

Systematic Review and Meta-Analysis on the Association between IL-1B Polymorphisms and Cancer Risk

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Abstract

Background: Interleukin-1 beta (IL-1 β), a pro-inflammatory cytokine, is emerging as a key mediator of carcinogenesis that characterizes host-environment interactions. Epidemiological studies investigating the association between two polymorphisms of IL-1B (–511C/T and +3954C/T) and cancer susceptibility have shown conflicting results. The aim of this study is to derive a more precise estimation of the relationship.

Methods: Related studies were identified through a systematic literature search of PubMed and Web of Science from their inception to September 15, 2012. Summary odds ratios (ORs) and 95% confidence intervals (CIs) for the IL-1B –511C/T and +3954C/T polymorphisms and cancer risk were calculated. Heterogeneity among studies and publication bias were also tested.

Results: The meta-analysis included 91 case-control studies in 85 publications, 81 studies for the –511C/T (19547 cases and 23935 controls) and 26 studies for the +3954C/T polymorphisms (8083 cases and 9183). The pooled results indicated that IL-1B +3954C/T (dominant model: OR = 1.15, 95% CI: 1.01–1.30) was significantly associated with increased overall cancer risk, especially among hospital-based case-control studies (dominant model: OR = 1.30, 95% CI: 1.02–1.66). As for –511C/T, we observed an inverse relationship in cervical cancer (dominant model: OR = 1.74, 95% CI: 1.35–2.23) and hepatocellular carcinoma (dominant model: OR = 0.68, 95% CI: 0.47–0.99). Moreover, –511C/T was associated with risk of specific subtypes of gastric carcinoma.

Conclusion: This meta-analysis suggested that both the IL-1B –511C/T and +3954C/T polymorphisms might modulate cancer susceptibility. Further well-designed studies based on larger sample sizes should be performed to confirm the findings.

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Introduction

Cancer is considered to be a complex, multistep and fatal disease that results from interactions between environmental and genetic factors [1]. It is increasingly recognized that inflammation contributes to pathogenesis of many cancers [2,3]. Chronic inflammation may result in oxidative stress and potentiate tumor promotion and progression [4–7]. Cytokines are glycoproteins or soluble proteins that act as mediators of inflammatory response and are integral to the function of immune cells. The role of cytokines in cancer immunity and carcinogenesis in general has been well established [8,9]. They are aberrantly produced by tumor cells, macrophages and other phagocytic cells [10,11]. These cytokines then activate transcription factors such as NF- κ B, AP-1 and STAT3, thus inducing genes that stimulate cell proliferation and survival. In addition to enhancing the prolifer-

ation of mutated cells, an inflammatory microenvironment can also increase DNA mutation rates [12]. On the other hand, immune cells affect malignant cells through the production of cytokines, chemokines, reactive oxygen and others [11]. Thus, cytokines are particularly important in neoplastic initiation.

Interleukin-1 (IL-1) is a pro-inflammatory cytokine with multiple biological effects [13]. The IL-1 gene family on chromosome 2q13-14 encodes three proteins: IL-1 α , IL-1 β and their naturally occurring inhibitor IL-1RN. IL-1 β , mainly produced by blood monocytes and tissue macrophages, has been implicated in mediating both acute and chronic inflammation [14]. Moreover, its property of stimulating the tumor microenvironment in favor of increased cell proliferation and tissue angiogenesis has been given much attention [15–18]. IL-1 β is

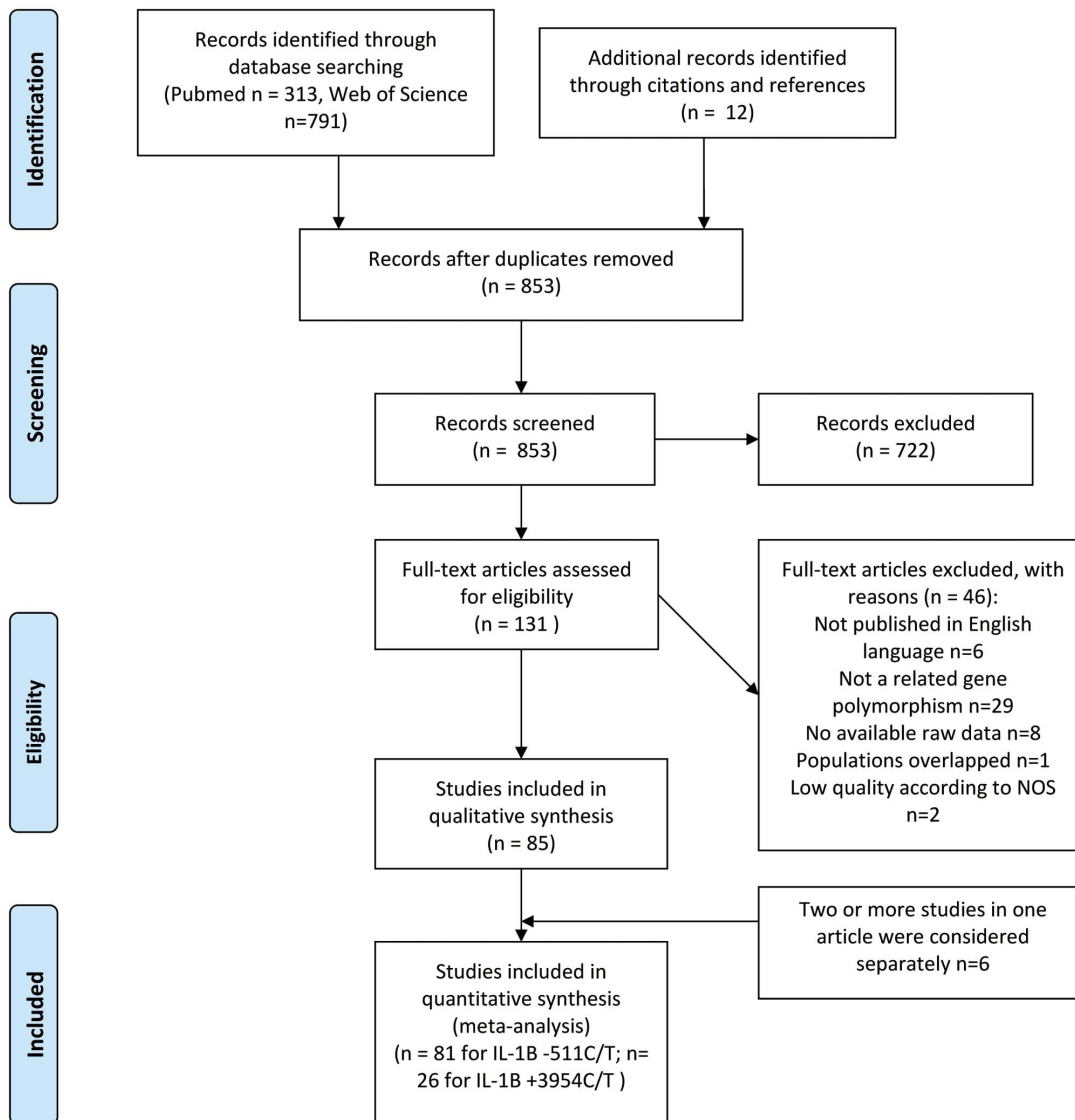


Figure 1. Flow chart of study selection.
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emerging as a key mediator of carcinogenesis that characterizes host-environment interactions.

The IL-1B gene is highly polymorphic and base transitions between C and T at positions -511 (C-T; dbSNP: rs16944), -31 (T-C; dbSNP: rs1143627) and +3954 (C-T; dbSNP: rs1143634) base pairs from the transcriptional site have been widely reported. In particular, the first two polymorphisms are located in the promoter region, and show high linkage disequilibrium [19,20]. The IL-1B -31T/C substitution causes disruption of a TATA-box motif and has been found to markedly affect the binding affinity of several transcription factors [19,21,22] and thereby affect the transcription activity of IL-1B [21]. The IL-1B +3954 C/T in exon 5 is a synonymous single nucleotide polymorphism (SNP). In vitro studies have shown that both -511T and +3954T are associated with increased IL-1 β secretion from lipopolysaccharide (LPS)-induced IL-1 β protein secretion [23–25].

It is not surprising that these functionally important polymorphisms in the IL-1B gene might be associated with cancer susceptibility. Recently, a meta-analysis of IL-1B -31T/C polymorphism and cancer risk has suggested that the -31C allele

is a low-penetrance protective factor for the development of cancer [26]. Furthermore, numerous epidemiological studies have investigated the association between IL-1B -511C/T and +3954C/T and different cancers, such as gastric, lung and breast cancers. However, the results remain inconsistent and inconclusive. A clearer understanding of the relationship between these two SNPs and cancer susceptibility is of clinical significance. In this report, a meta-analysis was conducted to provide an overview of all the relevant studies and synthesize conclusions on the associations between the IL-1B -511C/T, +3954C/T polymorphisms and cancer susceptibility.

