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Effects of the interleukin-1β-511 C/T gene polymorphism on the risk of gastric cancer in the context of the relationship between race and *H. pylori* infection: a meta-analysis of 20,000 subjects

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Abstract The interleukin (IL)-1β-511 C/T polymorphism has been shown to be functional and to contribute to the risk of gastric cancer. However, the relationship between the IL-1β-511 C/T polymorphism and gastric carcinogenesis remains inconclusive. A systematical electronic search was conducted of the MEDLINE, EMBASE, and CENTRAL databases. A random and a fixed effects model were exploited to estimate summary odds ratios and 95 % confidence intervals. Subgroup and sensitivity analyses were carried out with respect to ethnicity, quality assessment scores, control sources, genotyping methods, cancer histopathology and location, and *Helicobacter pylori* (*H. pylori*) infection. A total of 45 studies containing 9,066 cases of gastric cancer and 11,192 control subjects satisfied the inclusion criteria. The IL-1β-511 C/T polymorphism was found to enhance the risk of stomach cancer for overall and HWE-satisfying studies. Asians showed a positive relationship in both the overall and HWE-satisfying groups, whereas Caucasians did not. Based on subgroup analysis, *H. pylori* infection and genotype analysis using PCR–RFLP methods increase the association between IL-1β-511 T allele carrier and risk of stomach cancer. A positive relationship was found between the IL-1β-511 C/T SNP and stomach carcinoma susceptibility, and the results suggest that Asian ethnicity, *H. pylori* infection and methodologically, PCR–RFLP genotyping strengthen this relationship. Reflecting on prevalence of *H. pylori* in Asian countries, additional studies on the IL-1β-511 C/T SNP in the context of ethnicity and *H. pylori* infection may provide key insights into the mechanism underlying gastric cancer carcinogenesis. It was found PCR–RFLP is the most reliable genotyping method, and thus, it is recommendable to adopt it to determine the presence of the IL-1β-511 C/T SNP.

Keywords Interleukin-1beta · IL-1β-511 · Cytokine · Stomach neoplasm · Single-nucleotide polymorphism

Introduction

Interleukin (IL)-1β initiates inflammatory reactions and amplifies immunologic responses against harmful stimuli [1]. Furthermore, in chronic inflammatory states, IL-1β generates COX-2 and iNOS, which inhibit apoptosis, induce DNA damage, and modulate cell adhesion [2]. In addition, the signaling cascade from IL-1β is the basis of the carcinogenesis. In addition to persistent inflammatory reaction caused by gastric injury, IL-1β suppresses acid secretion 6,000 times as effectively as H2 antagonist and 100 times more than proton pump inhibitor [3]. The expression of this cytokine creates a hypoacidic condition that favors the survival of *Helicobacter pylori* (*H. pylori*), and consequently leads to atrophy of stomach tissues or adenocarcinoma [4, 5], and overgrowth of *H. pylori* induces an assembly of neutrophils and lymphocytes, particularly Th1 and Th17 CD4+ cells, which induce IL-1β

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secretion [6, 7]. Three single-nucleotide polymorphisms (SNPs), namely −31 T/C, +3954 C/T, and −511 C/T have been discovered in the promoter region of chromosome 2q and are regarded to trigger the overexpression of IL-1β [8]. This study focuses on the IL-1β-511 C/T polymorphism because many studies have investigated it, whereas relatively few have examined the +3954 C/T polymorphism. In addition, the −31 T/C SNP has been reported to show linkage disequilibrium with −511 C/T [9].

However, previous studies, including meta-analyses, have produced mixed results [10–15], which may have been caused by dissimilar characteristics among studies, such as, sample sizes, ethnicities, cancer type, inconsistent inclusion criteria (e.g., involving premalignant lesions as a case group), and a lack of comprehensive subgroup analyses. In this regard, the present study provides a comprehensive and systematic review based on sophisticated subgroup analysis that excluded methodological discrepancies. In addition, overall susceptibility results were verified by sensitivity analysis based on considerations of Hardy–Weinberg equilibrium (HWE) as a crucial standard for determining the reliability of subject for case–control studies [16].

Materials and methods

Search strategy

A systematic search was conducted utilizing the MEDLINE, EMBASE, and CENTRAL databases (last search on February 05, 2013). The following terms were combined: "Interleukins," "IL-1β," "IL-1β-511," "Interleukin-1," "Interleukin-1β," "Interleukin-1β-511," "Interleukin-1beta," "IL-1beta," "Interleukin-1beta," "polymorphisms," "SNP," "single nucleotide," "mutation,"

