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ORIGINAL PAPER

The TNF-α, IL-1B and IL-10 polymorphisms and risk for hepatocellular carcinoma: a meta-analysis

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Abstract
Objective TNF-α-308 G/A, TNF-α-238 G/A, IL-1B-31 T/C, IL-1B-511 C/T, and IL-10-1082 G/A polymorphisms have been reported to influence the risk for hepatocellular carcinoma (HCC) in many studies; however, the results still remains controversial and ambiguous. The aim of this study was to determine more precise estimations for the relationship between TNF-α, IL-1B, and IL-10 polymorphisms and the risk for HCC by meta-analysis.
Methods Electronic searches for all publications were conducted on associations between these variants and HCC in several databases through September 2010. Odds ratios (OR) with 95% confidence intervals (95% CI) were calculated to estimate the strength of this association in a random-effect model. Twenty studies were identified, involving 2,763 HCC patients and 4,152 controls.
Results This meta-analysis showed significant association between TNF-α-308 polymorphism and HCC (AA + GA vs. GG: OR = 1.74, 95% CI = 1.12–2.72). In Caucasian and Asian subgroups, OR values (95% CI) were 1.49 (0.58–3.82) and 1.84 (1.06–3.20), respectively. While the ORs for TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T and IL-10-1082 G/A polymorphisms and HCC were 1.37 (0.95–2.00), 1.24 (0.99–1.55), 1.12 (0.66–1.88) and 0.91 (0.74–1.12), respectively. The sensitivity analysis further strengthened the overall strong positive correlations. No publication bias was observed in this study.
Conclusions TNF-α-308 G/A polymorphism is assumed to confer a higher risk for HCC, especially in Asian population. TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T, and IL-10-1082 G/A polymorphisms were not detected to be related to the risk for HCC.

Keywords Meta-analysis · Polymorphism · TNF-α · Interleukin · Hepatocellular carcinoma

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Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer worldwide and the third most common cause of death from cancer (Parkin 2008). The etiological factors involved in HCC are well known (Ho et al. 2004), but genetic factors of HCC have been incompletely understood, which has been postulated to influence the progression of HCC. Because risk for HCC increases with the severity of

hepatic inflammation and chronic inflammation developing through the action of various inflammatory mediators is known as a cofactor of carcinogenesis (Coussens and Werb 2002, Tarao et al. 1999), among inflammatory mediators, pro-inflammatory cytokine, TNF-α has been postulated to have a crucial role in the pathogenesis of cancers. It is one of the most important pro-inflammatory cytokines involved in the growth, differentiation, cellular function and survival of many cells, produced by diverse kinds of cells comprising macrophages, neutrophils, fibroblasts, keratinocytes, NK cells, T and B cells, and tumor cells (Anderson et al. 2004). IL-1B and IL-10 are also well known to mediate several immune responses in HCV/HBV infection (Okamoto et al. 2010, Tanaka et al. 2003, Wang et al. 2003), which is the major risk factor for HCC. There existed a network of TNF-α, IL-1B, and IL-10 secretion and interactive bio-function in the immune responses. Because of their close relationship, they should be included simultaneously in each study.

Since expression of TNF-α is under genetic controls at the transcription and post-transcription levels, its promoter polymorphisms (rs1800629, rs361525, rs1799724, and rs1799964) have been reported to influence TNF-α production (Hellmig et al. 2005, Huizinga et al. 1997). Of them, TNF-α-308 G/A, -α-238 G/A polymorphisms have superior consideration as a risk factor of cancers in the past ten years, and many studies have focused on its association with HCC. Interleukins as another critical cytokines were related to TNF-α secretion. In recent years, IL-1B and IL-10 polymorphisms were also investigated as important factors and associated with susceptibility to HCC. Despite these studies were well conducted, apparent discrepancy existed in their results (Akkiz et al. 2009, Ben-Ari et al. 2003, Bouzgarrou et al. 2009, Chen et al. 2005, Heneghan et al. 2003, Hirankarn et al. 2006, Ho et al. 2004, Jeng et al. 2009, Jeng et al. 2007, Jung et al. 2009, Kummee et al. 2007, Migita et al. 2005, Nieters et al. 2005, Niro et al. 2005, Ognjanovic et al. 2009, Okamoto et al. 2010, Sakamoto et al. 2008, Shin et al. 2003, Tanaka et al. 2003, Wang et al. 2003). Considering that currently published studies only refer to a small sample size and unified ethnicity, each of these studies might not achieve a stable and reliable conclusion. It is important to find the specific genetic background in screening and preventing of HCC in susceptible individuals. Thus, we conducted this meta-analysis to combine the available studies and validate whether the TNF-α-308, 238 G/A, IL-1B-31 T/C, -511 C/T, and IL-10-1082 G/A polymorphisms could contribute to the susceptibility of HCC.

