Original Article
Polymorphisms in the *interleukin-10* gene and hepatocellular carcinoma: an updated meta-analysis of 12 case-control studies

Sheng Zhang[1*], Yafeng Wang[2*], Chao Liu[3*], Jiakai Jiang[1], Heping Jiang[4], Weifeng Tang[3], Yu Chen[5,6], Zhenzhou Xiao[7]

[1]Department of General Surgery, Changzhou No. 3 People's Hospital, Changzhou, Jiangsu Province, People's Republic of China; [2]Department of Cardiology, The People's Hospital of Xishuangbanna Dai Autonomous Prefecture, Jinghong, Yunnan Province, People's Republic of China; [3]Department of Cardiothoracic Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu Province, People's Republic of China; [4]Department of Emergency, Affiliated Jintan People's Hospital of Jiangsu University, Jintan, Jiangsu Province, People's Republic of China; [5]Department of Medical Oncology, Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, Fujian Province, People's Republic of China; [6]Fujian Provincial Key Laboratory of Translational Cancer Medicine, Fuzhou, Fujian Province, People's Republic of China; [7]Department of Clinical Laboratory, Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou, Fujian Province, People's Republic of China. *Equal contributors.

Abstract: Polymorphisms occurred in *interleukin-10 (IL-10)* gene may contribute to hepatocellular carcinoma (HCC) susceptibility. Since 2003, a number of epidemiological studies have explored the relationship between three common polymorphisms [rs1800896 A>G (-1082 A>G), rs1800872 A>C (-592 A>C) and rs3021097 C>T (-819 C>T)] located on *IL-10* gene and HCC risk; however, the results remain inconclusive. We carried out a meta-analysis of twelve case-control studies with 2,267 HCC cases and 3,994 controls to identify the correlation. Crude odds ratios (ORs) and their 95% confidence intervals (95% CIs) were harnessed to measure the strength of relationship. The findings indicated that *IL-10* -592 A>C polymorphism was associated with the risk of HCC in dominant genetic comparison model (CC+AC versus AA, fixed-effects OR = 1.18, 95% CI 1.04-1.35, P = 0.011). Begg's funnel plot and Egger's linear regression test were harnessed to assess the potential publication bias in our study. No obvious publication bias was found among the included studies. Results of one-way sensitivity analysis highlighted that our findings were robust. These results indicate that *IL-10* -592 A>C polymorphism conferred an increased risk for the development of HCC.

Keywords: Polymorphism, *IL-10*, hepatocellular carcinoma, susceptibility, meta-analysis

Introduction

During 2012, it is estimated that 782,500 new liver cancer (LC) cases and 745,500 LC-relative deaths occurred worldwide [1], with most (70% to 90%) primary LC cases being hepatocellular carcinoma (HCC). HCC is a complex disease that results from interactions of genetic predisposition with multiple environmental factors. To the best of our knowledge, it is established that chronic infection with virus, such as hepatitis B virus (HBV) and hepatitis C virus (HCV), is one of the most environmental risk factors for HCC. Nevertheless, only a few chronic infection cases with HBV and HCV develop HCC later in life

[2]. Thus, there might have a crowd of genetic predisposition genes contributing to the remaining unexplained risk of HCC, which have not yet been well-elucidated.

Accumulating evidences showed that variants of the immune related genes may alter the risk of malignancy [3-6]. The human interleukin-10 (IL-10), which encoding region is located on chromosome 1q32.2, is an important immune regulatory related inhibitory factor produced by monocytes, macrophages, Th2 cells and regulatory T cells. IL-10 acts as an anti-inflammatory inhibitory factor by decreasing the synthesis of cytokines such as tumor necrosis factor-alpha
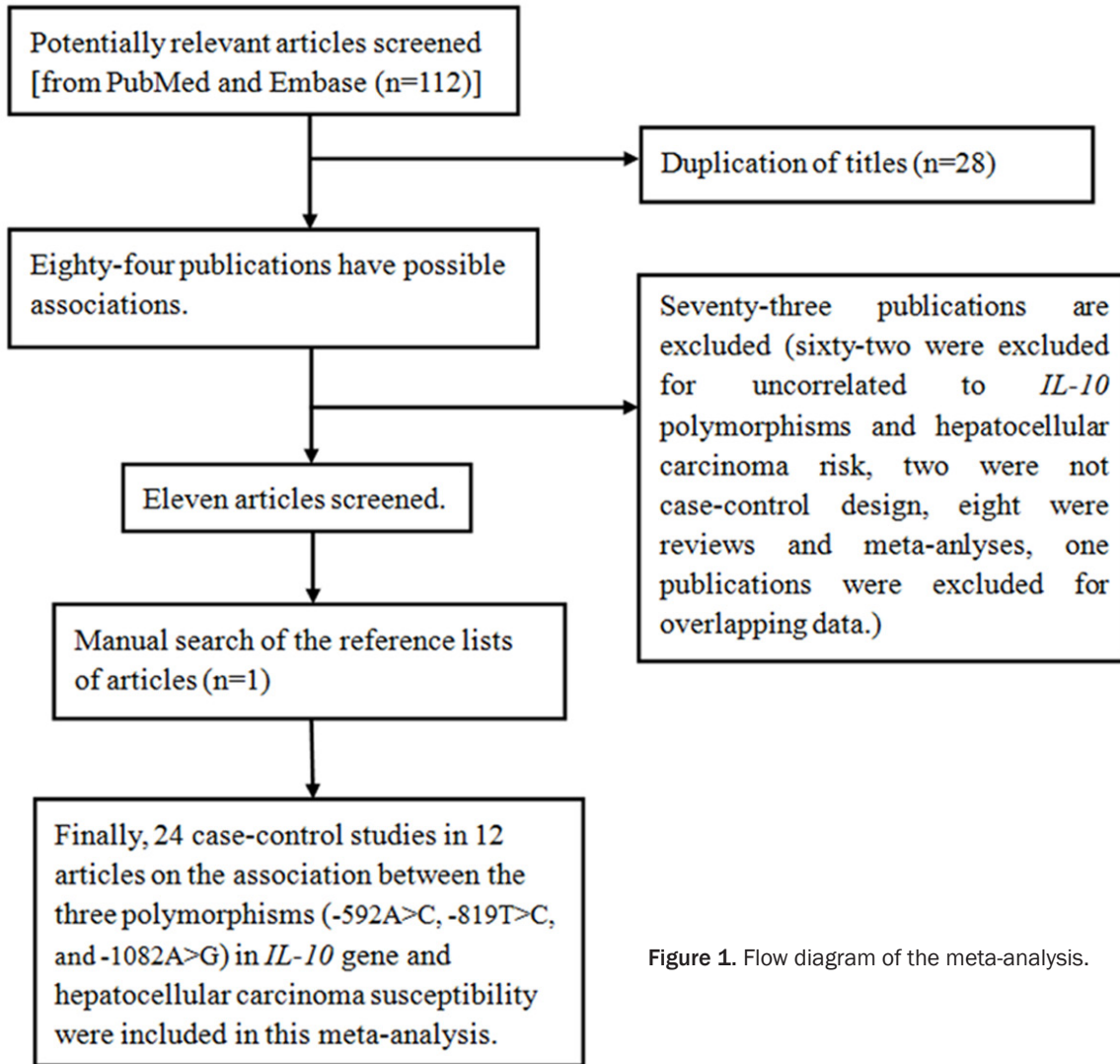
Potentially relevant articles screened [from PubMed and Embase (n=112)]