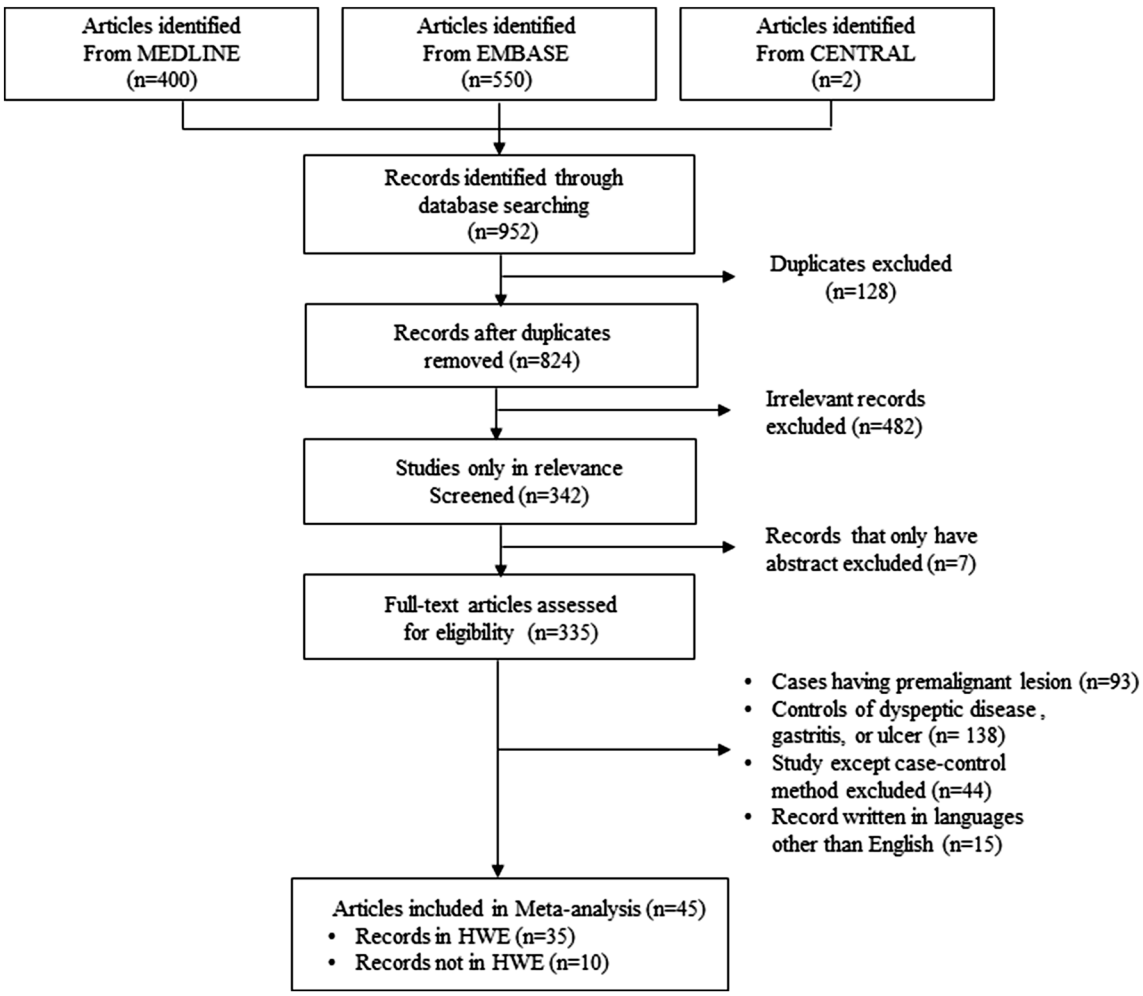


Fig. 1 Study flow chart

Table 1 Characteristics of included studies

Author (year)	Country (ethnicity)	Quality score	Control source	Case			Control			Genotyping method	HWE P^a	Subgroup findings (OR, [CIs])
				TT	CT	CC	TT	CT	CC			
Burada et al. [27]	Romania (C)	7.5	P	11	42	52	30	102	110	RT-PCR	0.40438	Cardia[b] (0.66, [0.12, 2.64]), diffuse[‡] (0.80, [0.28, 2.27]) intestinal[‡] (0.79, [0.30, 2.07]), noncardia[b] (0.84, [0.28, 1.94])
Zhao et al. [26]	China:Han (A)	6.5	P	65	101	31	38	99	65	PCR–DHPLC	0.97765	Diffuse[‡] (1.23, [0.5–3.02]), intestinal[b] (5.66, [2.82, 11.33])
	China:Hui (A)	6.5	P	37	88	33	52	110	43	PCR–DHPLC	0.28134	Diffuse[b] (0.92, [0.34, 2.50]), intestinal[b] (0.91, [0.53, 1.89])
	China:Tibet (A)	6.5	P	41	80	34	62	93	55	PCR–DHPLC	0.10061	Diffuse[b] (0.62, [0.24, 1.63]), intestinal[b] (1.25, [0.64, 2.42])
He et al. [28]	China (A)	5	H	124	196	72	94	266	148	PCR–RFLP	0.40438	*H. pylori* positive[b] (5.88, [3.14, 11.04])
Wex et al. [29]	Germany (C)	5.5	H	13	45	58	10	41	43	PCR–RFLP	0.96107	Diffuse (1.68, [0.59–4.77]), intestinal (1.05, [0.34,3.28])
Yu et al. [30]	China (A)	6.5	P	100	269	132	65	253	182	PCR–RFLP	0.11429	Diffuse or mixed[b] (1.09, [0.50, 2.37]), intestinal[b] (3.16, [1.74, 5.71])
Balbosa et al. [31]	Brazil (O)	4.25	H	13	11	6	23	25	55	PCR–RFLP	0.45885	None
Kumar et al. [32]	India (A)	4.25	H	48	59	29	25	55	30	PCR–RFLP	0.98268	*H. pylori* positive[b] (32.93, [3.953, 274.36])
Persson et al. [25]	Sweden (C)	8.5	P	33	132	120	29	108	104	PCR	0.90577	Cardia[‡] (0.8, [0.2, 2.4], diffuse[b] (1, [0.4, 2.2]), intestinal[b] (1, [0.5, 1.8]), noncardia[b] (1.0, [0.6, 1.9])
	Sweden (C)	5.5	H	7	31	27	43	147	107	PCR	0.51140	None
Feng et al. [33]	China (A)	6.5	P	54	54	42	30	33	91	PCR–RFLP	0.00000	None
Shin et al. [34]	Korea (A)	5.5	H	30	69	23	24	60	16	PCR–RFLP	0.03777	Diffuse[b] (0.82, [0.32,2.12]), intestinal[b] (1.12, [0.58,2.17])
Garcia-Gonzalez et al. [35]	Spain (C)	7.5	H	39	174	191	47	171	186	PCR	0.42373	Cardia (0.67, [0.26–1.71], diffuse[b] (0.76, [0.37, 1.57]), intestinal[b] (0.82, [0.44, 1.53]), noncardia[b] (0.85, [0.52-1.39])
Sun et al. [36]	China (A)	2.5	H	14	12	39	17	23	25	PCR–RFLP	0.02327	None
Sugimoto et al. [37]	Japan (A)	4.5	H	28	47	30	40	90	42	PCR–RFLP	0.54064	None
Li et al. [38]	China (A)	4	H	39	174	191	47	171	186	PCR–RFLP	0.51154	*H. pylori* positive[b] (3.01, [1.27, 7.11])
Ito et al. [39]	Japan (A)	4.5	H	45	87	54	32	80	24	PCR–SSCP	0.03524	None
Zhang et al. [40]	China (A)	2	H	62	97	55	73	101	56	PCR	0.07621	None
Kamangar et al. [41]	Finland (C)	7.5	H	17	45	42	32	63	70	PCR	0.01289	Intestinal[b] (0.82,[0.38–1.73]), noncardia[b] (0.62, [0.29–1.34])