Materials and Methods

Literature Search Strategy

Electronic databases (PubMed and Web of Science) were comprehensively searched using combinations of the terms “interleukin-1/IL-1” or “Interleukin-1B/IL-1B/IL-1 beta”, “polymorphism” and “cancer” or “tumor” (the last search update on September 15, 2012). For each identified study, additional studies

Table 1. Stratification analyses of the IL-1B -511C/T polymorphism on cancer susceptibility.

Variables	n ^a	Homozygote comparison		Heterozygote comparison		Dominant model		Recessive model	
		(TT versus CC)		(CT versus CC)		(TT+CT versus CC)		(TT versus CT+CC)	
		OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b
Total	81	1.09(0.96–1.23)	0.000	1.02(0.94–1.11)	0.000	1.04(0.95–1.13)	0.000	1.07(0.98–1.18)	0.000
Studies in HWE^d	67	1.10(0.97–1.26)	0.000	1.08(0.99–1.18)	0.000	1.09 (0.99–1.19)	0.000	1.05(0.95–1.15)	0.000
Cancer types									
Gastric cancer	40	1.18(0.96–1.44)	0.000	1.07(0.93–1.23)	0.000	1.08(0.95–1.22)	0.000	1.14(0.99–1.31)	0.000
Lung cancer	5	0.73(0.39–1.35)	0.000	0.86(0.71–1.03)	0.121 ^c	0.82(0.58–1.15)	0.007	0.80(0.49–1.31)	0.000
Blood cancers	5	1.31(0.88–1.94)	0.038	1.04(0.76–1.44)	0.002	1.07(0.77–1.47)	0.001	1.19(1.04–1.37)	0.104 ^c
Cervical cancer	4	1.74(1.28–2.36)	0.206 ^c	1.71(1.32–2.23)	0.302 ^c	1.74(1.35–2.23)	0.338 ^c	1.32(0.78–2.24)	0.001
Esophageal cancer	4	1.17(0.62–2.21)	0.006	0.98(0.83–1.16)	0.680 ^c	1.00(0.86–1.18)	0.330 ^c	1.19(0.72–1.95)	0.009
Hepatocellular Carcinoma	4	0.67(0.34–1.34)	0.006	0.75(0.60–0.94)	0.187 ^c	0.68(0.47–0.99)	0.091	0.90(0.49–1.66)	0.003
Skin cancer	3	0.96(0.71–1.28)	0.209 ^c	0.98(0.81–1.19)	0.303 ^c	0.97(0.81–1.17)	0.180 ^c	0.96(0.73–1.27)	0.404 ^c
Prostate cancer	3	0.85(0.65–1.11)	0.121 ^c	0.96(0.80–1.16)	0.309 ^c	0.93(0.78–1.11)	0.156 ^c	0.87(0.68–1.12)	0.243 ^c
Breast cancer	3	1.10(0.70–1.73)	0.040	0.97(0.82–1.15)	0.166 ^c	0.99(0.74–1.33)	0.048	1.09(0.96–1.48)	0.116 ^c
Others	10	0.85(0.62–1.18)	0.043	0.96(0.67–1.38)	0.000	0.95(0.68–1.32)	0.000	0.92(0.76–1.11)	0.597 ^c
Ethnicities									
Asian	45	1.03(0.85–1.23)	0.000	0.97(0.84–1.11)	0.000	0.98(0.85–1.14)	0.000	1.05(0.93–1.18)	0.000
Caucasian	27	1.05(0.90–1.23)	0.001	1.07(0.96–1.19)	0.000	1.06(0.95–1.19)	0.000	1.06(0.89–1.16)	0.009
Others	9	1.79(0.55–3.36)	0.000	1.05(0.88–1.24)	0.203 ^c	1.25(0.89–1.73)	0.003	1.66(1.03–2.70)	0.000
Source of control									
Population-based	34	1.14(0.96–1.35)	0.000	1.07(0.97–1.17)	0.000	1.08(0.97–1.19)	0.000	1.08(0.94–1.24)	0.000
Hospital-based	47	1.03(0.86–1.25)	0.000	0.98(0.84–1.14)	0.000	1.00(0.86–1.16)	0.000	1.07(0.95–1.21)	0.000

^aNumber of studies;

^bP-value of Q-test for heterogeneity test;

^cA Fixed-effects model was used when the P-value for heterogeneity test was >0.10; otherwise, a random-effects model was used;

^dHWE, Hardy–Weinberg equilibrium.

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were sought from its citations, references and from the database option “Related Articles”.

Inclusion and Exclusion Criteria

Eligible studies were selected according to the following explicit inclusion criteria: (i) case-control study evaluating the association between at least one of the two polymorphisms (IL-1B -511C/T and +3954C/T) and cancer susceptibility, (ii) sufficient genotype data presented to calculate the odds ratios (ORs) and 95% confidence intervals (CIs). Major reasons for exclusion of studies were: (i) only cancer group, (ii) no usable genotype frequency data, (iii) duplicate of earlier publication, (iv) publication not in English.

Data Extraction and Quality Assessment

Two investigators (Jiali Xu and Zhiqiang Yin) extracted information from all eligible publications independently according to the criteria listed above. The following information was gathered from each study: the first author’s name, year of publication, cancer type, country of origin, ethnicity of subjects, source of control, genotyping method, number of cases and controls and genotype frequency (Table S1). The quality assessment of each study was carried out independently by the two investigators using the Newcastle-Ottawa Scale (NOS) [27]. Studies with a score equal to or higher than 5 were considered “high-quality”, whereas those scored less than 4 were considered

“low-quality”. All item-specific ambiguities were discussed by investigators’ consultation until consensus was achieved.

Statistical Analysis

We first calculated Hardy–Weinberg equilibrium (HWE) in the controls for each included study using a goodness-of-fit test and for which $P < 0.05$ was considered not compliant with HWE. The strength of the association between the two SNPs (IL-1B -511C/T and +3954C/T) and cancer risk was measured by ORs with 95% CIs. Pooled ORs were obtained from combination of single studies by homozygote comparison (TT vs. CC), heterozygote comparison (CT vs. CC), dominant model (TT+CT vs. CC) and recessive model (CC+CT vs. TT), respectively. The heterogeneity among different studies was checked by the Q-test [28]. If the P value is < 0.10 , a random effect model with the DerSimonian and Laird method was used to pool the results. Otherwise, a fixed-effect model with the Mantel-Haenszel method was then used [29].

Sensitivity analysis was performed to assess the stability of the results by omitting a single study in this meta-analysis each time to reflect the influence of individual data on the pooled OR. To further explore the potential source of heterogeneity among studies and test the effects of study characteristics on the overall estimates, subgroup analyses and meta regression were performed stratified by cancer types (if one cancer type contained fewer than three individual studies, it was grouped into the “other cancers”),

Table 2. Stratification analyses of the IL-1B -511C/T polymorphism on gastric cancer susceptibility.

Variables	n ^a	Dominant model (TT+CT versus CC)	
		OR (95% CI)	P ^b
Total	40	1.08(0.95–1.22)	0.000
Studies in HWE^d	31	1.16(1.02–1.32)	0.000
Ethnicities			
Asian	24	1.01(0.87–1.19)	0.000
Caucasian	11	1.25(0.78–2.00)	0.089
Mixed	5	1.50(1.14–1.97)	0.000
Source of control			
Population-based	15	1.20(1.00–1.43)	0.000
Hospital-based	25	0.99(0.84–1.17)	0.000
Tumor site			
Cardia type	5	1.24(0.94–1.65)	0.942 ^c
Non-cardia type	5	1.57(1.06–2.31)	0.003
Histology			
Intestinal type	11	1.24(1.04–1.49)	0.033
Diffuse/Mixed type	11	1.03(0.78–1.36)	0.003
HP status			
HP ^e +	13	1.14(0.85–1.51)	0.000
HP-	7	1.19(0.92–1.54)	0.581 ^c

^aNumber of studies;

^bP-value of Q-test for heterogeneity test;

^cA Fixed-effects model was used when the P-value for heterogeneity test was >0.10; otherwise, a random-effects model was used;

^dHWE, Hardy-Weinberg equilibrium;

^eHP, *Helicobacter pylori*.

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ethnicity (Caucasian, Asian or Others; Others included African and Mixed populations), and source of controls (population-based or hospital-based).

Publication bias was diagnosed with Begg's funnel plot and Egger's linear regression method [30]. Asymmetric or incomplete funnel shaped plots and $P < 0.05$ in Egger's test indicated the presence of potential publication bias. All statistical analyses used STATA 12.0 (STATA Corp, College Station, Texas). Except for heterogeneity statistics (where significance was declared if $P < 0.10$), each P -value < 0.05 was considered to be statistically significant. All P -values were 2-sided.