Duplication of titles (n=28)

Eighty-four publications have possible associations.

Seventy-three publications are excluded (sixty-two were excluded for uncorrelated to *IL-10* polymorphisms and hepatocellular carcinoma risk, two were not case-control design, eight were reviews and meta-anlyses, one publications were excluded for overlapping data.)

Eleven articles screened.

Manual search of the reference lists of articles (n=1)

Finally, 24 case-control studies in 12 articles on the association between the three polymorphisms (-592A>C, -819T>C, and -1082A>G) in *IL-10* gene and hepatocellular carcinoma susceptibility were included in this meta-analysis.

Figure 1. Flow diagram of the meta-analysis.

(TNF-α), interferon gamma (IFNγ) IL-1α, IL-1β, IL-6, IL-8, and IL-12 [7], and then it significantly reduces fibrosis in some disease [8, 9]. Previous studies have indicated that *IL-10* gene variants and haplotypes may influence the circulating levels of this interleukin [10, 11]. Polymorphisms in *IL-10* gene have been reported to be associated with the susceptibility and prognosis of multiple human malignancy, such as colorectal cancer [12, 13], breast cancer [14], esophageal cancer [15], oral cancer [16, 17], lung cancer [18, 19], gastric cancer *et al.* [20].

Recently, many studies have focused on the relationship of *IL-10* polymorphisms [rs1800-896 (-1082 A>G), rs1800872 (-592 A>C) and rs3021097 (-819 C>T)] with the risk of HCC [21-32]. Wei *et al.* has reported a pooled-analysis with a positive result on the correlation between

IL-10 -592 A>C polymorphism and HCC susceptibility [33]; however, the enrolled studies were limited in this study. Up to now, more epidemiological studies were performed on the association between *IL-10* polymorphisms and HCC risk, and the results remained inconsistent and inconclusive [21-25]. To further address this potential association, a comprehensively updated meta-analysis was needed to derive a more precise estimation.

Materials and methods

Publication search

An extensive literature search up to May 10, 2016, was performed in PubMed and EMBASE databases. The following terms was used as key word: (IL-10 or interleukin-10) and (polymor-

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

Study	Year	Country	Ethnicity	Case/Control	Study design	Adjusted factor	Genotype method	Polymorphism	Quality score [1-3]
Peng et al.	2016	China	Asians	173/182	Case-control study	Sex, ethnic background, and geographic origin	PCR-RFLP	-1082 A>G, -592 A>C and -819 T>C	4.5
Aroucha et al.	2016	Brasil	Mixed	108/280	Case-control study	Ethnic background, and geographic origin	TaqMan	-1082 A>G, -592 A>C and -819 T>C	5.5
Bahgat et al.	2015	Egypt	Caucasians	50/25	Case-control study	Sex, ethnic background, and geographic origin	AS-PCR	-1082 A>G	4.5
Bei et al.	2014	China	Asians	720/784	Case-control study	Age, sex, ethnic background, and geographic origin	TaqMan	-592 A>C	8.0
Li et al.	2011	China	Asians	204/415	Case-control study	Ethnic background, and geographic origin	PCR-RFLP	-1082 A>G, -592 A>C and -819 T>C	6.0
Bouzgarrou et al.	2009	Tunisia	Caucasians	58/145	Case-control study	Sex, ethnic background, and geographic origin	AS-PCR	-1082 A>G	4.5
Ognjanovic et al.	2009	USA	Mixed	120/230	Case-control study	Age, sex and geographic origin	Taqman	-1082 A>G	7.0
Tseng et al.	2005	China	Asians	208/528	Case-control study	Ethnic background, and geographic origin	PCR-RFLP	-592 A>C	6.0
Migita et al.	2005	Japan	Asians	48/188	Case-control study	Sex, ethnic background, and geographic origin	PCR-SSP	-1082 A>G, -592 A>C and -819 T>C	7.5
Heneghan et al.	2003	China	Asians	98/175	Case-control study	Age, sex, ethnic background, and geographic origin	N/A	-1082 A>G, -592 A>C and -819 T>C	6.5
Shin et al.	2003	Korea	Asians	230/792	Case-control study	Ethnic background, and geographic origin	MAPA	-1082 A>G and -592 A>C	6.5
Nieters et al.	2005	China	Asians	250/250	Case-control study	Age, sex, ethnic background, and geographic origin	AS-PCR	-1082 A>G and -819 T>C	6.0

PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism; AS-PCR: Allele-specific polymerase chain reaction; PCR-SSP: polymerase chain reaction-sequence specific primer; MAPA: Multiplex automated primer extension analysis.