Table 1 continued

Author (year)	Country (ethnicity)	Quality score	Control source	Case			Control			Genotyping method	HWE P^a	Subgroup findings (OR, [CIs])
				TT	CT	CC	TT	CT	CC			
Kim et al. [42]	Korea (A)	4.75	H	55	134	48	131	259	84	PCR–RFLP	0.02399	Diffuse in *H. pylori* positive[b] (0.8, [0.4, 1.5]), intestinal in *H. pylori* positive[b] (0.8, [0.4, 1.6]),
Shirai et al. [43]	Japan (A)	4.5	H	36	88	44	97	24	138	PCR	0.47734	None
Ikehara et al. [44]	Japan (A)	4	P	51	142	77	58	123	86	PCR–RFLP	0.26366	None
Morgan et al. [45]	Honduras (O)	7	P	58	73	39	40	92	30	PCR	0.07446	None
Alpizar et al. [46]	CostaRica (O)	4	H	12	24	14	17	23	10	PCR–RFLP	0.66310	Intestinal[b] (0.28, [0.04, 1.73]), diffuse[b] (0.64, [0.09, 4.34])
Lu et al. [47]	China (A)	7	P	53	125	72	70	163	67	PCR–DHPLC	0.13284	None
Taguchi et al. [48]	Japan (A)	6.5	H	81	188	104	49	133	68	PCR–RFLP	0.26714	None
Muramatsu et al. [49]	Japan (A)	5	H	19	40	30	15	49	32	PCR–RFLP	0.59755	None
Sakuma et al. [50]	Japan (A)	4.5	H	34	71	35	22	56	25	PCR–RFLP	0.37016	*H. pylori* positive[b] (1.15, [0.61, 2.17]),
Chang et al. [51]	Korea (A)	6	H	52	128	54	102	245	87	PCR–RFLP	0.00660	None
Ruzzo et al. [52]	Italy (C)	6.5	H	27	58	53	7	48	45	PCR–RFLP	0.22239	Intestinal[b] (3.9, [1.4, 11.3], diffuse[b] (2.6, [0.9, 7.3])
Zhang et al. [53]	China (A)	6.5	P	42	78	34	52	71	43	PCR	0.06721	None
Perri et al. [24]	Italy-South (C)	7	P	8	44	34	14	64	68	PCR	0.84999	Diffuse[b] (1.18, [0.25,5.66]), intestinal[b] (0.91, [0.33,2.49])
	Italy-North (C)	7	P	13	37	48	28	99	89	PCR	0.95441	Diffuse[b] (0.39, [0.02,6.93]), intestinal[b] (1.13, [0.56,2.30])
Yang et al. [54]	China (A)	7.5	P	52	158	70	65	136	57	PCR–RFLP	0.37459	*H. pylori* positive[b] (0.60, [0.35, 1.03])
Lee et al. [55]	Korea (A)	6	H	89	180	62	130	208	95	PCR–RFLP	0.49304	Diffuse[b] (1.4, [0.8, 2.4]), intestinal[b] (0.6, [0.3, 1.2])
Glas et al. [56]	German (C)	5	H	20	35	33	22	58	65	PCR	0.13902	Diffuse[b] (1.18, [0.37,3.79]), intestinal[b] (1.97 [0.89,4.39])
Chen et al. [57]	Taiwan (A)	7	H	31	87	24	37	93	34	PCR	0.08493	*H. pylori* positive[c] (1.44, [0.67,3.07])
Kang et al. [58]	Korea (A)	5	H	53	125	60	21	42	24	PCR–RFLP	0.75587	Intestinal[b] (1.57, [0.72–3.41]), diffuse[b] (0.69, [0.32–1.47])
Hartland et al. [59]	Europe (C)	6.5	P	5	29	25	36	165	86	PCR	0.00164	None
Gatii et al. [60]	Brazil (O)	6.5	H	18	27	11	12	40	4	PCR–RFLP	0.00060	Intestinal[b] (1.22, [0.40–3.76]), diffuse[b] (2.51, [0.97–6.50])
Wu et al. [61]	Taiwan (A)	4	H	45	93	66	37	116	57	PCR	0.09598	None

Table 1 continued

Author (year)	Country (ethnicity)	Quality score	Control source	Case			Control			Genotyping method	HWE P^a	Subgroup findings (OR, [CIs])
				TT	CT	CC	TT	CT	CC			
Machado et al. [62]	Portugal (C)	4.5	H	26	171	90	40	129	137	PCR–SSCP	0.27291	Diffuse[c] (1.62 [0.99, 2.65]), intestinal[c] (2.24, [1.43, 3.52])
Zeng et al. [23]	China:G (A)	3.5	H	21	45	18	27	78	87	PCR–RFLP	0.16770	*H. pylori* positive OR[b] 17.1 [3.8–76.4]
	China:S (A)	3.5	H	22	45	19	38	97	34	PCR–RFLP	0.05343	*H. pylori* positive OR[b] = 5.0 [1.3–20.3]
El omar et al. [63]	USA (C)	7	P	56	154	104	9	97	104	PCR	0.01926	Noncardia[b] (9.5, [4.0, 22.7]), cardia[b] (3.1, [1.2, 8.0])
Wu et al. [61]	China (A)	6.5	H	45	106	69	45	124	61	PCR	0.20537	None
Hausen et al. [65]	German (C)	1	H	12	17	40	17	69	67	PCR–RFLP	0.90347	EBV positive[b] (0.96, [0.23, 4.08])
Machado et al. [62]	Portugal (C)	6.5	H	17	85	50	31	87	100	PCR–SSCP	0.09531	Intestinal[b] (2.0, [0.8, 4.6]), diffuse[b] (0.5, [0.1, 2.1]
El omar et al. [63]	Polish/ Scotland(C)	5	P	69	170	127	46	66	217	PCR–SSCP	0.09785	None

HWE, Hardy–Weinberg equilibrium; OR, odds ratio; CI, confidence interval; A, Asian; C, Caucasian; O, other ethnicity; P, population-based control group; H, hospital-based control group; *H. pylori*, *Helicobacter pylori*; USA, United States of America; EBV, Epstein-Barr virus; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; SSCP, single-strand conformation polymorphism; DHPLC, denaturing high-performance liquid chromatography; RT-PCR, real-time polymerase chain reaction; G, Guangzhou; S, Shanxi

[†] Hardy–Weinberg equilibrium in the control group (groups with *P* value less than 0.05 did not satisfy the Hardy–Weinberg equilibrium)

[b] TT versus CC+CT

[c] TT+TC versus CC

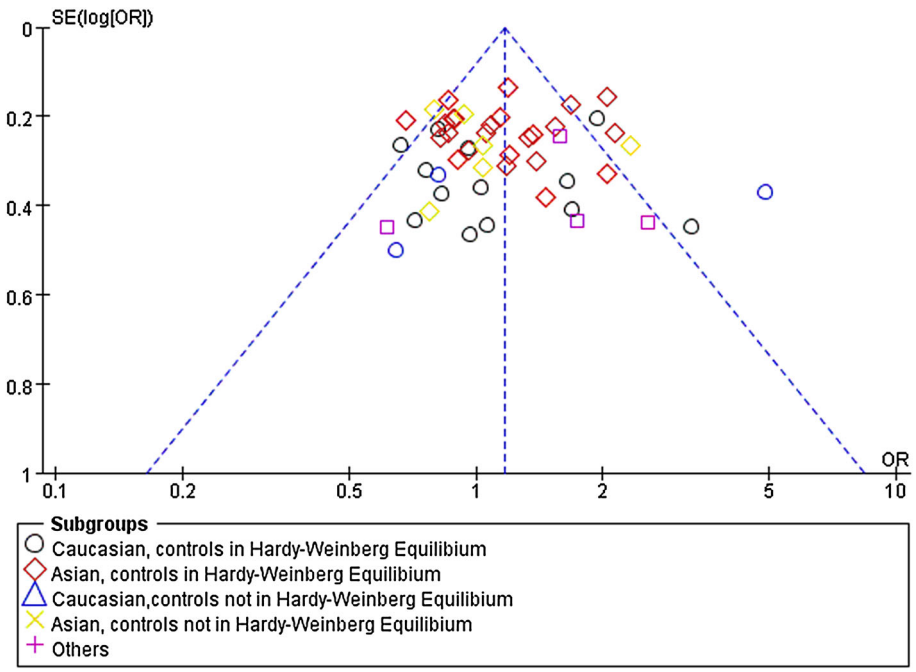


Fig. 2 A funnel plot of publication bias

"stomach cancer," "gastric adenocarcinoma," and "gastric cancer." Supplement S1 describes the detailed search strategy, which was reviewed by two independent investigators (M.J.P and M.H.H) and a third reviewer (S.S.P).