Methods

Electronic databases for all publications (PubMed, EMBase, Cochrane Central Register of Controlled Trials and ISI Web of Science) were searched on the association between TNF-α-308, TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T, and IL-10-1082 G/A polymorphisms and HCC through September 2010. The keywords were used as follows: hepatocellular, cancer or carcinoma, polymorphism or variant or genotype or SNP, and tumor necrosis factor or TNF-α or IL or interleukin. All the references of identified articles were also reviewed for additional studies. The studies included must meet the following criteria: (1) case–control study; (2) the outcome had to be HCC; and (3) at least two comparison groups (HCC group vs. control group); (4) published in English language.

This meta-analysis included a total of 20 articles on TNF-α-308 G/A ($n = 13$), TNF-α-238 G/A ($n = 5$), IL-1B-31 T/C ($n = 5$), -511 C/T ($n = 5$), and IL-10-1082 G/A ($n = 6$) polymorphisms in relation to the risk for HCC. Two investigators reviewed and extracted the data independently and in duplicate. Items of the author's last name, year of publication, country of origin, source of the study population, genotypes and numbers of cases and controls and genotyping method were extracted. All the results were compared, disagreements were discussed, and consensus was reached.

Statistical analysis

The meta-analysis was performed by Review manager 5.0. The crude odds ratios (OR) and 95% CI were estimated for each study in a fixed- or random-effect model. Heterogeneity among studies was examined with I^2 statistic interpreted as the proportion of total variation contributed by between-study variation. If there was a statistical difference in terms of heterogeneity ($P < 0.05$), a random-effect model was selected to combine the data. A fixed-effect model, otherwise, was employed. Relative influence of each study was assessed on the pooled estimate by omitting one study at a time for sensitivity analysis. Funnel plots were used to evaluate publication bias. All P-values were two tailed.

Results

A total of 20 studies fulfilling the inclusion criteria were identified. The detailed characteristics of these studies were listed in Table 1. Totally 2,763 HCC patients and 4,152 controls were included in the analyses. Among these 20 studies, there were 13 studies reported TNF-α-308 G/A, 5 for TNF-α-238 G/A, 5 and 5 for IL-1B-31 T/C, -511 C/T and 6 for IL-10-1082 G/A, respectively.

As shown in Table 2, the OR for HCC (95% CI) of TNF-α-308 G/A polymorphism with AA + AG versus GG was 1.74 (1.12–2.72, $P = 0.01$) in overall studies. In Caucasian and Asian populations, ORs (95% CI) were 1.49 (0.58–3.82, $P = 0.34$) and 1.84 (1.06–3.20, $P = 0.03$), respectively.

Table 1 Characteristics of studies included in the meta-analysis

Study	Year	Country	Ethnicity	Case/control	Control	Genotyping	SNPs
Ben-Ari	2003	Israel	Caucasian	10/48	GP	PCR-SSP	TNF-308
Akkiz	2009	Turkey	Caucasian	110/110	HP	PCP-RFLP	TNF-308
Chen	2005	China	Asian	483/331	HP	PCP-RFLP	TNF-308, IL-1B31, 511
GA	2005	Italy	Caucasian	30/96	HP	Sequencing	TNF-308,-238
Heneghan	2003	China	Asian	98/97	GP	Taqman	TNF-308,-238, IL10 1082
Ho	2004	China	Asian	74/289	GP	Taqman	TNF-308
Jeng	2007	China	Asian	108/108	GP	Sequencing	TNF-308
Jeng	2009	China	Asian	200/200	GP	Sequencing	TNF-308
Kummee	2007	Thailand	Asian	50/150	GP	PCR–RFLP	TNF-308, -238
Ognjanovic	2009	US	Mixed	120/230	GP	Sequencing	TNF-308, IL-10-1082
Sakamoto	2008	Japan	Asian	209/275	HP	PCR–RFLP	TNF-308, IL-1B31
Migita	2005	Japan	Asian	48/188	HP	PCR-SSP	TNF-308, IL-10-1082, IL-1B31, -511
Wang	2003	Japan	Asian	125/55	HP	Sequencing	TNF-308,-238, IL-1B-31, -511
Jung	2009	Korea	Asian	277/365	GP	Sequencing	TNF-238
Bouzgarrou	2009	Tunisia	Caucasian	58/103	GP	PCR–RFLP	IL-10-1082
Nieters	2004	Germany	Asian	249/250	HP	PCR–RFLP	IL-10-1082
Shin	2003	Korea	Asian	230/792	HP	MAPA	IL-10-1082
Okamoto	2010	Japan	Asian	92/83	HP	PCR–RFLP	IL-1B-31
Tanaka	2003	Japan	Asian	146/230	GP	PCR–RFLP	IL-1B-511
Hirankarn	2006	Thailand	Asian	46/152	HP	PCR-SSP	IL-1B-511