[1] Guo J, Jin M, Zhang M, Chen K. A genetic variant in miR-196a2 increased digestive system cancer risks: a meta-analysis of 15 case-control studies. PLoS One 2012; 7: e30585.
[2] Qiu MT, Hu JW, Ding XX, Yang X, Zhang Z, Yin R, Xu L. Hsa-miR-499 rs3746444 polymorphism contributes to cancer risk: a meta-analysis of 12 studies. PLoS One 2012; 7: e50887.
[3] Wang L, Jiang Z, Qiu H, Tang W, Duan T, Wang L. Associations between CTLA-4 +49 A/G (rs231775) polymorphism and cancer risk: a meta-analysis based on 52 case-control studies. Int J Clin Exp Med 2015; 8: 6835-6851.

Table 2. Distribution of *IL-10* -592 A>C, -819 T>C, and -1082 A>G genotypes and alleles

Polymorphism	Study	Year	Case			Control			Case		Control		HWE
-1082 A>G			-1082AA	-1082AG	-1082GG	-1082AA	-1082 AG	-1082GG	-1082G	-1082A	-1082 G	-1082A	
	Peng et al.	2016	83	74	16	96	74	12	106	240	98	266	Yes
	Bahgat et al.	2015	16	26	8	6	15	4	42	58	23	27	Yes
	Aroucha et al.	2016	61	37	10	125	122	33	57	159	188	372	Yes
	Bouzgarrou et al.	2009	24	24	10	56	68	21	44	72	110	180	Yes
	Migita et al.	2005	42	5	1	176	10	2	7	89	14	362	No
	Heneghan et al.	2003	86	12	0	160	15	0	12	184	15	335	Yes
	Shin et al.	2003	201	28	1	675	112	5	30	430	122	1462	Yes
	Nieters et al.	2005	130	119*		115	135*	-	-	-		-	Yes
	Li et al.	2011	132	26*		278	77*	-	-	-		-	Yes
	Ognjanovic et al.	2009	39	79*	-	67	147*	-	-			-	Yes
-592 A>C			-592AA	-592AC	-592CC	-592AA	-592AC	-592CC	-592C	-592A	-592 C	-592 A	
	Peng et al.	2016	57	81	35	79	81	22	151	195	125	239	Yes
	Bei et al.	2014	356	312	52	392	313	79	416	1024	471	1097	Ye
	Aroucha et al.	2016	16	49	43	30	121	129	135	81	379	181	Yes
	Tseng et al.	2005	93	84	31	259	223	46	146	270	315	741	Yes
	Migita et al.	2005	17	23	8	85	78	25	39	57	128	248	Yes
	Heneghan et al.	2003	49	38	11	95	60	19	60	136	98	250	Yes
	Shin et al.	2003	89	101	26	384	299	65	153	279	429	1067	Yes
	Li et al.	2011	134**	-	16	313**	-	34	-	-	-	-	Yes
-819 T>C			-819CC	-819CT	-819TT	-819CC	-819CT	-819TT	-819T	-819C	-819 T	-819 C	
	Peng et al.	2016	22	77	74	17	78	86	225	121	250	112	Yes
	Aroucha et al.	2016	43	49	16	129	121	30	81	135	181	379	Yes
	Migita et al.	2005	8	23	17	25	78	85	57	39	248	128	Yes
	Heneghan et al.	2003	11	38	49	19	60	95	136	60	250	98	Yes
	Nieters et al.	2005	119#	-	130	135#	-	115	-	-	-	-	Yes
	Li et al.	2011	22	144##	-	39	323##	-	-	-	-	-	Yes

HWE: Hardy-Weinberg equilibrium; *indicating AG+GG; **indicating AA+AC; #indicating CC+CT; ##indicating CT+TT.

Table 3. Meta-analysis of the *IL-10* polymorphisms and hepatocellular carcinoma

Polymorphism		No. of study	Allelic comparison			Homozygote comparison			Dominant comparison			Recessive comparison		
			OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	OR (95% CI)	P	P (Q-test)	OR (95%CI)	P	P (Q-test)
-1082 A>G	Overall	10	0.96 (0.81-1.14)	0.655	0.185	0.97 (0.63-1.49)	0.888	0.660	0.87 (0.74-1.02)	0.081	0.318	1.07 (0.71-1.61)	0.744	0.865
	Overall in HWE	9	0.94 (079-1.12)	0.487	0.277	0.95 (0.62-1.46)	0.815	0.579	0.85 (0.72-1.00)	0.050	0.475	1.05 (0.70-1.59)	0.804	0.802
	Asians	6	1.11 (0.88-1.40)	0.373	0.252	1.42 (0.70-2.88)	0.333	0.739	0.92 (0.76-1.12)	0.401	0.181	1.35 (0.68-2.70)	0.394	0.778
	Caucasians	2	0.95 (0.66-1.38)	0.800	0.696	1.01 (0.46-2.18)	0.989	0.663	0.83 (0.49-1.42)	0.497	0.658	1.16 (0.58-2.33)	0.680	0.793
	Mixed	2	0.71 (0.51-1.01)	0.054	-	0.62 (0.29-1.34)	0.226	-	0.75 (0.54-1.03)	0.079	0.237	0.76 (0.36-1.61)	0.478	-
-592 A>C	Overall	8	1.15 (0.97-1.37)	0.101	0.012	1.27 (0.85-1.91)	0.239	0.004	1.18 (1.04-1.35)	0.011	0.168	1.16 (0.86-1.56)	0.339	0.017
-819 T>C	Overall	6	0.94 (0.79-1.13)	0.510	0.208	0.92 (0.62-1.35)	0.665	0.276	0.95 (0.73-1.26)	0.740	0.534	1.00 (0.81-1.24)	0.990	0.201