Results

Flow of Included Studies

Figure 1 depicts the results of the literature search. After review of abstracts, 131 full-text potentially relevant publications were retrieved to be assessed for eligibility. Among the 46 full-text articles excluded, one article [20] was updated by a new publication [31], and two case-control studies were considered "low-quality" (score = 3 and 4) using the NOS quality assessment instrument and thus were excluded [32,33]. By contrast, five articles each mentioned two or more independent case-control studies, and studies included in these articles were treated as separate studies [34–38]. Finally, a total of 91 case-control studies in 85 publications, of which there were 81 studies for the -511C/T polymorphism [19,31,35,37–83][34,36,84–106] and 26 studies

for the +3954C/T polymorphism [19,34,36,42,50,51,54,56,61,65,74,81,82,105,107–116], were included in the meta-analysis based on our search strategy and eligibility criteria.

Study Characteristics

Detailed characteristics of the aggregated data for 91 case-control studies are summarized in Table S1. The vast majority of the included studies – all except 14 studies for -511C/T and 2 studies for +3954C/T – indicated that the genotype distributions in the controls were consistent with HWE. There were 47 studies of subjects of Asian descent, 32 studies of subjects of Caucasian descent and 12 studies of subjects with ethnicity "Others" (7 mixed-ethnicity studies and 3 African studies). Minor allele frequencies (MAFs) of -511C/T and +3954C/T of controls in different populations are graphed as Figure S1.

Quantitative Data Synthesis

Association of the IL-1B -511C/T polymorphism with cancer susceptibility: Analyses of 81 case-control studies including 19547 cases and 23935 controls were conducted to explore the relationship between -511C/T and cancer risk (Table 1). Overall, no significant association was detected in any genetic model (homozygote comparison: OR = 1.09, 95% CI: 0.96–1.23; dominant model: OR = 1.04, 95% CI: 0.95–1.13). The pooled estimates remained stable when restricted to studies not deviating from HWE. Intriguingly, in the subgroup analysis stratified by cancer type, the IL-1B -511T allele showed evidence of an association with increased cervical cancer risk (dominant model: OR = 1.74, 95% CI: 1.35–2.23), but demonstrated a protective role in the development of hepatocellular carcinoma (dominant model: OR = 0.68, 95% CI: 0.47–0.99). Increased risk was also observed in blood cancers (recessive model: OR = 1.19, 95% CI: 1.04–1.37).

The data were additionally stratified for gastric cancer in the dominant model (Table 2). The association became significant when excluded studies not in HWE (OR = 1.16, 95% CI: 1.02–1.32). Statistically significant findings were also found in population-based case-control studies (OR = 1.20, 95% CI: 1.00–1.43) but not in analysis stratified by ethnicities. When gastric carcinoma was classified according to tumor site (cardia or non-cardia) and histopathology subtypes (intestinal or diffuse/mixed), significant associations were detected in non-cardia gastric cancer (OR = 1.57, 95% CI: 1.06–2.31) and intestinal gastric cancer (OR = 1.24, 95% CI: 1.04–1.49).

The genotype distribution of -511C/T among cases and infection-match controls was available in 20 studies that investigated gastric cancer infected by *Helicobacter pylori* (HP). However, there were no significant gene-environment interactions in this case.

Association of the IL-1B +3954C/T polymorphism with cancer susceptibility:

The analysis eventually included 26 case-control studies with 8083 cases and 9183 controls for IL-1B +3954C/T. Table 3 presents the main results of the pooled analysis and Figure 2 shows the association between +3954C/T and cancer risk in the form of forest plots. Overall, the results of combined analyses of all studies suggested that the +3954C/T polymorphism was significantly associated with increased cancer susceptibility in the dominant model (OR = 1.15, 95% CI: 1.01–1.30). This association remained consistently strong when limited to studies in HWE (heterozygote comparison: OR = 1.14, 95% CI: 1.00–1.31; dominant model: OR = 1.16, 95% CI: 1.02–1.33). When stratified by source of controls, hospital-based studies

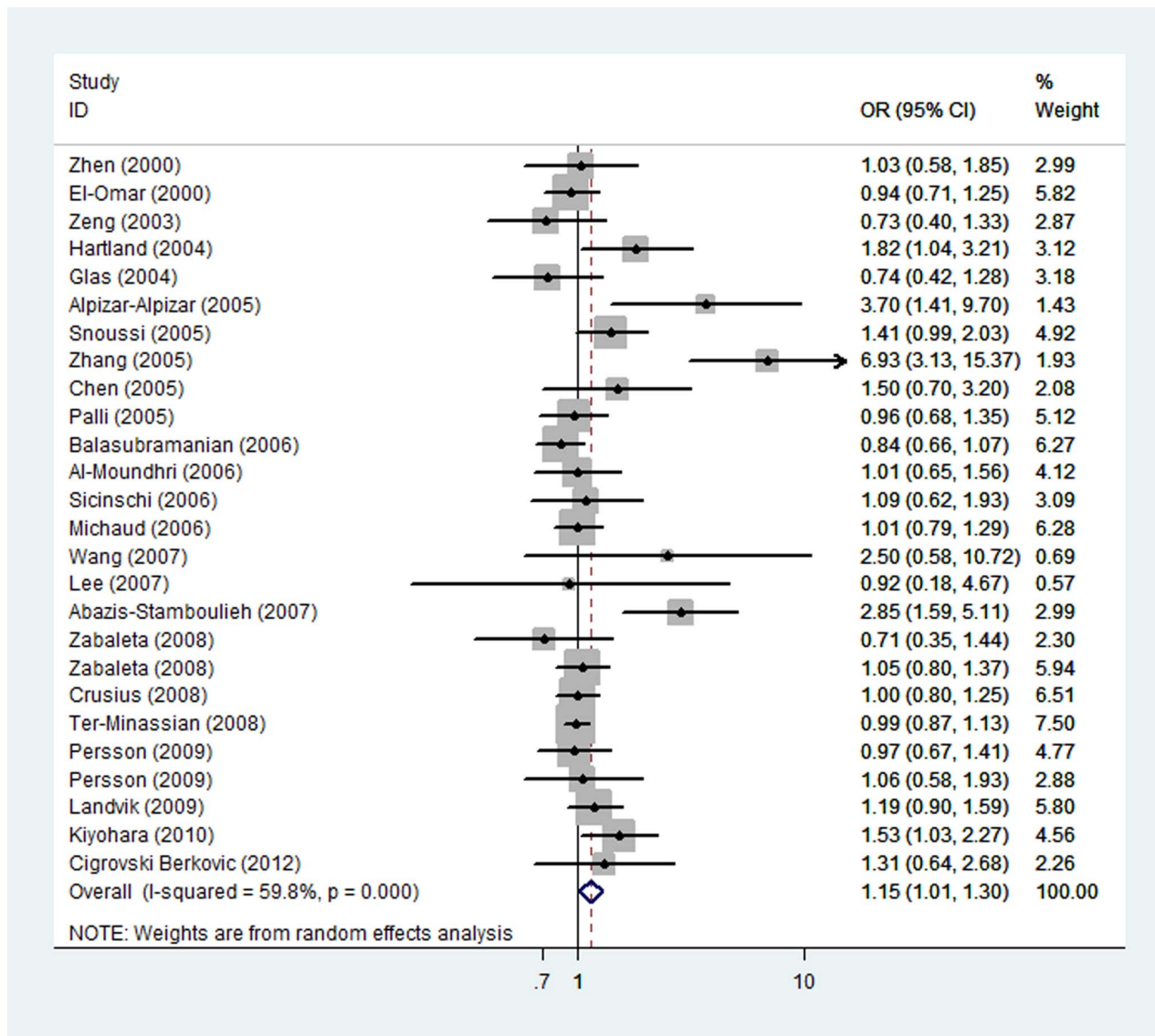


Figure 2. Forest plots describing the association of the IL-1B +3954C/T polymorphism with cancer susceptibility in the dominant model. The squares and horizontal lines correspond to the OR and 95% CI for each study. The area of the squares reflects the weight. The diamond represents the summary OR and 95% CI. doi:10.1371/journal.pone.0063654.g002

exhibited significantly increased risk (dominant model: OR = 1.30, 95% CI: 1.02–1.66).

Meta Regression

Since there was significant heterogeneity for IL-1B -511C/T in all genetic models, a univariable regression was conducted to explore the predefined possible source of heterogeneity (Table S2). We identified that it is variability in MAF of this polymorphism across different ethnicities that was a significant source of heterogeneity (dominant model: β coefficient = -1.60 (-2.67 to -0.47), $P=0.006$; recessive model: β coefficient = -1.40 (-2.45 to -0.35), $P=0.010$), but not cancer type or source of control. Using dominant model, we also did meta regression for +3954C/T (Table S3). However, cancer type ($P=0.816$), MAF ($P=0.050$) and source of control ($P=0.308$) only explained little of the heterogeneity.