Study selection

The studies included: (i) described the relationship between the IL-1β-511 C/T SNP and stomach carcinoma; (ii)

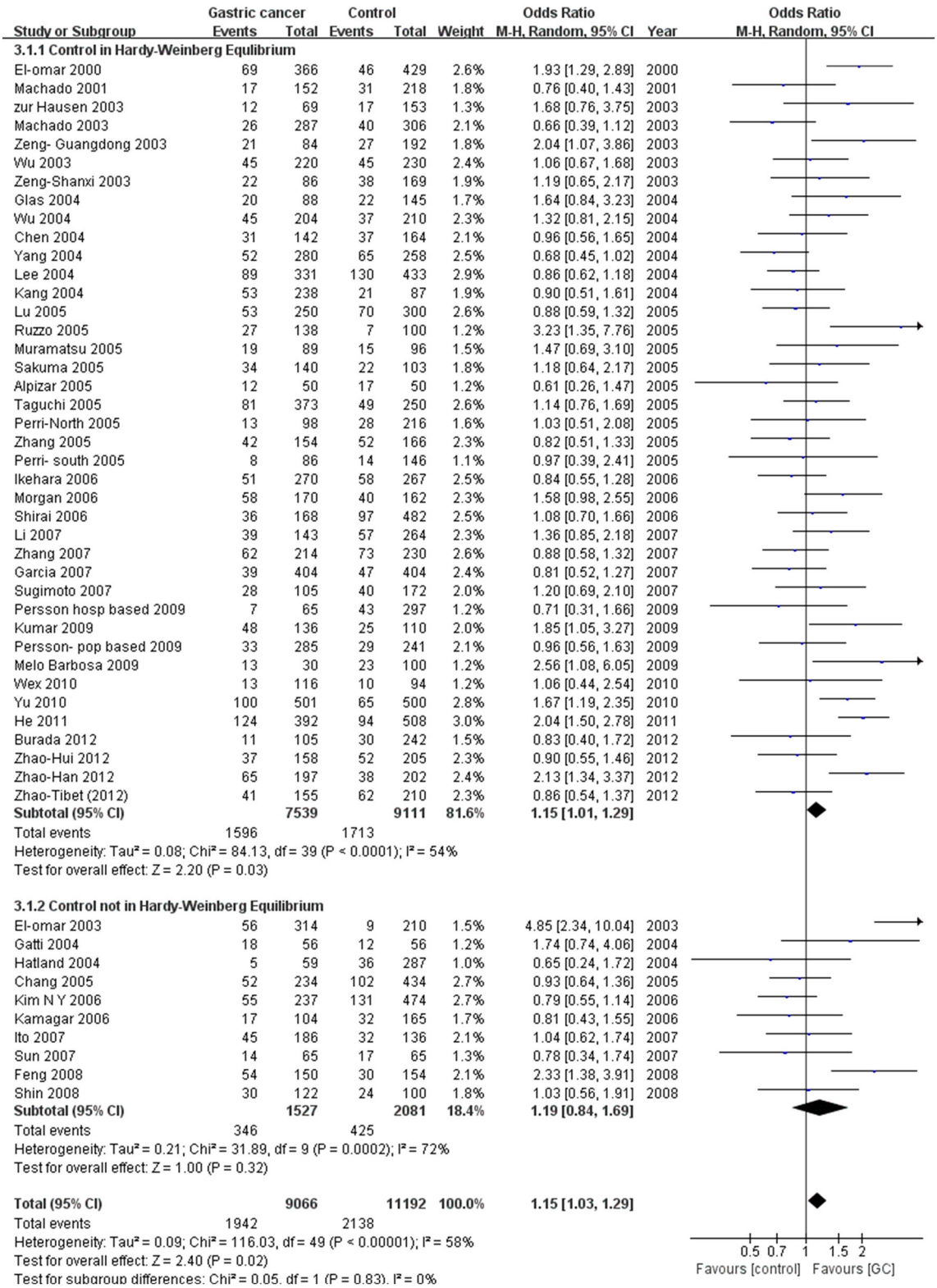


Fig. 3 A forest plot of the stomach carcinoma risk of relevance to the interleukin-1β-511 C/T polymorphism (TT vs. CC+CT) based on the Hardy–Weinberg equilibrium by publication year. The *areas* of the *squares* indicate the relative weights of the specific studies. *Bars* represent 95 % confidence intervals, and "GC," gastric cancer

Table 2 Stratification analyses of the interleukin-1β -511 C/T polymorphism (TT vs. CC+CT) for stomach carcinoma risk according to the Hardy–Weinberg equilibrium

Subgroup	Overall						In HWE					
	Data set (case/control)	OR [CIs]	*P* value	Heterogeneity		Statistical model†	Data set (case/control)	OR [CIs]	P-value	Heterogeneity		Statistical model†
				HG I^2 (%)	HG *P*					HG I^2 (%)	HG *P*	
Total	9,066/11,192	1.15 [1.03, 1.29]	0.02	58	<0.01	RE	7,539/9,111	1.15 [1.01, 1.29]	0.03	54	<0.01	RE
Subgroup by ethnicity												
Caucasian	2,736/3,653	1.15 [0.87, 1.52]	0.32	65	<0.01	RE	2,259/2,991	1.10 [0.85, 1.42]	0.47	51	0.02	RE
Asian	6,460/7,775	1.14 [1.01, 1.29]	0.04	55	<0.01	RE	5,466/6,412	1.16 [1.01, 1.33]	0.03	55	<0.01	RE
Other	306/368	1.48 [1.05, 2.08]	0.02	47	0.13	FE	250/312	1.39 [0.69, 2.78]	0.36	64	0.06	RE
Subgroup by study quality												
High quality	6,592/7,928	1.17 [1.00, 1.36]	0.05	65	<0.01	RE	5,553/6,522	1.12 [0.96, 1.36]	0.15	61	<0.01	RE
Low or moderate quality	2,474/3,483	1.10 [0.93, 1.30]	0.25	36	0.07	FE	1,986/2,808	1.17 [0.97, 1.41]	0.10	38	0.07	RE
Subgroup by control source												
Population	3,223/3,686	1.26 [0.97, 1.63]	0.08	74	<0.01	RE	2,700/3,035	1.14 [0.90, 1.44]	0.28	66	<0.01	RE
Hospital	5,827/7,486	1.09 [1.00, 1.19]	0.05	46	0.02	FE	4,823/6,056	1.15 [0.99, 1.33]	0.07	52	<0.01	RE
Subgroup by genotyping method												
PCR–RFLP	4,435/5,189	1.24 [1.05, 1.47]	0.01	61	<0.01	RE	3,571/3,906	1.28 [1.05, 1.56]	0.01	61	<0.01	RE
Other	4,631/6,003	1.07 [0.92, 1.26]	0.38	54	<0.01	RE	4,072/5,370	1.04 [0.90, 1.20]	0.59	38	0.04	FE
Subgroup by location												
Cardia	272/1,097	0.98 [0.46, 2.08]	0.96	51	0.11	RE	146/887	0.66 [0.35, 1.24]	0.20	0	0.97	FE
Noncardia	913/1,262	1.25 [0.60, 2.60]	0.55	85	<0.01	RE	648/887	0.91 [0.66, 1.26]	0.58	0	0.85	FE
Subgroup by pathology												
Intestinal	2,164/4,287	1.34 [0.88, 2.03]	0.17	88	<0.01	RE	1,851/3,492	1.47 [0.90, 2.42]	0.13	89	<0.01	RE
Diffuse	1,243/4,127	1.18 [0.78, 1.79]	0.42	81	<0.01	RE	1,106/3,553	1.22 [0.76, 1.95]	0.41	83	<0.01	RE
Subgroup by *H. pylori* infection												
H. pylori positive	1,107/1,651	1.70 [1.03, 2.80]	0.04	85	<0.01	RE	821/1,175	2.04 [1.15, 3.62]	0.02	84	<0.01	RE