HWE: Hardy-Weinberg equilibrium.
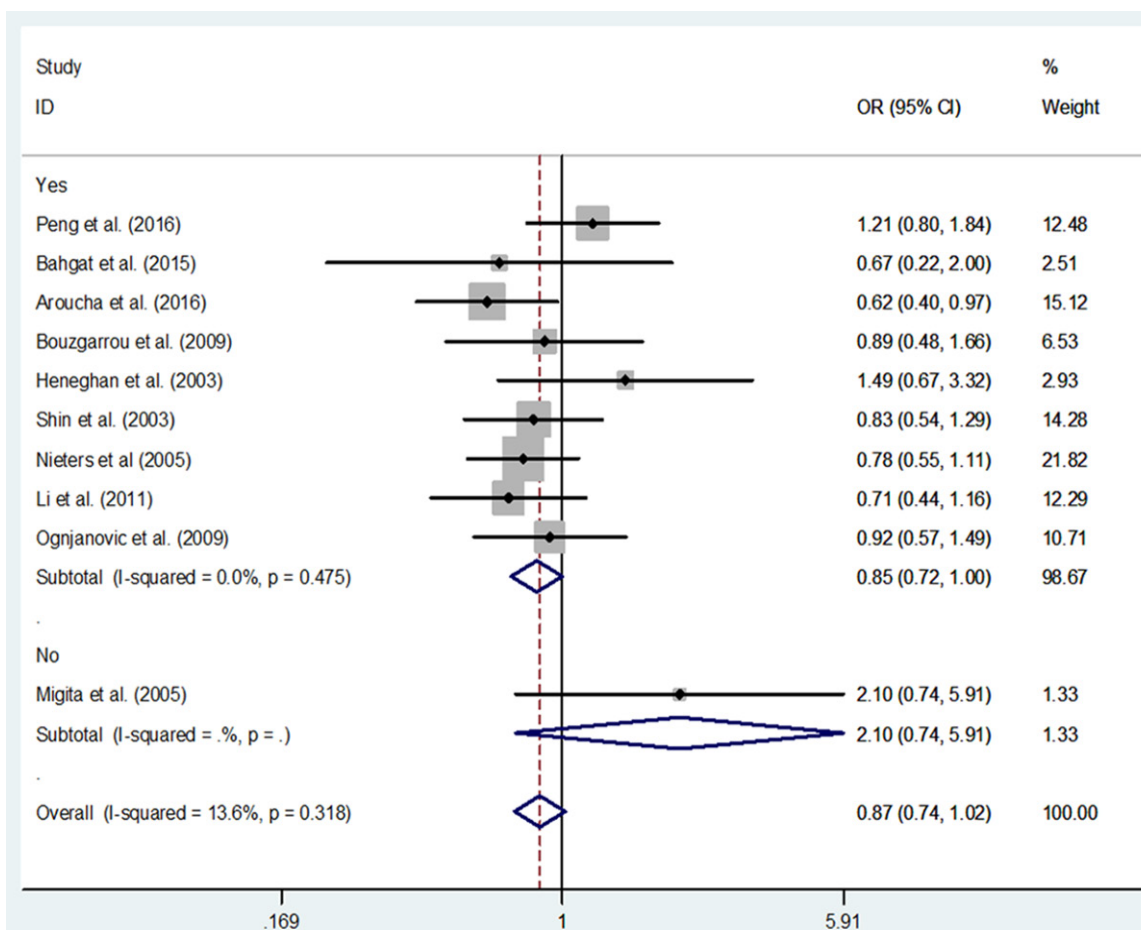
Figure 2. Meta-analysis of the relationship between *IL-10* -1082 A>G polymorphism and hepatocellular carcinoma (GG+AG vs. AA compare genetic model, fixed-effects model).

phism or variant or SNP) and (liver cancer or hepatocellular carcinoma). References of included articles and eligible literature in reviews were also manual search.

Inclusion and exclusion criteria and data extraction

The major inclusion criteria were: (a) information on the assessment of *IL-10* polymorphisms and HCC susceptibility; (b) case-control study designed; (c) focus on human subjects and (d) data can be extracted to calculate the odds ratios (ORs) with 95% confidence intervals (CIs). The major exclusion criteria were the following: (a) not case-control design; (b) overlapping data; 3) review, letter, comment or meta-analysis. Data were carefully extracted by three authors (S. Zhang, Y. Wang and C. Liu) according to these selection criteria independently. For conflicting evaluation, disagreement was resolved by counseling another author (W. Tang).