Sensitivity Analyses and Publication Bias

The influence of each study on the pooled OR was examined by repeating the meta-analyses while sequentially omitting individual studies. Both sensitivity analyses for -511C/T and +3954C/T indicated that no single study influenced the pooled ORs qualitatively, suggesting that the results of our meta-analyses are robust and stable. The shape of funnel plots was symmetrical for -511C/T, and the Egger's test P -value were 0.628, 0.788, 0.888 and 0.579 for homozygote comparison, heterozygote comparison, dominant model and recessive model, respectively (Figure 3). As for the +3954C/T polymorphism, symmetrical funnel plots were found in homozygote comparison ($P=0.382$) and recessive model ($P=0.509$), but not in heterozygote comparison and dominant model (Egger's test $P=0.026$ and 0.020, respectively, Figure 3), implying the existence of publication bias.

The PRISMA Checklist for our study is shown as Table S4 [117].

Table 3. Stratification analyses of the IL-1B +3954C/T polymorphism on cancer susceptibility.

Variables	n ^a	Homozygote comparison		Heterozygote comparison		Dominant model		Recessive model	
		(TT versus CC)		(CT versus CC)		(TT+CT versus CC)		(TT versus CT+TT)	
		OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b	OR (95% CI)	P ^b
Total	26	1.13(0.97–1.31)	0.163 ^c	1.13(0.99–1.28)	0.001	1.15(1.01–1.30)	0.000	1.01(0.95–1.29)	0.362 ^c
Studies in HWE^d	24	1.14(0.98–1.33)	0.113 ^c	1.14(1.00–1.31)	0.000	1.16(1.02–1.33)	0.000	1.12(0.96–1.31)	0.280 ^c
Cancer types									
Gastric cancer	13	0.92(0.71–1.19)	0.506 ^c	1.20(0.94–1.53)	0.001	1.19(0.94–1.50)	0.000	0.91(0.70–1.17)	0.539 ^c
Lung cancer	4	1.16(0.89–1.51)	0.442 ^c	1.05(0.93–1.18)	0.198 ^c	1.06(0.95–1.19)	0.168 ^c	1.14(0.88–1.48)	0.423 ^c
Prostate cancer	3	1.52(0.77–1.72)	0.626 ^c	0.98(0.82–1.18)	0.403 ^c	1.00(0.84–1.19)	0.597 ^c	1.15(0.78–1.71)	0.533 ^c
Others	6	1.74(0.91–3.34)	0.048	1.25(0.88–1.75)	0.018	1.33(0.92–1.93)	0.003	1.47(1.04–2.10)	0.220 ^c
Ethnicities									
Asian	6	3.01(0.97–9.32)	0.887 ^c	1.66(0.85–3.24)	0.001	1.73(0.91–3.29)	0.001	2.92(0.94–9.01)	0.863 ^c
Caucasian	14	1.05(0.89–1.25)	0.124 ^c	1.01(0.93–1.10)	0.120 ^c	1.05(0.93–1.18)	0.051	1.04(0.88–1.23)	0.335 ^c
Others	6	1.33(0.94–1.88)	0.435 ^c	1.12(0.84–1.90)	0.069	1.15(0.88–1.51)	0.073	1.28(0.91–1.78)	0.427 ^c
Source of control									
Population-based	14	1.03(0.87–1.22)	0.657 ^c	1.07(0.92–1.24)	0.002	1.07(0.92–1.23)	0.002	1.03(0.87–1.22)	0.601 ^c
Hospital-based	12	1.57(1.13–2.18)	0.148 ^c	1.25(0.98–1.59)	0.029	1.30(1.02–1.66)	0.014	1.44(1.04–1.99)	0.343 ^c

^aNumber of studies;^bP-value of Q-test for heterogeneity test;^cA Fixed-effects model was used when the P-value for heterogeneity test was >0.10; otherwise, a random-effects model was used;^dHWE, Hardy–Weinberg equilibrium.

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Discussion

Large sample epidemiological studies of predisposition gene polymorphisms could provide insight into the in vivo association between candidate genes and diseases. The present meta-analysis, including 91 high-quality case-control studies, is the most comprehensive meta-analysis to have evaluated the IL-1B polymorphisms (–511C/T and +3954C/T) and their relationship to cancer susceptibility. Its strength was based on the accumulation of published data providing greater information to detect significant differences. Our results demonstrated that IL-1B +3954C/T was significantly associated with increased overall cancer risk, especially among hospital-based case-control studies. No significant association was observed between –511C/T and overall cancer risk. However, results from subgroup analyses indicated that –511C/T was associated with susceptibility of certain types of cancer. Given the critical roles of IL-1β in inflammation and carcinogenesis, it is possible that both IL-1B –511C/T and +3954C/T polymorphisms may modulate the risk of cancer development.

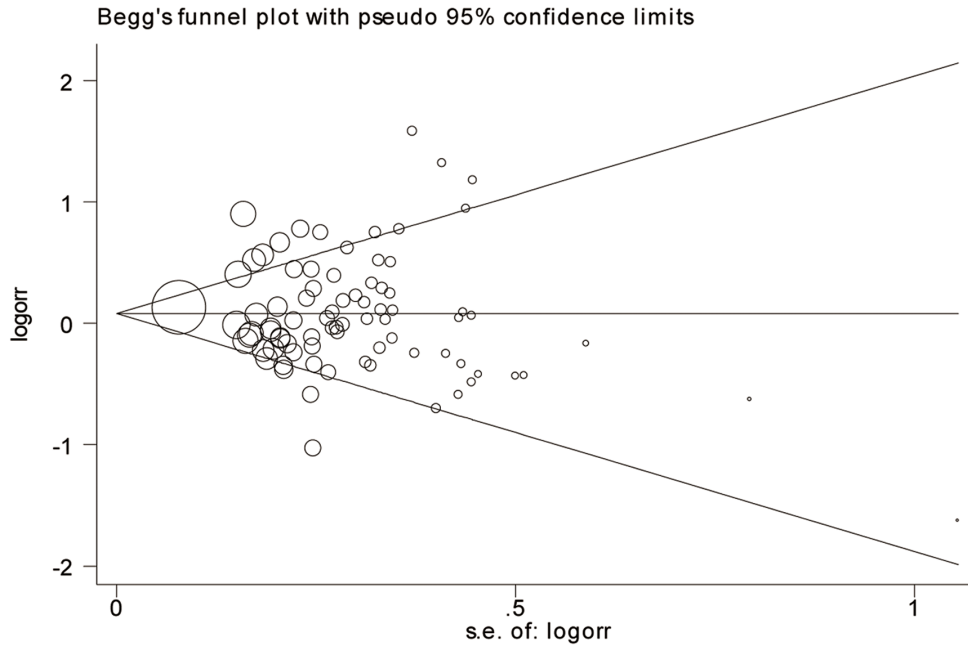
Cumulative evidence suggests that IL-1β plays an important role in tumorigenesis and development. It is well known that IL-1 expression is elevated in most human cancers. High plasma IL-1β levels are associated with a significantly increased risk of cancer, and tumor patients with high IL-1 expression have worse prognosis than those without [99,115,118]. IL-1β promotes invasiveness, including tumor angiogenesis, and also induces immune suppression in the host [16,17]. Moreover, IL-1β has been found to combine with estrogen receptor (ER)α in breast cancer cells, resulting in transcriptional activation [119]. In pancreatic cancer cells, IL-1β has been shown to mediate adhesion and invasion, as well as modulating chemoresistance by activating the NF-κB and ERK signaling pathways [120–123]. IL-1β can also attenuate interferon-induced antiviral activity and STAT1

activation in the liver, and modulate immune responses in hepatitis virus-related hepatocellular carcinoma [43,124].

In the subgroup analysis according to cancer type, a significant association was detected between the –511T variant allele polymorphism and increased cervical cancer risk. Interestingly, this allele seemed to be a protective factor for the development of hepatocellular carcinoma. Some possible reasons may explain this discrepancy. First, the relatively small number of eligible studies in each subgroup might induce significant/insignificant association by chance due to insufficient statistical power. Second, there are some conflicting data regarding the effect of the IL-1B –511/–31 haplotype on gene expression. Ex vivo blood stimulation assay suggests that the –511T/–31C haplotype is significantly associated with an increase in LPS-induced IL-1β intracellular secretion [23]. IL-1B –511T/–31C is associated with a high level of IL-1β in the plasma [125]. However, the IL-1B –31 polymorphism involves a TATA-box motif and the –31T allele is associated with a five-fold elevated binding activity with the transcription initiation factor [19,21,22]. In vivo study indicates that a disease-related haplotype including –511C/–31T has higher IL-1B mRNA expression in the lungs compared with the non-risk haplotype [115]. In HP-infected gastric cancer patients, the mucosal IL-1B level is higher in –31T carriers than in –31C carriers [57]. It is likely that gene expression in each organ, such as the cervix and liver, is differently regulated. Functional study in specific tissue is required for better understanding of the role of IL-1B genotype in carcinogenesis.