PCR–RFLP Polymerase chain reaction–restriction fragment length polymorphism, *PCR-SSP* PCR-Sequence-Specific Primer, *MAPA* Multiplex automated primer extension analysis, *GP* General population, *HP* Hospital population

Table 2 Results of pooled ORs in the meta-analysis

SNPs	*N*	Model	OR (95% CI)	*P*	I^2(%)
TNF-α-308 G/A	13	Random	1.74 (1.12,2.72)	0.01	75
TNF-α-238 G/A	5	Fix	1.37 (0.95,2.00)	0.1	29
IL-1B-31 T/C	5	Fix	1.24 (0.99,1.55)	0.06	0
IL-1B-511 C/T	5	Random	1.12 (0.66,1.88)	0.68	71
IL-10-1082 G/A	6	Fix	0.91 (0.74,1.12)	0.38	10

The forest plots of TNF-α-308 G/A polymorphism were shown in Fig. 1. For TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T, and IL-10-1082 G/A, the ORs for HCC were 1.37 (0.95–2.00), 1.24 (0.99–1.55), 1.12 (0.66–1.88), and 0.91 (0.74–1.12), respectively, which did not reach the significance.

However, there was some evidence of heterogeneity among the overall 13 and ethnic stratified studies on the association between TNF-α-308 G/A, IL-1B-511 C/T polymorphisms and the risk for HCC ($I^2 = 77$ and 71%, respectively, Table 2). Subsequently, a random-effect model was employed in the ORs calculation of these polymorphisms. To further strengthen the results, we conducted the sensitivity analysis for TNF-α-308 G/A and IL-1B-511 C/T polymorphisms. In the sensitivity analysis, exclusion of individual studies did not substantially modify the estimates (data not shown), with pooled ORs ranging from 1.59 to 1.87 for TNF-α-308 polymorphism and 0.97 to 1.26 for IL-1B-511 C/T polymorphism.

The shape of the funnel plots was symmetrical, suggesting that there was no evidence of publication bias among these studies (Funnel plots of TNF-α-308 G/A polymorphism in Fig. 2). Together with the above results, this meta-analysis showed that TNF-α-308 polymorphism significantly increased the risk for HCC. The associations between TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T, and IL-10-1082 G/A polymorphisms and risk for HCC were not detected.

Discussion

As inflammation is involved in the pathogenesis of cancer, TNF-α, the most crucial inflammatory cytokine, has been reported to have multiple roles in both cancer development and progression in vitro and human cancer studies, involving pathways of the NF-κB and AP-1 transcription factor complexes activation (Jang et al. 2001). TNF-α gene locates within the class III region of the major histocompatibility complex (MHC) between *human leukocyte antigen-B* (HLA-B) and *human leukocyte antigen-DR* (HAL-DR). Because allele A of TNF-α-308, 238 G/A was reported to contribute to the increase of TNF-α production (Huizinga et al. 1997), this variant has been extensively investigated