Statistical methods

We used crude ORs with 95% CIs to measure the strength of relationship of the *IL-10* polymorphisms with HCC risk. We used the goodness-of-fit test (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl) to evaluate Hardy-Weinberg equilibrium (HWE) for control subjects in each study [3, 34], and we considered $P < 0.05$ (two-sided) as statistical significance. The heterogeneity among the included studies was verified using the Chi-square-based Q-test. If the result for heterogeneity was $I^2 > 50\%$ or $P < 0.10$ (two-sided), indicating a significant heterogeneity between the enrolled studies, we used the DerSimonian-Laird method (the random-effect model) to evaluate the pooled ORs [35]. In contrast, if the results of heterogeneity test suggested a lack of heterogeneity, so the summary ORs was calculated using the Mantel-Haenszel method (the fixed-effect model) [36]. We performed a sensitivity analysis test by excluding each study in
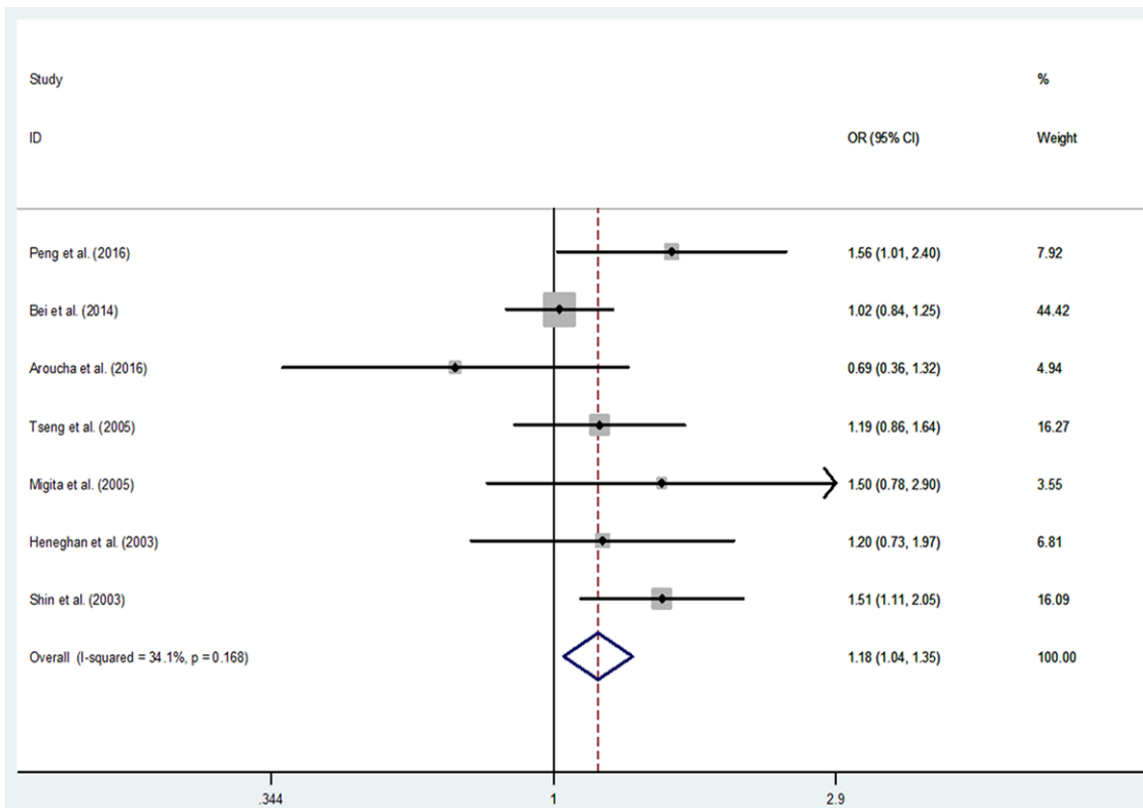
Figure 3. Meta-analysis of the relationship between *IL-10* -592 A>C polymorphism and hepatocellular carcinoma (CC+AC vs. AA compare genetic model, fixed-effects model).

turn, and re-calculating the results to measure the influences of certain study on the pooled susceptibility of HCC [37, 38]. The potential publication bias was also assessed using Begg's funnel plot and Egger's linear regression test, in which the standard error of log (OR) of each included study was plotted against its log (OR) [39, 40], and a symmetric plot suggested no significant publication bias. A $P < 0.10$ (two-sided) was defined representative of significant publication bias [39]. STATA version 12.0 software (Stata Corporation, TX, USA) was used to perform all of the statistical analysis.

Results

Characteristics

Totally, there were 112 papers relevant to the search words. Finally, a total of twelve valid papers met the major inclusion criteria and were enrolled in our study with 2,267 HCC cases and 3,994 controls [21-32] (**Figure 1**). Overall, there were ten publications on the *IL-10* -1082 A>G polymorphism [21, 22, 24-27,

29-32], eight publications on the *IL-10* -592 A>C polymorphism [21, 23-25, 28-31] and six publications on the *IL-10* -819 C>T polymorphism [21, 24, 25, 29, 30, 32]. Among twelve articles, eight were from Asians [21, 23, 24, 28-32], two were from Caucasians [22, 26] and one was from mixed population [25-27]. There were several genotyping methods were used, including allele-specific polymerase chain reaction, TaqMan, PCR-restriction fragment length polymorphism, PCR-sequence specific primer and multiplex automated primer extension analysis. **Table 1** showed the characteristics of enrolled studies. The genotype numbers for *IL-10* -1082 A>G, -592 A>C and -819 C>T polymorphism are listed in **Table 2**. The quality score was also assessed according to the 'methodological quality assessment scale'.