Our results for gastric cancer were partly consistent with results from a previous meta-analysis performed by Xue et al. [126]. Both our meta-analysis and Xue's demonstrated no association between IL-1B +3954C/T and gastric cancer risk. They found IL-1B –511T carriers were associated with a significantly increased risk of gastric cancer. However, we observed significant associations only among population-based studies. Our work may be interpreted as an update of Xue's, because another 30 or more

A



B

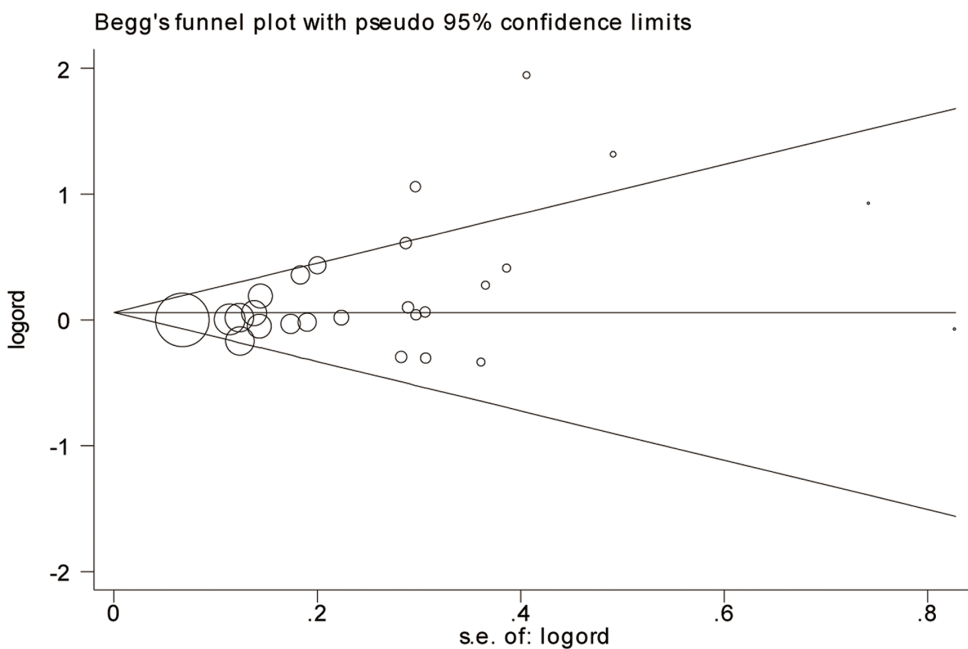


Figure 3. Begg's funnel plots of publication bias. Each study is represented by a circle, the area of which presents the study's precision. A, funnel plot for IL-1B -511C/T in the recessive model (Egger's test $P=0.579$). B, funnel plot for IL-1B +3954C/T in the dominant model (Egger's test $P=0.020$).

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studies concerning -511C/T or +3954C/T polymorphisms and gastric susceptibility with inconsistent results have been published in the past 2 years. We also found that -511T carriers are significantly associated with risk of the non-cardia and intestinal types of gastric cancer, whereas association was not detected in HP-positive group nor in the HP-negative group, and this is

consistent with Xue's meta-analysis. Further in-depth research focused on IL-1B -511C/T and specific subtypes of gastric cancer is warranted.

In the stratification analysis of source of control, significantly increased risk between the IL-1B +3954C/T polymorphism and cancer risk was detected among hospital-based studies, but not

among population-based studies. This may be due to some selection biases existing in hospital-based studies because such controls might come from a population with a related disease and may not be a representative of the general population, especially when there is a relationship between the investigated genotypes and the disease conditions that hospital-based controls might have. Although it is more convenient to recruit hospital controls, to reduce biases in such genetic association studies it may be preferable to use population controls.

Significant heterogeneity existed among studies for IL-511C/T in all comparisons, and meta regression indicated that MAF in different ethnicities partly accounts for the heterogeneity. Although we observed a wide variation of -511T allele frequency of control resources in different populations, and the MAF might reflect an environmental impact on gene distribution, subgroup analysis stratified by ethnicity did not detect any significant association between -511C/T and cancer risk in Asians nor in Caucasians. Cancer is a multi-factorial disease resulting from complex interactions between environmental and genetic factors [1]. Some other factors may weaken the effect of IL-1B -511C/T on cancer risk in different ethnic groups.

Some limitations of our meta-analysis should be mentioned. Our results were based on unadjusted estimates because of the absence of available information. If more detailed individual data such as age, sex and exposure were available, a more precise analysis would be performed. Additionally, both the asymmetric funnel plot and Egger's test indicated the existence of publication bias in two comparisons for the IL-1B +3954C/T polymorphism. This may be explained by the restriction of the meta-analysis to studies published in English. In spite of these limitations, our meta-analysis also had some advantages. First, it is the most comprehensive meta-analysis to evaluate the two polymorphisms (-511C/T and +3954C/T) and their relationship to cancer susceptibility. The number of cases and controls through the pooled studies could significantly increase the statistical power of the analysis. Second, all included studies had acceptable quality (scored at least 5).

References

- Pharoah PD, Dunning AM, Ponder BA, Easton DF (2004) Association studies for finding cancer-susceptibility genetic variants. *Nat Rev Cancer* 4: 850–860.
- Coussens LM, Werb Z (2002) Inflammation and cancer. *Nature* 420: 860–867.
- Schottenfeld D, Beebe-Dimmer J (2006) Chronic inflammation: a common and important factor in the pathogenesis of neoplasia. *CA Cancer J Clin* 56: 69–83.
- Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A (2009) Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis* 30: 1073–1081.
- Germano G, Allavena P, Mantovani A (2008) Cytokines as a key component of cancer-related inflammation. *Cytokine* 43: 374–379.
- Mantovani A (2010) Molecular pathways linking inflammation and cancer. *Curr Mol Med* 10: 369–373.
- Mantovani A, Savino B, Locati M, Zammataro L, Allavena P, et al. (2010) The chemokine system in cancer biology and therapy. *Cytokine Growth Factor Rev* 21: 27–39.
- Smyth MJ, Cretney E, Kershaw MH, Hayakawa Y (2004) Cytokines in cancer immunity and immunotherapy. *Immunol Rev* 202: 275–293.
- Seruga B, Zhang H, Bernstein LJ, Tannock IF (2008) Cytokines and their relationship to the symptoms and outcome of cancer. *Nat Rev Cancer* 8: 887–899.
- Jin P, Panelli MC, Marincola FM, Wang E (2004) Cytokine polymorphism and its possible impact on cancer. *Immunol Res* 30: 181–190.
- Kurzrock R (2001) Cytokine deregulation in cancer. *Biomed Pharmacother* 55: 543–547.
- Grivnenkov SI, Greten FR, Karin M (2010) Immunity, inflammation, and cancer. *Cell* 140: 883–899.
- Dinarello CA (1996) Biologic basis for interleukin-1 in disease. *Blood* 87: 2095–2147.
- Bird S, Zou J, Wang T, Munday B, Cunningham C, et al. (2002) Evolution of interleukin-1beta. *Cytokine Growth Factor Rev* 13: 483–502.

Conclusions

In conclusion, this meta-analysis indicated that IL-1B +3954C/T was associated with significantly increased overall cancer risk, especially among hospital-based case-control studies. The IL-1B -511T allele showed evidence of an association with increased cervical cancer risk but demonstrated a protective role in the development of hepatocellular carcinoma. Moreover, -511C/T was associated with risk of specific subtypes of gastric carcinoma. Further large-sample research should use standardized unbiased homogeneous cancer patients and well-matched controls to confirm our findings. Additionally, gene-environment interactions should be considered in future studies.

Supporting Information

Figure S1 Minor allele frequencies of IL-1B -511C/T and +3954C/T polymorphisms among ethnicities of Asian, Caucasian and Others in controls.
(TIF)

Table S1 Main characteristics of the selected studies.
(DOC)

Table S2 Results of random effect meta-regression for search of source of heterogeneity for IL-1B -511C/T.
(DOC)

Table S3 Results of random effect meta-regression for search of source of heterogeneity for IL-1B +3954C/T in the dominant model.
(DOC)

Table S4 PRISMA Checklist for current meta-analysis.
(DOC)

Author Contributions

Conceived and designed the experiments: JX. Performed the experiments: JX ZY. Analyzed the data: JX ZY SC. Wrote the paper: JX. Helped to answer reviewers' comments: SC WG LL YP PL. Provided experimental guidance and helped to answer reviewers' comments: YS.