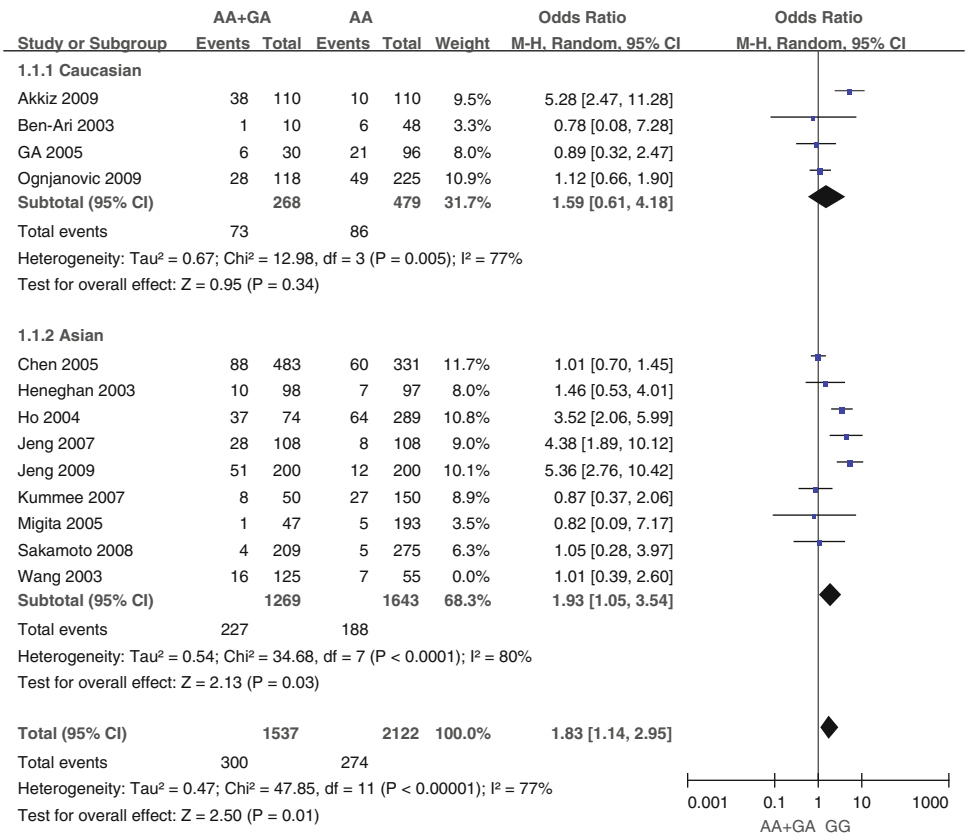

Fig. 1 ORs and 95% confidence interval (CI) of hepatocellular carcinoma according to TNF-α-308 G/A polymorphism in 13 studies using random-effect model. AA + GA, AA and GA genotypes of TNF-α-308 G/A polymorphism; GG, GG genotype of TNF-α-308 polymorphism; ORs, odds ratios

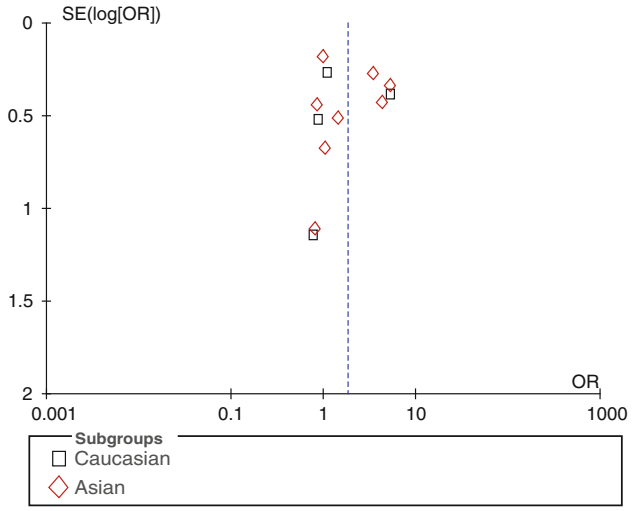

Fig. 2 Funnel plots analysis to detect publication bias. Each point represents an independent study for the indicated association

in previous cancer studies during recent decades. It has been related to risk for Hodgkin's lymphoma, breast carcinoma, prostate cancer, uterine endometrial cancer, and gastric carcinoma (Akkiz et al. 2009). IL-1B also mediates the immune response by inducing expression of many other genes by transcription or stabilizing their messenger RNA and plays an important role in inflammation of the liver (Wang et al. 2003). The secretion of TNF-α and IL-1B is regulated by IL-10. IL-10-1082 G/A polymorphism correlates with low IL-10 production in vitro (Heneghan et al. 2003). Due to these cytokines' bio-functions in inflammation and development of HCC, many studies have investigated the relations between their polymorphisms and risk for HCC. However, the results were inconsistent, for their rather small sample size and unified ethnicity (Akkiz et al. 2009, Ben-Ari et al. 2003, Bouzgarrou et al. 2009, Chen et al. 2005, Heneghan et al. 2003, Hirankarn et al. 2006, Ho et al. 2004, Jeng et al. 2009, 2007, Jung et al. 2009, Kummee et al.2007, Migita et al. 2005, Nieters et al. 2005, Niro et al. 2005, Ognjanovic et al. 2009, Okamoto et al. 2010, Sakamoto et al. 2008, Shin et al. 2003, Tanaka et al. 2003, Wang et al. 2003). To provide further investigation into these controversial points, a meta-analysis is needed to achieve a more reliable and comprehensive conclusion.