Quantitative synthesis

IL-10 -1082 A>G polymorphism: In total, 1,339 HCC cases and 2,682 controls from ten studies were recruited in the pooled-analysis of the association between IL-10 -1082 A>G polymor-
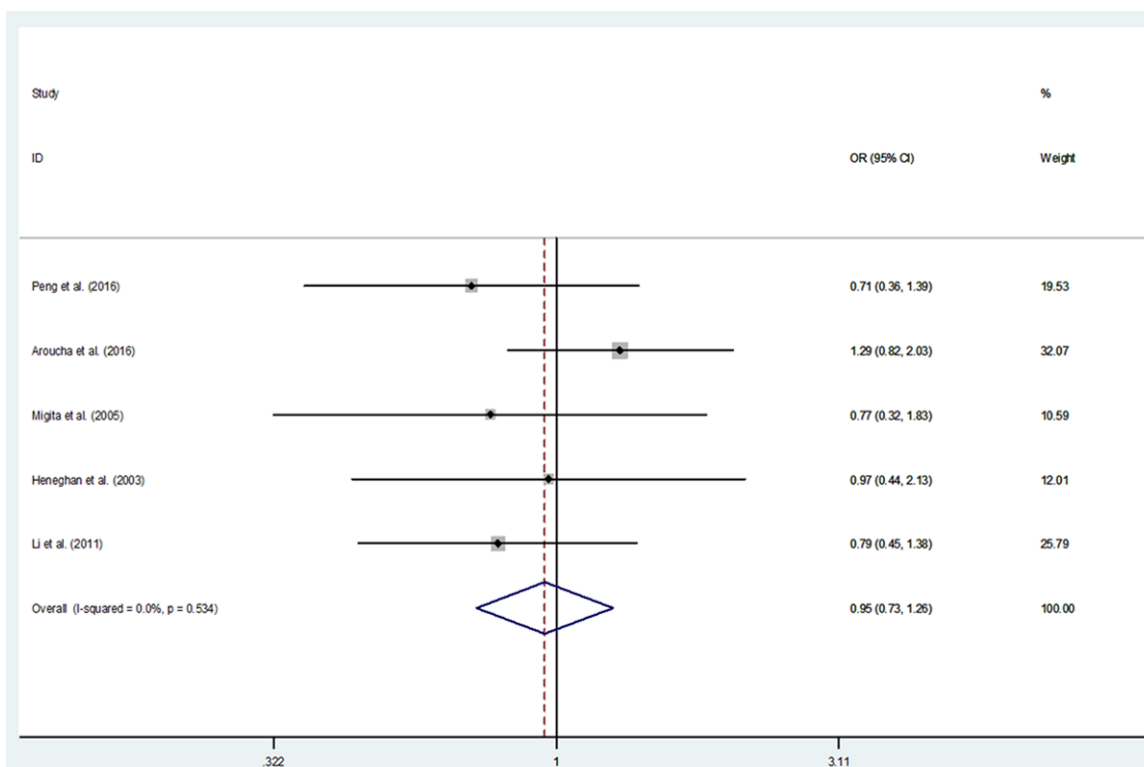
Figure 4. Meta-analysis of the relationship between *IL-10* -819 C>T polymorphism and hepatocellular carcinoma (TT+CT vs. CC compare genetic model, fixed-effects model).
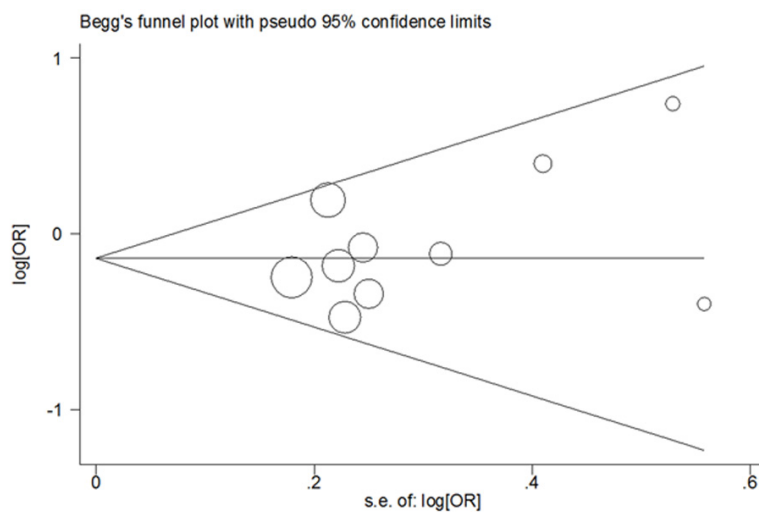

Figure 5. Begg's funnel plot of meta–analysis of the relationship between *IL-10* -1082 A>G polymorphism and the risk of hepatocellular carcinoma (GG+AG vs. AA compare genetic model).

homozygote genotype was used as the reference group, the GG+AG genotype groups had a borderline statistically decreased risk of HCC (GG+AG vs. AA; OR = 0.87, 95% CI 0.74-1.02, P = 0.081). In our study, one case-control study deviated from the HWE [29]. When we discarded this study, the trend of increasing risk with HCC was more significant in the dominant genetic models (GG+AG vs. AA; OR = 0.85, 95% CI 0.72-1.00, P = 0.050) (**Table 3** and **Figure 2**).

IL-10-592 A>C polymorphism: A total of 1,790 HCC cases and 3,344 controls from eight studies were enrolled in our analysis of the association between IL-10 -592 A>C polymorphism and the susceptibility of HCC [21, 23-25, 28-31]. Seven case-control studies were from Asians [21, 23, 24, 28-31] and one was from mixed populations [25]. The

phism and the susceptibility of HCC [21, 22, 24-27, 29-32]. Six case-control studies were from Asia [21-24, 29-32], and two were from Caucasians [22, 26] and two was from mixed populations [25-27]. When the IL-10 -1082 AA
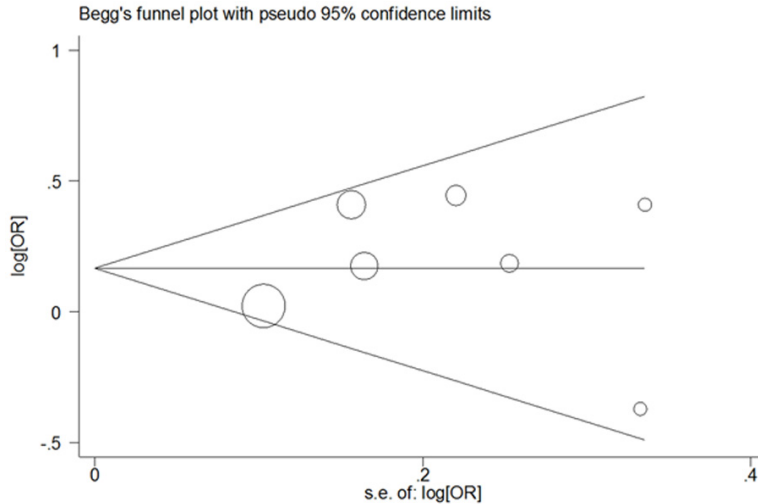
Figure 6. Begg's funnel plot of meta-analysis of the relationship between *IL-10* -592 A>C polymorphism and hepatocellular carcinoma (CC+AC vs. AA compare genetic model).
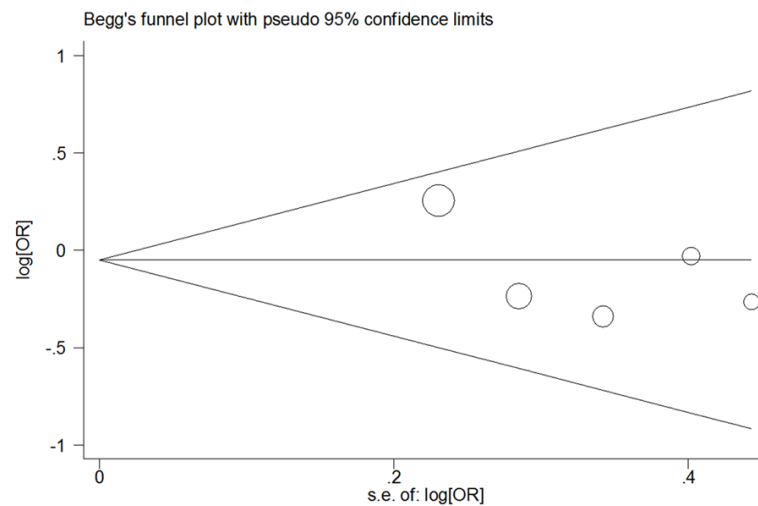