25. Hernandez-Guerrero C, Monzon-Bordonaba F, Jimenez-Zamudio L, Ahued-Ahued R, Arechavaleta-Velasco F, et al. (2003) In-vitro secretion of proinflammatory cytokines by human amniochorion carrying hyper-responsive gene polymorphisms of tumour necrosis factor-alpha and interleukin-1beta. *Mol Hum Reprod* 9: 625–629.
26. He B, Zhang Y, Pan Y, Xu Y, Gu L, et al. (2011) Interleukin 1 beta (IL1B) promoter polymorphism and cancer risk: evidence from 47 published studies. *Mutagenesis* 26: 637–642.
27. Wells GA, Shea B, O'Connell D, Petersen J, Welch V (Accessed 2012 Sep 30.) The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available: http://www.ohrica/programs/clinical_epidemiology/oxford.htm.
28. Handoll HH (2006) Systematic reviews on rehabilitation interventions. *Arch Phys Med Rehabil* 87: 875.
29. Higgins JP, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. *Stat Med* 21: 1539–1558.
30. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L (2006) Comparison of two methods to detect publication bias in meta-analysis. *Jama* 295: 676–680.
31. Machado JC, Figueiredo C, Canedo P, Pharoah P, Carvalho R, et al. (2003) A proinflammatory genetic profile increases the risk for chronic atrophic gastritis and gastric carcinoma. *Gastroenterology* 125: 364–371.
32. Gatti LL, Burbano RR, de Assumpcao PP, Smith Mde A, Payao SL (2004) Interleukin-1beta polymorphisms, *Helicobacter pylori* infection in individuals from Northern Brazil with gastric adenocarcinoma. *Clin Exp Med* 4: 93–98.
33. zur Hausen A, Crusius JB, Murillo LS, Alizadeh BZ, Morre SA, et al. (2003) IL-1B promoter polymorphism and Epstein-Barr virus in Dutch patients with gastric carcinoma. *Int J Cancer* 107: 866–867.
34. Persson C, Engstrand L, Nyren O, Hansson LE, Enroth H, et al. (2009) Interleukin 1-beta gene polymorphisms and risk of gastric cancer in Sweden. *Scand J Gastroenterol* 44: 339–345.
35. Ito H, Kaneko K, Makino R, Konishi K, Kurahashi T, et al. (2007) Interleukin-1beta gene in esophageal, gastric and colorectal carcinomas. *Oncol Rep* 18: 473–481.
36. Zabaleta J, Lin HY, Sierra RA, Hall MC, Clark PE, et al. (2008) Interactions of cytokine gene polymorphisms in prostate cancer risk. *Carcinogenesis* 29: 573–578.
37. Wu MS, Chen LT, Shun CT, Huang SP, Chiu HM, et al. (2004) Promoter polymorphisms of tumor necrosis factor-alpha are associated with risk of gastric mucosa-associated lymphoid tissue lymphoma. *Int J Cancer* 110: 695–700.
38. El-Omar EM, Rabkin CS, Gammon MD, Vaughan TL, Risch HA, et al. (2003) Increased risk of noncardia gastric cancer associated with proinflammatory cytokine gene polymorphisms. *Gastroenterology* 124: 1193–1201.
39. Hwang IR, Kodama T, Kikuchi S, Sakai K, Peterson LE, et al. (2002) Effect of interleukin 1 polymorphisms on gastric mucosal interleukin 1beta production in *Helicobacter pylori* infection. *Gastroenterology* 123: 1793–1803.
40. Wang Y, Kato N, Hoshida Y, Yoshida H, Taniguchi H, et al. (2003) Interleukin-1beta gene polymorphisms associated with hepatocellular carcinoma in hepatitis C virus infection. *Hepatology* 37: 65–71.
41. Howell WM, Turner SJ, Theaker JM, Bateman AC (2003) Cytokine gene single nucleotide polymorphisms and susceptibility to and prognosis in cutaneous malignant melanoma. *Eur J Immunogenet* 30: 409–414.
42. Zeng ZR, Hu PJ, Hu S, Pang RP, Chen MH, et al. (2003) Association of interleukin 1B gene polymorphism and gastric cancers in high and low prevalence regions in China. *Gut* 52: 1684–1689.
43. Tanaka Y, Furuta T, Suzuki S, Orito E, Yebo AE, et al. (2003) Impact of interleukin-1beta genetic polymorphisms on the development of hepatitis C virus-related hepatocellular carcinoma in Japan. *J Infect Dis* 187: 1822–1825.
44. Zhang Z, Liu W, Jia X, Gao Y, Hemminki K, et al. (2004) Use of pyrosequencing to detect clinically relevant polymorphisms of genes in basal cell carcinoma. *Clin Chim Acta* 342: 137–143.
45. Yang J, Hu Z, Xu Y, Shen J, Niu J, et al. (2004) Interleukin-1B gene promoter variants are associated with an increased risk of gastric cancer in a Chinese population. *Cancer Lett* 215: 191–198.
46. Chen A, Li CN, Hsu PI, Lai KH, Tseng HH, et al. (2004) Risks of interleukin-1 genetic polymorphisms and *Helicobacter pylori* infection in the development of gastric cancer. *Aliment Pharmacol Ther* 20: 203–211.
47. Zienoldiny S, Ryberg D, Maggini V, Skaug V, Canzian F, et al. (2004) Polymorphisms of the interleukin-1 beta gene are associated with increased risk of non-small cell lung cancer. *Int J Cancer* 109: 353–356.
48. Lee KA, Ki CS, Kim HJ, Sohn KM, Kim JW, et al. (2004) Novel interleukin 1beta polymorphism increased the risk of gastric cancer in a Korean population. *J Gastroenterol* 39: 429–433.
49. Grimm C, Berger I, Tomovski C, Zeillinger R, Concin N, et al. (2004) A polymorphism of the interleukin-1 receptor antagonist plays a prominent role within the interleukin-1 gene cluster in vulvar carcinogenesis. *Gynecol Oncol* 92: 936–940.
50. Hartland S, Newton JL, Griffin SM, Donaldson PT (2004) A functional polymorphism in the interleukin-1 receptor-1 gene is associated with increased risk of *Helicobacter pylori* infection but not with gastric cancer. *Dig Dis Sci* 49: 1545–1550.
51. Glas J, Torok HP, Schneider A, Brunner G, Kopp R, et al. (2004) Allele 2 of the interleukin-1 receptor antagonist gene is associated with early gastric cancer. *J Clin Oncol* 22: 4746–4752.