HWE, Hardy–Weinberg equilibrium; OR, odds ratio; CI, confidence interval, HG, heterogeneity; RE, random effects model; FE, fixed effects model; PCR–RFLP, polymerase chain reaction restriction fragment length polymorphism; *H. pylori*, *Helicobacter pylori*

† The random effects model was used if heterogeneity *P* value <0.1 or heterogeneity $I^2 > 50$ % and the fixed effects model otherwise

contained sufficient number of subjects to yield odds ratios (ORs) and 95 % confidence intervals (CIs); (iii) had a case–control design; (iv) included case samples consisting of gastric cancer (not premalignant lesions), and control samples free of any gastric disease, such as, gastritis or gastric ulcer; and (v) were written in English. A PRISMA checklist and a flow chart of the study inclusion procedure are presented in Supplements S2 and S3, respectively.

Methodological quality assessment

The methodologic quality of each study was assessed using the scale proposed by Thakkinstian et al. [7] and refined by Camargo et al. [12] and Xue et al. [13]. Any disagreement between evaluation results was resolved by the third reviewer (S.S. Park). Evaluations were conducted to determine the representativeness of cases and controls, to assess reliability of stomach carcinoma confirmation and genotyping tests, and to assess potential confounding factors, as shown in Supplement S4. Quality assessment scores ranged from 0 (lowest) to 9 (highest). We classified reports that scored <5.0 as "low to moderate quality" and those that scored ≥5.0 as "high quality."

Data extraction

To enhance the reliability of data, two investigators (M.J. Park and M.H. Hyun) independently performed and verified data extraction. The following information was collected: authors' names, subject ethnicity, sex ratio, origin of control samples, numbers of cases and controls, and the genotyping method. In addition, the genotype frequencies of each pathologic type of cancer, each anatomical classification of cancer, and of *H. pylori*-positive populations were determined when reports provided relevant information.

Statistical analysis

We utilized Review Manager 5.2 (Cochrane Collaboration, London, UK) to conduct the statistical analysis. ORs and 95 % CIs were calculated from extracted raw data, and strengths of association were estimated [17]. Meta-analysis was conducted using the following models: (1) T allele versus C allele (an allelic contrast model), (2) TT genotype versus CC genotype (a homozygote contrast model), (3) TT+TC genotype versus. CC genotype (a dominant contrast model), and (4) TT vs. TC+CC (a recessive contrast model).

Heterogeneities of included studies were calculated based on Q statistics using the Mantel–Haunszel weight and I^2 statistics. [18]. Heterogeneity between studies was confirmed when studies have a P value of <0.10 and an I^2 value >50 %. For studies with heterogeneity, a random effects model was employed based on the DerSimonian–Laird method [19]. Otherwise, a fixed effects model was employed based on the Mantel–Haenszel method [18].

We conducted Chi square analysis to assess the control group fit with the Hardy–Weinberg equilibrium (HWE). The groups deviating from the HWE have a P value of <0.05 [20]. Begg's test and Egger's funnel plot asymmetry test were used to evaluate publication bias [21, 22].

Results

Literature search, characteristics of included studies, and publication bias

The overall flow of the searching procedure is shown in Fig. 1. First, a total of 824 studies were identified by systematic search after excluding duplicates. Screening of full texts for relevance and accessibility resulted in the exclusion of 482 irrelevant studies and 7 abstract-only articles. 290 of the remaining 335 studies were excluded for the following reasons: 93 for including premalignant lesions, not gastric cancer, 138 for including control populations with gastritis or dyspeptic disease, 44 for not having a case–control design, and 15 for being written in other than English. In addition, 2 studies included data from two different geographic areas [23, 24]. Persson et al. [25] recruited control subjects from two sources: hospitals and general population. Zhao et al. [26] considered three ethnic groups from the same area. In the present study, each geographic area, control source, and ethnicity were considered separate data sets. As a result, 45 studies (50 data sets) were included in this meta-analysis, reflecting 9,066 gastric cancer patients and 11,192 control subjects [8, 23–66]. Table 1 shows the characteristics of each study. Of the 45 studies, control groups deviated from the HWE in 10 [33, 34, 36, 39, 41, 42, 51, 59, 60, 63]. In addition, 14 studies involved Caucasian populations, 27 Asian populations, and 4 other ethnicities. Twenty-four studies employed the PCR–RFLP genotyping, and the remainder used other genotyping techniques, such as, RCP–SSCP and PCR–DHPLC. Twenty-nine studies were classified as high quality, and 16 as low to moderate quality. Supplement S5 summarizes quality assessment criteria. Finally, we used a funnel plot and Egger's regression to assess the heterogeneity of studies and publication bias. Figure 2 presents the qualitative results for publication bias and shows a symmetrical distribution for the overall studies. Egger's regression revealed no publication bias ($P > 0.1$).