Figure 7. Begg's funnel plot of meta–analysis of the relationship between *IL-10* -819 C>T polymorphism and hepatocellular carcinoma (TT+CT vs. CC compare genetic model).

findings indicated there was a correlation between IL-10 -592 A>C polymorphism and the risk of HCC under one genetic comparison model (CC+AC versus AA, fixed-effects OR = 1.18, 95% CI 1.04-1.35, P = 0.011) (**Figure 3** and **Table 3**).

IL-10 -819 C>T polymorphism: Finally, 881 HCC cases and 1,490 controls from six studies were recruited in this analysis of the association between IL-10 -819 C>T polymorphism and the susceptibility of HCC [21, 24, 25, 29, 30, 32]. Five case-control studies were from Asia [21,

24, 29, 30, 32] and one was from mixed populations [25]. Overall, there was null correlation of IL-10 -819 C>T polymorphism with HCC susceptibility in all comparison models (**Figure 4** and **Table 3**).

Tests for publication bias, sensitivity analyses

Begg's funnel plot and Egger's linear regression test [39] were harnessed to measure the potential publication bias in our study. No obvious publication bias was found among the included studies (*IL-10* -1082 A>G polymorphism: G vs. A: $P_{Begg's}$ = 0.230, $P_{Egger's}$ = 0.314; GG vs. AA: $P_{Begg's}$ = 0.707, $P_{Egger's}$ = 0.912; GG+AG vs. AA: $P_{Begg's}$ = 0.474, $P_{Egger's}$ = 0.256; GG vs. AG+AA: $P_{Begg's}$ = 1.000, $P_{Egger's}$ = 0.909; *IL-10* -592 A>C polymorphism: C vs. A: $P_{Begg's}$ = 1.000, $P_{Egger's}$ = 0.457; CC vs. AA: $P_{Begg's}$ = 0.764, $P_{Egger's}$ = 0.501; CC+AC vs. AA: $P_{Begg's}$ = 1.000, $P_{Egger's}$ = 0.654; CC vs. AC+AA: $P_{Begg's}$ = 0.536, $P_{Egger's}$ = 0.272; *IL-10* -819 C>T polymorphism: C vs. A: $P_{Begg's}$ = 0.734, $P_{Egger's}$ = 0.537; CC vs. AA: $P_{Begg's}$ = 0.734, $P_{Egger's}$ = 0.511; CC+AC vs. AA: $P_{Begg's}$ = 0.806, $P_{Egger's}$ = 0.225; CC vs. AC+AA: $P_{Begg's}$ = 0.462, $P_{Egger's}$ = 0.590) (**Figures 5-7**).

To measure the potential influence of a single study on the overall assessment, we omitted one of them in turn, and re-calculating the results [37, 38]. We found that the omission of anyone did not substantively change the final decision, highlighting that the robustness of our findings (**Figures 8-10**).

Discussion

Infection and inflammation are vital risk factors involved in carcinogenesis, and people with HBV and HCV chronic infection are at high susceptibility of HCC. Therefore, some variants of
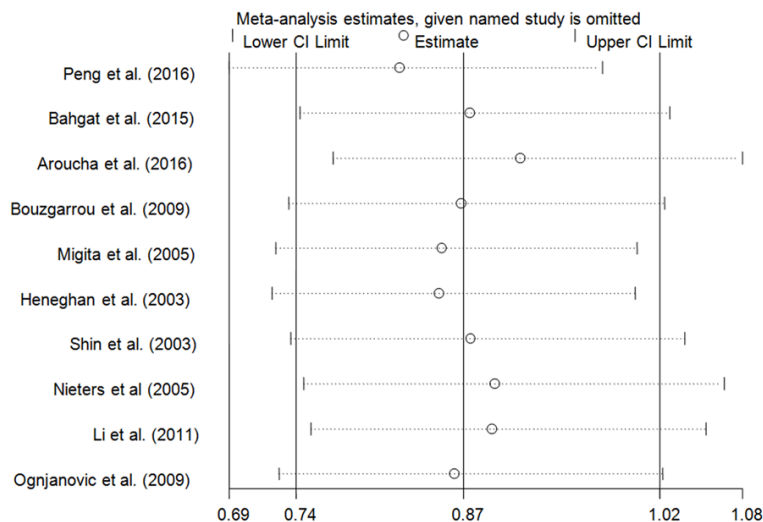
Figure 8. Sensitivity analysis of the influence of GG+AG vs. AA comparison (fixed-effects estimates for *IL-10* -1082 A>G polymorphism).
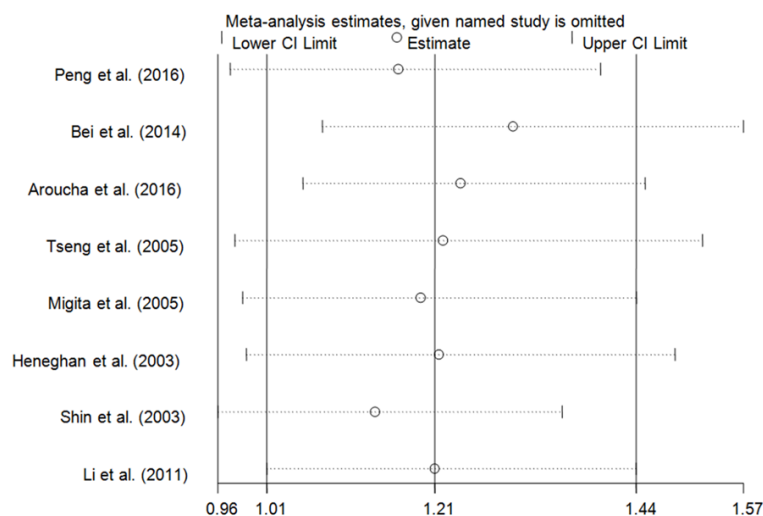