52. Tsai FJ, Chang CH, Chen CC, Hsia TC, Chen HY, et al. (2005) Interleukin-4 gene intron-3 polymorphism is associated with transitional cell carcinoma of the urinary bladder. *BJU Int* 95: 432–435.
53. Sakuma K, Uozaki H, Chong JM, Hironaka M, Sudo M, et al. (2005) Cancer risk to the gastric corpus in Japanese, its correlation with interleukin-1beta gene polymorphism (+3953*T) and Epstein-Barr virus infection. *Int J Cancer* 115: 93–97.
54. Alpizar-Alpizar W, Perez-Perez GI, Une C, Cuenca P, Sierra R (2005) Association of interleukin-1B and interleukin-1RN polymorphisms with gastric cancer in a high-risk population of Costa Rica. *Clin Exp Med* 5: 169–176.
55. Perri F, Piepoli A, Bonvicini C, Gentile A, Quitadamo M, et al. (2005) Cytokine gene polymorphisms in gastric cancer patients from two Italian areas at high and low cancer prevalence. *Cytokine* 30: 293–302.
56. Zhang WH, Wang XL, Zhou J, An LZ, Xie XD (2005) Association of interleukin-1B (IL-1B) gene polymorphisms with risk of gastric cancer in Chinese population. *Cytokine* 30: 378–381.
57. Chang YW, Jang JY, Kim NH, Lee JW, Lee HJ, et al. (2005) Interleukin-1B (IL-1B) polymorphisms and gastric mucosal levels of IL-1beta cytokine in Korean patients with gastric cancer. *Int J Cancer* 114: 465–471.
58. Lu W, Pan K, Zhang L, Lin D, Miao X, et al. (2005) Genetic polymorphisms of interleukin (IL)-1B, IL-1RN, IL-8, IL-10 and tumor necrosis factor {alpha} and risk of gastric cancer in a Chinese population. *Carcinogenesis* 26: 631–636.
59. Ruzzo A, Graziano F, Pizzagalli F, Santini D, Battistelli V, et al. (2005) Interleukin 1B gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms in *Helicobacter pylori*-negative gastric cancer of intestinal and diffuse histotype. *Ann Oncol* 16: 887–892.
60. Tsai MH, Chen WC, Tsai CH, Hang LW, Tsai FJ (2005) Interleukin-4 gene, but not the interleukin-1 beta gene polymorphism, is associated with oral cancer. *J Clin Lab Anal* 19: 93–98.
61. Chen CC, Yang SY, Liu CJ, Lin CL, Liaw YF, et al. (2005) Association of cytokine and DNA repair gene polymorphisms with hepatitis B-related hepatocellular carcinoma. *Int J Epidemiol* 34: 1310–1318.
62. Taguchi A, Ohmiya N, Shirai K, Mabuchi N, Itoh A, et al. (2005) Interleukin-8 promoter polymorphism increases the risk of atrophic gastritis and gastric cancer in Japan. *Cancer Epidemiol Biomarkers Prev* 14: 2487–2493.
63. Hefler LA, Grimm C, Lantzsch T, Lampe D, Leodolter S, et al. (2005) Interleukin-1 and interleukin-6 gene polymorphisms and the risk of breast cancer in caucasian women. *Clin Cancer Res* 11: 5718–5721.
64. Asada M, Yasuda H, Ebihara S, Tomita N, Suzuki S, et al. (2006) Interleukin-1beta gene polymorphisms associated with risk of lung cancer in Japanese. *Lung Cancer* 54: 261–263.
65. Balasubramanian SP, Azmy IA, Higham SE, Wilson AG, Cross SS, et al. (2006) Interleukin gene polymorphisms and breast cancer: a case control study and systematic literature review. *BMC Cancer* 6: 188.
66. Kim N, Cho SI, Yim JY, Kim JM, Lee DH, et al. (2006) The effects of genetic polymorphisms of IL-1 and TNF-A on *Helicobacter pylori*-induced gastro-ododenal diseases in Korea. *Helicobacter* 11: 105–112.
67. Kamangar F, Abnet CC, Hutchinson AA, Newschaffer CJ, Helzlsouer K, et al. (2006) Polymorphisms in inflammation-related genes and risk of gastric cancer (Finland). *Cancer Causes Control* 17: 117–125.
68. Starzynska T, Ferenc K, Wex T, Kahne T, Lubinski J, et al. (2006) The association between the interleukin-1 polymorphisms and gastric cancer risk depends on the family history of gastric carcinoma in the study population. *Am J Gastroenterol* 101: 248–254.
69. Rothman N, Skibola CF, Wang SS, Morgan G, Lan Q, et al. (2006) Genetic variation in TNF and IL10 and risk of non-Hodgkin lymphoma: a report from the InterLymph Consortium. *Lancet Oncol* 7: 27–38.
70. Hiranarn N, Kimkong I, Kummee P, Tangkijvanich P, Poovorawan Y (2006) Interleukin-1beta gene polymorphism associated with hepatocellular carcinoma in hepatitis B virus infection. *World J Gastroenterol* 12: 776–779.
71. Ikehara SK, Ikehara Y, Matsuo K, Hirose K, Niwa T, et al. (2006) A polymorphism of C-to-T substitution at -31 IL1B is associated with the risk of advanced gastric adenocarcinoma in a Japanese population. *J Hum Genet* 51: 927–933.
72. Yamada S, Matsuhsu T, Makonkawkeyoon L, Chaidatch S, Kato S, et al. (2006) *Helicobacter pylori* infection in combination with the serum pepsinogen I/II ratio and interleukin-1beta-511 polymorphisms are independent risk factors for gastric cancer in Thais. *J Gastroenterol* 41: 1169–1177.
73. Liu J, Zhai X, Jin G, Hu Z, Wang S, et al. (2006) Functional variants in the promoter of interleukin-1beta are associated with an increased risk of breast cancer: a case-control analysis in a Chinese population. *Int J Cancer* 118: 2554–2558.
74. Michaud DS, Daugherty SE, Berndt SI, Platz EA, Yeager M, et al. (2006) Genetic polymorphisms of interleukin-1B (IL-1B), IL-6, IL-8, and IL-10 and risk of prostate cancer. *Cancer Res* 66: 4525–4530.
75. Sugimoto M, Furuta T, Shirai N, Nakamura A, Xiao F, et al. (2007) Different effects of polymorphisms of tumor necrosis factor-alpha and interleukin-1 beta on development of peptic ulcer and gastric cancer. *J Gastroenterol Hepatol* 22: 51–59.
76. Kang S, Kim JW, Park NH, Song YS, Park SY, et al. (2007) Interleukin-1 beta-511 polymorphism and risk of cervical cancer. *J Korean Med Sci* 22: 110–113.
77. Sun H, Wang Y, Ma X, Pei F, Sun H, et al. (2007) A method of oligochip for single nucleotide polymorphism genotyping in the promoter region of the