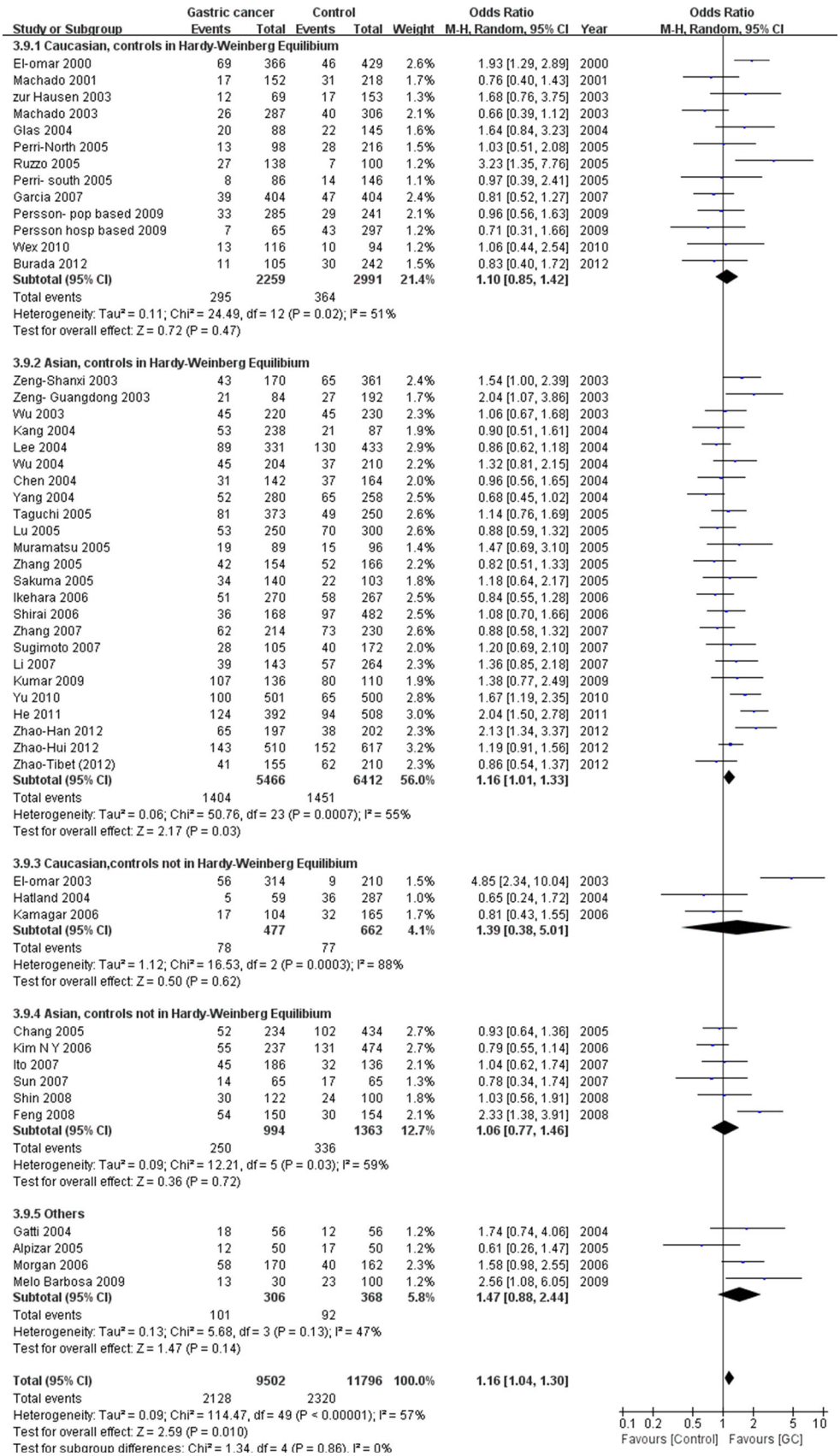


Fig. 4 A forest plot of the stomach carcinoma risk of relevance to the interleukin-1β-511 C/T polymorphism (TT vs. CC+CT) by ethnicity subgroups based on the Hardy–Weinberg equilibrium. The *areas* of the *squares* indicate the relative weights of the specific studies. *Bars* represent 95 % confidence intervals, and "GC," gastric cancer

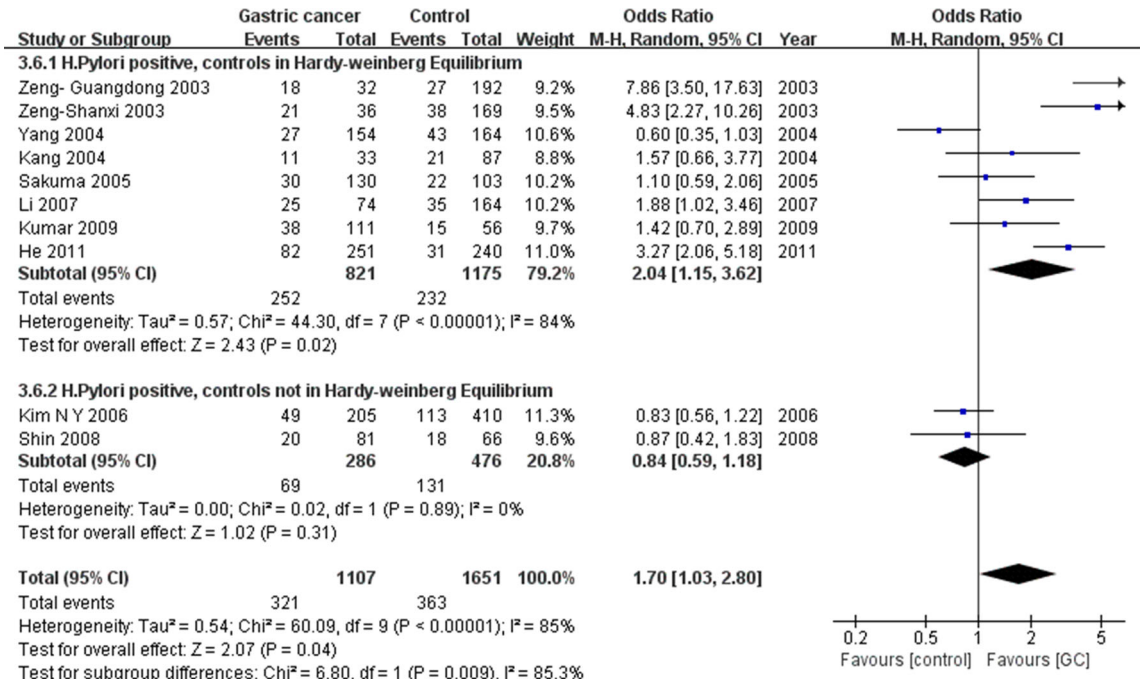


Fig. 5 A forest plot of the stomach carcinoma risk of relevance to the interleukin-1β-511 C/T polymorphism (TT vs. CC+CT) in the *H. pylori*-positive subgroup based on the Hardy–Weinberg equilibrium. The *areas* of the *squares* indicate the relative weights of the specific studies *Bars* represent 95 % confidence intervals, and "GC," gastric cancer

Overall results on the relationship between the IL-1β-511 C/T SNP and gastric cancer