This meta-analysis, to the best of our knowledge, investigated the association between TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T, and IL-10-1082 G/A polymorphisms and risk of HCC for the first time. With 2,763 patients with cancer and 4,152 controls included, this study had greater power than all previous ones. We detected a significant positive association between TNF-α-308 G/A polymorphism and HCC susceptibility in the overall population, with summary OR 1.83 (1.14–2.95), and no significant association for TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T and IL-10-1082 G/A polymorphisms and risk for HCC. For TNF-α-308

G/A polymorphism, the same positive association was also indicated in the Asian population when the subgroup analyses were stratified according to ethnicity. However, a negative result was acquired in the Caucasian population.

When heterogeneity was found among the studies of TNF-α-308 G/A and IL-1B-511 C/T polymorphisms, we selected random-effect model. Then, we performed a sensitivity analysis by removing one study for each time and re-running the model to determine the effect on each overall estimate. The estimates changed quite little, which validated the confidence of our results. Heterogeneity, however, still existed in the sensitivity analysis of TNF-α-308 G/A and IL-1B-511 C/T polymorphisms, which indicated the variability in frequency of these polymorphisms between the populations may be the source of heterogeneity. There was no publication bias shown in the study, suggesting this possible truth of the results.

For HCC mostly occurs in Asia where hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are endemic, the positive association between TNF-α-308 G/A polymorphism and HCC are very important for Asian to identify the subjects with greater risk of HCC. Majority of HCC are related to HBV/HCV; however, most studies did not provide the numbers of HBV/HCV patients or HBV/HCV infection recovered patients in the controls and HHC patients. In contrast, the studies where investigators considered the infection factor reported more precise ORs for HCC risk (Ho et al. 2004, Jeng et al. 2007). Thus, this conclusion suggested that clarifying the independent role of each polymorphisms on HBV/HCV and HCC, respectively, should be quite necessary.

This meta-analysis has pooled all the available results from the case–control studies, which has significantly increased the statistical power. However, several potential concerns must be discussed on the lack of association between TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T and IL-10-1082 G/A polymorphisms and HCC. First, HCC is a multi-factorial disease that results from complex interactions between environmental and genetic factors. Some environmental factors, however, may strongly influence the development of HCC, such as living habits, HBV/HCV infection and exposure to carcinogens. Without considering these factors, it might suffer from failure in detecting the independent role of suspected polymorphism in HCC. Second, some other single-nucleotide polymorphisms of cytokines, such as polymorphisms of interleukin-8-251, interleukin-10-819 and transforming growth factor beta1-50, may exert their complex and interacting functions with each other, which might affect the association of each polymorphism included with the development of HCC. Therefore, more risk polymorphisms of HCC should be induced as covariants in the studies to conclude the true effect. It is very difficult indeed, however, to obtain data compromised with frequency of many SNPs in one study. Third, the range of frequencies between populations even in the same ethnic population was wide and the number of current studies is relative small, which means more investigations involving more subjects of different races are needed to clarify this relation. According to the problems as we discussed, the confounding variables in the polymorphism research should be excluded or fully considered to detect the independent role of each polymorphism. For IL-1B-31 T/C polymorphism, the combined OR nearly reached significance ($P = 0.06$). With more studies published, this association might be significant. Therefore, IL-1B-31 T/C polymorphism cannot be excluded as a risk factor for HCC. For the small numbers of studies on TNF-α-238 G/A, IL-1B-511 C/T and IL-10-1082 G/A polymorphisms were reported, more evidence are needed to confirm their null association with HCC.

TNF-α-308 G/A polymorphism was found to confer a higher risk of HCC in meta-analysis for the first time. In future of clinic and public health medicine, the attention of this variant should be paid in early HCC diagnosis and prevention, which might improve the survival rates for patients diagnosed with HCC. Significant association was not detected between TNF-α-238 G/A, IL-1B-31 T/C, -511 C/T, and IL-10-1082 G/A polymorphisms and HCC. However, case–control studies cannot provide a causal association or exclude the potential bias and confounding; it would be more valuable to conduct larger well-designed cohort studies in the susceptibility of HCC, to further confirm this association in different ethnic populations and incorporate both environmental (such as alcohol, smoking habits, and HBV/HCV) and genetic risk factors in the future.

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Conflict of interest The authors do not have any conflicts of interest to report with for this manuscript.

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