Figure 9. Sensitivity analysis of the influence of CC+AC vs. AA compare genetic model (fixed-effects estimates for *IL-10* -592 A>C polymorphism).

with HCC risk [33]. Recently, more studies was conducted on the association between *IL-10* polymorphisms and HCC; however, the result of these studies remains ambiguous [21-25]. Therefore, an updated meta-analysis was needed to get a comprehensive assessment. A total of twelve eligible papers were enrolled to explore the relationship between polymorphisms in *IL-10* gene and HCC risk. According to our findings, the *IL-10* -592 A>C polymorphism conferred an increased risk in the development of HCC (CC+AC versus AA; fixed-effects, OR = 1.18, 95% CI 1.04-1.35, P = 0.011, **Table 3**).

Our results were supported by several previously epidemiological studies. In two case-control studies conducted by Peng *et al*. and Shin *et al*., compared with the AA homozygote, the CC+AC genotype groups had an increased risk of HCC [21, 31]. Previous studies suggested that *IL-10* -592 C-allele was associated with lower IL-10 serum levels [41, 42]. The *IL-10* -592 A>C polymorphism may decrease the IL-10 production and influence the process of HBV/HCV chronic inflammation and confer higher susceptibility of HCC. However, all of these findings should be addressed with very caution. Because, for sample sizes, only 1,790 HCC cases and 3,344 controls were enrolled in the present study, which might have insufficient power to obtain an association. In additional, for *IL-10* -1082 A>G polymorphism, compared with the AA homozygote, the GG+AG genotype groups had a borderline statistically decreased risk of HCC (GG+AG vs. AA; OR = 0.87, 95% CI 0.74-1.02, P = 0.081). In our study, one case-control study deviated from the HWE, which indicated the presence of population stratification error [29]. When we discarded this study

inflammation and immune related genes have been considered as potential biomarkers of HCC risk. IL-10, a major immune regulatory inhibitory factor, decreases the synthesis of multiple cytokines and plays a role in anti-inflammatory. Previous studies indicated the circulating levels of IL-10 were greatly influenced by *IL-10* gene variants and haplotypes [10, 11, 41, 42]. The *IL-10* polymorphism could, therefore, confer certain influence in immune surveillance of malignancy and might modulate the risk of HCC. One meta-analyses focused on the relationship of polymorphisms in *IL-10* gene
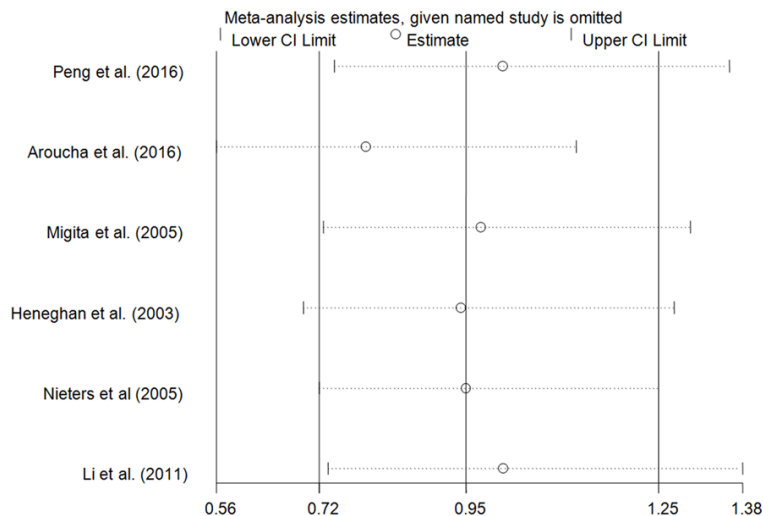
Figure 10. Sensitivity analysis of the influence of CC+CT vs. TT compare genetic model (fixed-effects estimates for *IL-10* -819 T>C polymorphism).

[29], the trend of increasing risk with HCC was more significant in the dominant genetic models (GG+AG vs. AA; OR = 0.85, 95% CI 0.72-1.00, *P* = 0.050, **Table 3**). Further studies based on larger sample sizes with further functional assessment are needed to be undertaken in order to confirm or refute such an association.

However, in the present analysis, there are some limitations should be addressed. First, all included studies were from Asians, Caucasians, and mixed population; thus, results could be suitable for these ethnic groups. Second, due to the lack of sufficient risk factor data for eligible studies, stratified analysis was not conducted by these environmental factors (such as age, gender, the status of HBV and HCV chronic infection, smoking, drinking, and other lifestyle factors *et al.*). Third, as the etiology of HCC is very complex, the influence of polymorphisms in *IL-10* gene might be covered by some as-yet-unidentified genes and environmental factors. Therefore, the comprehensive analysis of gene-gene and gene-environment interactions might be more powerful. Fourth, in the present meta-analysis, quality score of some included studies was relatively low. In the future, more high qualify are needed to further address these potential association. Finally, the number of included studies and sample sizes of the eligible studies in this meta-analysis was limited; thus, the results should be adopted with cautions.

In summary, in spite of these potential limitations, the meta-analysis highlights that *IL-10* -592 A>C polymorphism confers an increased risk for the development of HCC. In the future, larger sample size with sufficient gene-environment data studies are needed to confirm or refute such an association.

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Disclosure of conflict of interest

None.

Address correspondence to: Zhenzhou Xiao, Department of Clinical Laboratory, Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou 350014, Fujian Province, People's Republic of China. E-mail: 13515026867@163.com; Yu Chen, Department of Medical Oncology, Fujian Provincial Cancer Hospital, Fujian Medical University Cancer Hospital, Fuzhou 350014, Fujian Province, People's Republic of China. E-mail: 13859089836@139.com

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