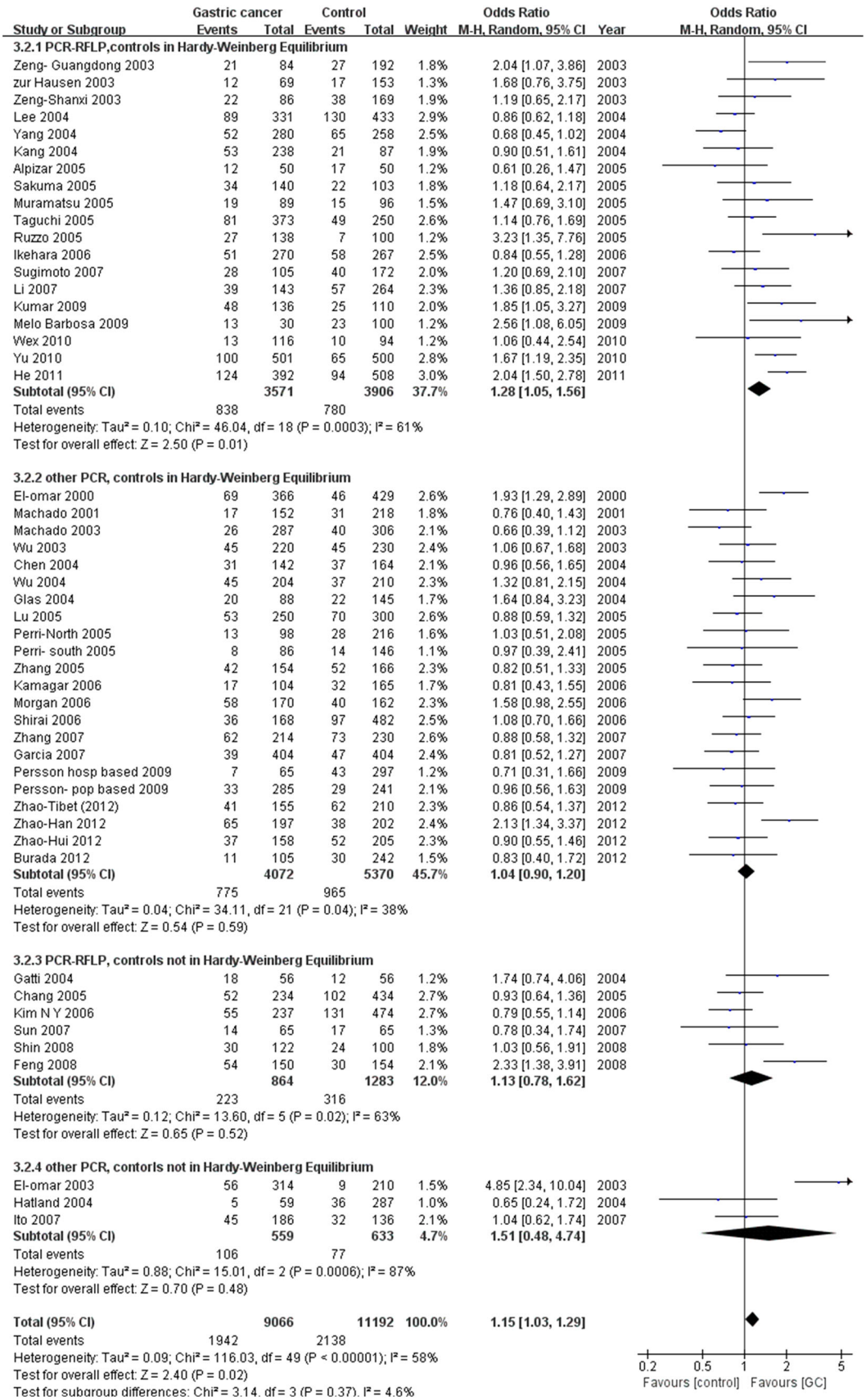
Figure 3 summarizes the results of sensitivity analysis based on the HWE principle using the recessive model (TT vs. CC+CT). For overall studies, interleukin 1β-511 C/T SNP was found to be positively related to the risk of stomach carcinoma (OR = 1.15; 95 % CI 1.03–1.29). Studies satisfying the HWE supported this relationship with a similar odds ratio (OR = 1.15; 95 % CI 1.01–1.29), whereas those deviating from the HWE showed no association between the IL-1β-511 C/T SNP and the risk of stomach carcinoma (OR = 1.19; 95 % CI 0.84–1.69).

Comprehensive subgroup analysis for overall studies and HWE studies

Table 2 summarizes the outcomes of comprehensive subgroup analysis with respect to ethnicity, study quality, control sources, genotyping methods, anatomical locations of cancer, pathologies of cancer, and *H. pylori* infection. When stratified by ethnicity, a positive relationship was observed for Asian populations for both overall (OR = 1.14; 95 % CI 1.01–1.29) and HWE satisfying (OR = 1.16; 95 % CI 1.01–1.33) studies. However, no such association was observed for Caucasian populations for overall (OR = 1.15; 95 % CI 0.87–1.52) and HWE satisfying (OR = 1.10; 95 % CI 0.85–1.42) studies (Fig. 4). *H. pylori*-positivity group was related to the risk of stomach carcinoma in overall (OR = 1.70; 95 % CI 1.03–2.80) and HWE satisfying (OR = 2.04; 95 % CI 1.15–3.62) studies (Fig. 5). In addition, PCR–RFLP genotyping method is better at revealing susceptibility of IL-1β-511 T allele carrier to gastric cancer than other PCR methods, such as, PCR–DHPLC and PCR–SSCP for both overall (OR = 1.24; 95 % CI 1.05–1.47) and HWE satisfying (OR = 1.28; 95 % CI 1.05–1.56) studies (Fig. 6). In terms of study quality, high-quality studies showed a correlation between IL-1β-511 T carrier and risk of stomach carcinoma. (OR = 1.17; 95 % CI 1.00–1.36) (Fig. 7). Anatomical location of cancer does not affect to the relationship between IL-1β-511 C/T SNP and stomach cancer in either overall (cardia OR = 0.98; 95 % CI 0.46–2.08, noncardia OR = 1.25; 95 % CI 0.60–2.60) or HWE satisfying (cardia OR = 0.66; 95 % CI 0.35–1.24, noncardia OR = 0.91, 95 % CI 0.66–1.26) studies (Fig. 8).

Discussion

Gastric cancer maintains its second place position amongst the causes of cancer-associated mortality, and therefore, researchers worldwide have concentrated on unearthing its etiology. *H. pylori* is a major causative agent in gastric cancer and produces oxidative radicals, which are harmful to DNA stability and stimulate the secretion of the