- interleukin-1 beta gene and its clinical application. *Oligonucleotides* 17: 336–344.
78. Seno H, Satoh K, Tsuji S, Shiratsuchi T, Harada Y, et al. (2007) Novel interleukin-4 and interleukin-1 receptor antagonist gene variations associated with non-cardia gastric cancer in Japan: comprehensive analysis of 207 polymorphisms of 11 cytokine genes. *J Gastroenterol Hepatol* 22: 729–737.
 79. Zunkeller N, Brenner H, Chang-Claude J, Hoffmeister M, Nieters A, et al. (2007) *Helicobacter pylori* infection, interleukin-1 gene polymorphisms and the risk of colorectal cancer: evidence from a case-control study in Germany. *Eur J Cancer* 43: 1283–1289.
 80. Li C, Xia HH, Xie W, Hu Z, Ye M, et al. (2007) Association between interleukin-1 gene polymorphisms and *Helicobacter pylori* infection in gastric carcinogenesis in a Chinese population. *J Gastroenterol Hepatol* 22: 234–239.
 81. Lee KM, Shen M, Chapman RS, Yeager M, Welch R, et al. (2007) Polymorphisms in immunoregulatory genes, smoky coal exposure and lung cancer risk in Xuan Wei, China. *Carcinogenesis* 28: 1437–1441.
 82. Abazis-Stamboulieh D, Oikonomou P, Papadoulis N, Panayiotidis P, Vrakidou E, et al. (2007) Association of interleukin-1A, interleukin-1B and interleukin-1 receptor antagonist gene polymorphisms with multiple myeloma. *Leuk Lymphoma* 48: 2196–2203.
 83. Ennas MG, Moore PS, Zucca M, Angelucci E, Cabras MG, et al. (2008) Interleukin-1B (IL1B) and interleukin-6 (IL6) gene polymorphisms are associated with risk of chronic lymphocytic leukaemia. *Hematol Oncol* 26: 98–103.
 84. Hoeffl B, Becker N, Deeg E, Beckmann L, Nieters A (2008) Joint effect between regular use of non-steroidal anti-inflammatory drugs, variants in inflammatory genes and risk of lymphoma. *Cancer Causes Control* 19: 163–173.
 85. Upadhyay R, Jain M, Kumar S, Ghoshal UC, Mittal B (2008) Potential influence of interleukin-1 haplotype IL-1 beta-511T*IL-1RN*1 in conferring low risk to middle third location of esophageal cancer: a case-control study. *Hum Immunol* 69: 179–186.
 86. Zhu Y, Xu Y, Wei Y, Liang W, Liao M, et al. (2008) Association of IL-1B gene polymorphisms with nasopharyngeal carcinoma in a Chinese population. *Clin Oncol (R Coll Radiol)* 20: 207–211.
 87. Vishnoi M, Pandey SN, Choudhuri G, Mittal B (2008) IL-1 gene polymorphisms and genetic susceptibility of gallbladder cancer in a north Indian population. *Cancer Genet Cytogenet* 186: 63–68.
 88. Singh H, Sachan R, Goel H, Mittal B (2008) Genetic variants of interleukin-1RN and interleukin-1beta genes and risk of cervical cancer. *Bjog* 115: 633–638.
 89. Shin WG, Jang JS, Kim HS, Kim SJ, Kim KH, et al. (2008) Polymorphisms of interleukin-1 and interleukin-2 genes in patients with gastric cancer in Korea. *J Gastroenterol Hepatol* 23: 1567–1573.
 90. Hamacher R, Diersch S, Scheibel M, Eckel F, Mayr M, et al. (2009) Interleukin 1 beta gene promoter SNPs are associated with risk of pancreatic cancer. *Cytokine* 46: 182–186.
 91. Ahirwar DK, Agrahari A, Mandhani A, Mittal RD (2009) Cytokine gene polymorphisms are associated with risk of urinary bladder cancer and recurrence after BCG immunotherapy. *Biomarkers* 14: 213–218.
 92. Kumar S, Kumar A, Dixit VK (2009) Evidences showing association of interleukin-1B polymorphisms with increased risk of gastric cancer in an Indian population. *Biochem Biophys Res Commun* 387: 456–460.
 93. Gehmert S, Velapattino B, Herrera P, Balqui J, Santivanez L, et al. (2009) Interleukin-1 beta single-nucleotide polymorphism's C allele is associated with elevated risk of gastric cancer in *Helicobacter pylori*-infected Peruvians. *Am J Trop Med Hyg* 81: 804–810.
 94. Melo Barbosa HP, Martins LC, Dos Santos SE, Demackhi S, Assumpcao MB, et al. (2009) Interleukin-1 and TNF-alpha polymorphisms and *Helicobacter pylori* in a Brazilian Amazon population. *World J Gastroenterol* 15: 1465–1471.
 95. Whiteman DC, Parmar P, Fahey P, Moore SP, Stark M, et al. (2010) Association of *Helicobacter pylori* infection with reduced risk for esophageal cancer is independent of environmental and genetic modifiers. *Gastroenterology* 139: 73–83; quiz e11–72.
 96. Wex T, Leodolter A, Bornschein J, Kuester D, Kahne T, et al. (2010) Interleukin 1 beta (IL1B) gene polymorphisms are not associated with gastric carcinogenesis in Germany. *Anticancer Res* 30: 505–511.
 97. Yu J, Zeng Z, Wang S, Tian L, Wu J, et al. (2010) IL-1B-511 polymorphism is associated with increased risk of certain subtypes of gastric cancer in Chinese: a case-control study. *Am J Gastroenterol* 105: 557–564.
 98. Yoo EJ, Park SY, Cho NY, Kim N, Lee HS, et al. (2010) Influence of IL1B polymorphism on CpG island hypermethylation in *Helicobacter pylori*-infected gastric cancer. *Virchows Arch* 456: 647–652.
 99. Qian N, Chen X, Han S, Qiang F, Jin G, et al. (2010) Circulating IL-1beta levels, polymorphisms of IL-1B, and risk of cervical cancer in Chinese women. *J Cancer Res Clin Oncol* 136: 709–716.
 100. Wu KS, Zhou X, Zheng F, Xu XQ, Lin YH, et al. (2010) Influence of interleukin-1 beta genetic polymorphism, smoking and alcohol drinking on the risk of non-small cell lung cancer. *Clin Chim Acta* 411: 1441–1446.
 101. Al-Tahhan MA, Etewa RL, El Behery MM (2011) Association between circulating interleukin-1 beta (IL-1beta) levels and IL-1beta C-511T polymorphism with cervical cancer risk in Egyptian women. *Mol Cell Biochem* 353: 159–165.
 102. Lim WY, Chen Y, Ali SM, Chuah KL, Eng P, et al. (2011) Polymorphisms in inflammatory pathway genes, host factors and lung cancer risk in Chinese female never-smokers. *Carcinogenesis* 32: 522–529.
 103. Rizzato C, Canzian F, Rudnai P, Gurzau E, Stein A, et al. (2011) Interaction between functional polymorphic variants in cytokine genes, established risk factors and susceptibility to basal cell carcinoma of skin. *Carcinogenesis* 32: 1849–1854.
 104. He BS, Pan YQ, Xu YF, Zhu C, Qu LL, et al. (2011) Polymorphisms in interleukin-1B (IL-1B) and interleukin 1 receptor antagonist (IL-1RN) genes associate with gastric cancer risk in the Chinese population. *Dig Dis Sci* 56: 2017–2023.
 105. Cigrovski Berkovic M, Catela Ivkovic T, Marout J, Zjacic-Rotkovic V, Kapitanovic S (2012) Interleukin 1beta gene single-nucleotide polymorphisms and susceptibility to pancreatic neuroendocrine tumors. *DNA Cell Biol* 31: 531–536.
 106. Santos JC, Ladeira MS, Pedrazzoli J, Jr., Ribeiro ML (2012) Relationship of IL-1 and TNF-alpha polymorphisms with *Helicobacter pylori* in gastric diseases in a Brazilian population. *Braz J Med Biol Res* 45: 811–817.
 107. Zheng C, Huang DR, Bergenbrant S, Sundblad A, Osterborg A, et al. (2000) Interleukin 6, tumour necrosis factor alpha, interleukin 1beta and interleukin 1 receptor antagonist promoter or coding gene polymorphisms in multiple myeloma. *Br J Haematol* 109: 39–45.
 108. Snoussi K, Stroberg AD, Bouaouina N, Ben Ahmed S, Chouchane L (2005) Genetic variation in pro-inflammatory cytokines (interleukin-1beta, interleukin-1alpha and interleukin-6) associated with the aggressive forms, survival, and relapse prediction of breast carcinoma. *Eur Cytokine Netw* 16: 253–260.
 109. Palli D, Saieva C, Luzzi I, Masala G, Topa S, et al. (2005) Interleukin-1 gene polymorphisms and gastric cancer risk in a high-risk Italian population. *Am J Gastroenterol* 100: 1941–1948.
 110. Al-Moundhri MS, Al-Nabhani M, Al-Bahrani B, Burney IA, Al-Madhani A, et al. (2006) Interleukin-1beta gene (IL-1B) and interleukin 1 receptor antagonist gene (IL-1RN) polymorphisms and gastric cancer risk in an Omani Arab population. *Gastric Cancer* 9: 284–290.
 111. Scincchi LA, Lopez-Carrillo L, Camargo MC, Correa P, Sierra RA, et al. (2006) Gastric cancer risk in a Mexican population: role of *Helicobacter pylori* CagA positive infection and polymorphisms in interleukin-1 and -10 genes. *Int J Cancer* 118: 649–657.
 112. Wang W, Ni K, Zhou G (2007) Association of IL1B polymorphisms with gastric cancer in a Chinese population. *Clin Biochem* 40: 218–225.
 113. Crusius JB, Canzian F, Capella G, Pena AS, Pera G, et al. (2008) Cytokine gene polymorphisms and the risk of adenocarcinoma of the stomach in the European prospective investigation into cancer and nutrition (EPIC-EUR-GAST). *Ann Oncol* 19: 1894–1902.
 114. Ter-Minassian M, Zhai R, Asomaning K, Su L, Zhou W, et al. (2008) Apoptosis gene polymorphisms, age, smoking and the risk of non-small cell lung cancer. *Carcinogenesis* 29: 2147–2152.
 115. Landvik NE, Hart K, Skaug V, Stangeland LB, Haugen A, et al. (2009) A specific interleukin-1B haplotype correlates with high levels of IL1B mRNA in the lung and increased risk of non-small cell lung cancer. *Carcinogenesis* 30: 1186–1192.
 116. Kiyohara C, Horiuchi T, Takayama K, Nakanishi Y (2010) IL1B rs1143634 polymorphism, cigarette smoking, alcohol use, and lung cancer risk in a Japanese population. *J Thorac Oncol* 5: 299–304.
 117. Moher D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 6: e1000097.
 118. Lewis AM, Varghese S, Xu H, Alexander HR (2006) Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment. *J Transl Med* 4: 48.
 119. Speirs V, Kerin MJ, Newton CJ, Walton DS, Green AR, et al. (1999) Evidence for transcriptional activation of ERalpha by IL-1beta in breast cancer cells. *Int J Oncol* 15: 1251–1254.
 120. Muerkoster S, Wegehenkel K, Arlt A, Witt M, Sipos B, et al. (2004) Tumor stroma interactions induce chemoresistance in pancreatic ductal carcinoma cells involving increased secretion and paracrine effects of nitric oxide and interleukin-1beta. *Cancer Res* 64: 1331–1337.
 121. Stefani AL, Basso D, Panozzo MP, Greco E, Mazza S, et al. (1999) Cytokines modulate MIA PaCa 2 and CAPAN-1 adhesion to extracellular matrix proteins. *Pancreas* 19: 362–369.
 122. ten Kate M, Hofland LJ, van Koetsveld PM, Jeekel J, van Eijk CH (2006) Pro-inflammatory cytokines affect pancreatic carcinoma cell. Endothelial cell interactions. *Jop* 7: 454–464.
 123. Angst E, Reber HA, Hines OJ, Eibl G (2008) Mononuclear cell-derived interleukin-1 beta confers chemoresistance in pancreatic cancer cells by upregulation of cyclooxygenase-2. *Surgery* 144: 57–65.
 124. Tian Z, Shen X, Feng H, Gao B (2000) IL-1 beta attenuates IFN-alpha beta-induced antiviral activity and STAT1 activation in the liver: involvement of proteasome-dependent pathway. *J Immunol* 165: 3959–3965.
 125. Hulkkonen J, Laippala P, Hurme M (2000) A rare allele combination of the interleukin-1 gene complex is associated with high interleukin-1 beta plasma levels in healthy individuals. *Eur Cytokine Netw* 11: 251–255.
 126. Xue H, Lin B, Ni P, Xu H, Huang G (2010) Interleukin-1B and interleukin-1RN polymorphisms and gastric carcinoma risk: a meta-analysis. *J Gastroenterol Hepatol* 25: 1604–1617.