD may mask the opposite tendencies between them, in terms of the TGF-β1 C-509T variants and HCC susceptibility.

In our study, Caucasians demonstrated a positive association between the TGF-β1 C-509T variants and HCC susceptibility. One possible explanation for this finding is that ethnicity may influence this association. However, the selected studies with Caucasians included more HCV-infected subjects than HBV-infected subjects [14, 16, 19]. Furthermore, a study of Caucasian HCV-infected subjects found a significant association between the TGF-β1 C-509T variants and increased HCC susceptibility [16], while a study with Caucasian HBV-infected subjects reported that the TGF-β1 C-509T variants were significantly associated with decreased HCC susceptibility [19]. Given these findings, it is likely that the association between the TGF-β1 C-509T variants and HCC susceptibility may be associated with the type of infecting hepatitis virus rather than differences in ethnicity.

In a subgroup analysis of the infecting hepatitis viruses, we observed a significant association between the TGF-β1 C-509T variants and HCC susceptibility among HCV-infected subjects in many genetic models, regardless of the control groups used. In contrast, we found a significant association between the TGF-β1 C-509T variants and HCC susceptibility among HBV-infected subjects in only two genetic models using CLD

controls. In a large-scale study of HBV-infected subjects, Xin et al. [17] reported no significant association, which could have influenced the results for HBV-infected subjects. Because of the small number of reported primary studies of viral causes, future studies are needed to confirm the influence of the infecting hepatitis virus on the association between TGF-β1 C-509T variants and HCC susceptibility.

The roles played by TGF-β during hepatocarcinogenesis are not completely understood. In particular, the role of this cytokine during the early stages of hepatocarcinogenesis is poorly understood. However, a recent experimental study demonstrated that TGF-β signaling contributes to tumor promotion during the early stages of tumorigenesis [33]. Furthermore, an animal study suggested that hepatoma-initiating cells may be derived from hepatic progenitor cells exposed to chronic and constant TGF-β stimulation in the cirrhotic liver [34]. These findings suggest that sustained activation of TGF-β signaling is essential for stimulating the early stages of human hepatocarcinogenesis.

Together, our results may indicate that combinations of promoter region position -509 genotypes of TGF-β1 and infecting hepatitis viruses that enhance TGF-β1 gene transcriptional activity may increase HCC susceptibility. In particular, the -509C genotype in HBV-infected subjects and the -509T genotype in HCV-infected subjects may increase their HCC susceptibility. Although further data accumulation is required to verify this hypothesis, our results should aid in HCC surveillance after the hypothesis has been confirmed in future large-scale studies.

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