Gastric cancer
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
3.2.1 PCR-RFLP,controls in Hardy-Weinberg Equilibrium
Zeng- Guangdong 2003 21 84 27 192 1.8% 2.04 [1.07, 3.86] 2003
zur Hausen 2003 12 69 17 153 1.3% 1.68 [0.76, 3.75] 2003
Zeng-Shanxi 2003 22 86 38 169 1.9% 1.19 [0.65, 2.17] 2003
Lee 2004 89 331 130 433 2.9% 0.86 [0.62, 1.18] 2004
Yang 2004 52 280 65 258 2.5% 0.68 [0.45, 1.02] 2004
Kang 2004 53 238 21 87 1.9% 0.90 [0.51, 1.61] 2004
Alpizar 2005 12 50 17 50 1.2% 0.61 [0.26, 1.47] 2005
Sakuma 2005 34 140 22 103 1.8% 1.18 [0.64, 2.17] 2005
Muramatsu 2005 19 89 15 96 1.5% 1.47 [0.69, 3.10] 2005
Taguchi 2005 81 373 49 250 2.6% 1.14 [0.76, 1.69] 2005
Ruzzo 2005 27 138 7 100 1.2% 3.23 [1.35, 7.76] 2005
Ikehara 2006 51 270 58 267 2.5% 0.84 [0.55, 1.28] 2006
Sugimoto 2007 28 105 40 172 2.0% 1.20 [0.69, 2.10] 2007
Li 2007 39 143 57 264 2.3% 1.36 [0.85, 2.18] 2007
Kumar 2009 48 136 25 110 2.0% 1.85 [1.05, 3.27] 2009
Melo Barbosa 2009 13 30 23 100 1.2% 2.56 [1.08, 6.05] 2009
Wex 2010 13 116 10 94 1.2% 1.06 [0.44, 2.54] 2010
Yu 2010 100 501 65 500 2.8% 1.67 [1.19, 2.35] 2010
He 2011 124 392 94 508 3.0% 2.04 [1.50, 2.78] 2011
Subtotal (95% CI) 3571 3906 37.7% 1.28 [1.05, 1.56]
Total events 838 780
Heterogeneity: Tau² = 0.10; Chi² = 46.04, df = 18 (P = 0.0003); I² = 61%
Test for overall effect: Z = 2.50 (P = 0.01)
3.2.2 other PCR, controls in Hardy-Weinberg Equilibrium
El-omar 2000 69 366 46 429 2.6% 1.93 [1.29, 2.89] 2000
Machado 2001 17 152 31 218 1.8% 0.76 [0.40, 1.43] 2001
Machado 2003 26 287 40 306 2.1% 0.66 [0.39, 1.12] 2003
Wu 2003 45 220 45 230 2.4% 1.06 [0.67, 1.68] 2003
Chen 2004 31 142 37 164 2.1% 0.96 [0.56, 1.65] 2004
Wu 2004 45 204 37 210 2.3% 1.32 [0.81, 2.15] 2004
Glas 2004 20 88 22 145 1.7% 1.64 [0.84, 3.23] 2004
Lu 2005 53 250 70 300 2.6% 0.88 [0.59, 1.32] 2005
Perri-North 2005 13 98 28 216 1.6% 1.03 [0.51, 2.08] 2005
Perri- south 2005 8 86 14 146 1.1% 0.97 [0.39, 2.41] 2005
Zhang 2005 42 154 52 166 2.3% 0.82 [0.51, 1.33] 2005
Kamagar 2006 17 104 32 165 1.7% 0.81 [0.43, 1.55] 2006
Morgan 2006 58 170 40 162 2.3% 1.58 [0.98, 2.55] 2006
Shirai 2006 36 168 97 482 2.5% 1.08 [0.70, 1.66] 2006
Zhang 2007 62 214 73 230 2.6% 0.88 [0.58, 1.32] 2007
Garcia 2007 39 404 47 404 2.4% 0.81 [0.52, 1.27] 2007
Persson hosp based 2009 7 65 43 297 1.2% 0.71 [0.31, 1.66] 2009
Persson- pop based 2009 33 285 29 241 2.1% 0.96 [0.56, 1.63] 2009
Zhao-Tibet (2012) 41 155 62 210 2.3% 0.86 [0.54, 1.37] 2012
Zhao-Han 2012 65 197 38 202 2.4% 2.13 [1.34, 3.37] 2012
Zhao-Hui 2012 37 158 52 205 2.3% 0.90 [0.55, 1.46] 2012
Burada 2012 11 105 30 242 1.5% 0.83 [0.40, 1.72] 2012
Subtotal (95% CI) 4072 5370 45.7% 1.04 [0.90, 1.20]
Total events 775 965
Heterogeneity: Tau² = 0.04; Chi² = 34.11, df = 21 (P = 0.04); I² = 38%
Test for overall effect: Z = 0.54 (P = 0.59)
3.2.3 PCR-RFLP, controls not in Hardy-Weinberg Equilibrium
Gatti 2004 18 56 12 56 1.2% 1.74 [0.74, 4.06] 2004
Chang 2005 52 234 102 434 2.7% 0.93 [0.64, 1.36] 2005
Kim N Y 2006 55 237 131 474 2.7% 0.79 [0.55, 1.14] 2006
Sun 2007 14 65 17 65 1.3% 0.78 [0.34, 1.74] 2007
Shin 2008 30 122 24 100 1.8% 1.03 [0.56, 1.91] 2008
Feng 2008 54 150 30 154 2.1% 2.33 [1.38, 3.91] 2008
Subtotal (95% CI) 864 1283 12.0% 1.13 [0.78, 1.62]
Total events 223 316
Heterogeneity: Tau² = 0.12; Chi² = 13.60, df = 5 (P = 0.02); I² = 63%
Test for overall effect: Z = 0.65 (P = 0.52)
3.2.4 other PCR, contorls not in Hardy-Weinberg Equilibrium
El-omar 2003 56 314 9 210 1.5% 4.85 [2.34, 10.04] 2003
Hatland 2004 5 59 36 287 1.0% 0.65 [0.24, 1.72] 2004
Ito 2007 45 186 32 136 2.1% 1.04 [0.62, 1.74] 2007
Subtotal (95% CI) 559 633 4.7% 1.51 [0.48, 4.74]
Total events 106 77
Heterogeneity: Tau² = 0.88; Chi² = 15.01, df = 2 (P = 0.0006); I² = 87%
Test for overall effect: Z = 0.70 (P = 0.48)
Total (95% CI) 9066 11192 100.0% 1.15 [1.03, 1.29]
Total events 1942 2138
Heterogeneity: Tau² = 0.09; Chi² = 116.03, df = 49 (P < 0.00001); I² = 58%
Test for overall effect: Z = 2.40 (P = 0.02)
Test for subgroup differences: Chi² = 3.14, df = 3 (P = 0.37), I² = 4.6%
0.2 0.5 1 2 5
Favours [control] Favours [GC]

◀**Fig. 6** A forest plot of the stomach carcinoma risk of relevance to the interleukin-1β-511 C/T polymorphism (TT vs. CC+CT) according to genotyping method based on the Hardy–Weinberg equilibrium. The *areas* of the *squares* indicate the relative weights of the specific studies. *Bars* represent 95 % confidence intervals. *GC* gastric cancer, *PCR* polymerase chain reaction, *RFLP* restriction fragment length polymorphism

proliferative factor gastrin [1, 67]. Interleukin 1β (IL-1β) amplifies this mechanism through hypochlorhydria, which is favorable to *H. pylori* [4]. Nevertheless, the fact that not every *H. pylori* carrier develops stomach carcinoma strongly suggests a relation between IL-1β polymorphisms and stomach carcinoma susceptibility. Many studies have investigated this potential relationship since El-Omar et al. [8] first described a positive correlation between the IL-1β-511 C/T SNP and risk of stomach carcinoma. However, such studies and even meta-analyses have produced mixed results. In this context, the present meta-analysis draws comprehensive analysis regarding the strength of the relationship between the IL-1β-511 C/T SNP and gastric cancer risk by in-depth analysis and the removal of presumed factors of heterogeneity from previous studies. A total of 45 recent studies with 50 population data sets were considered after eliminating selection bias from unrefined searches and systematically searching the MEDLINE, EMBASE, and CENTRAL databases. In addition, clear criteria for excluding and including studies were set. As a result, 12 new studies were added, and the homogeneity of control groups was elaborated by eliminating studies that included premalignant gastric patients as an eligible control group. In addition, HWE studies were analyzed because a deviation from the HWE implies that the study may exhibit selection bias or have suffered some erroneous event during genotyping [16, 20]. Consequently, consistency with the HWE is critical for guaranteeing the appropriateness of control subjects for a given case control study and for verifying the credibility of a genotyping procedure.

In this meta-analysis, we found that the IL-1β-511 C/T SNP confers susceptibility to stomach carcinoma, which is in accordance with the results of six of the seven previous meta-analyses. It is noteworthy that some of our subgroup analysis results are inconsistent with the findings of previous meta-analyses.

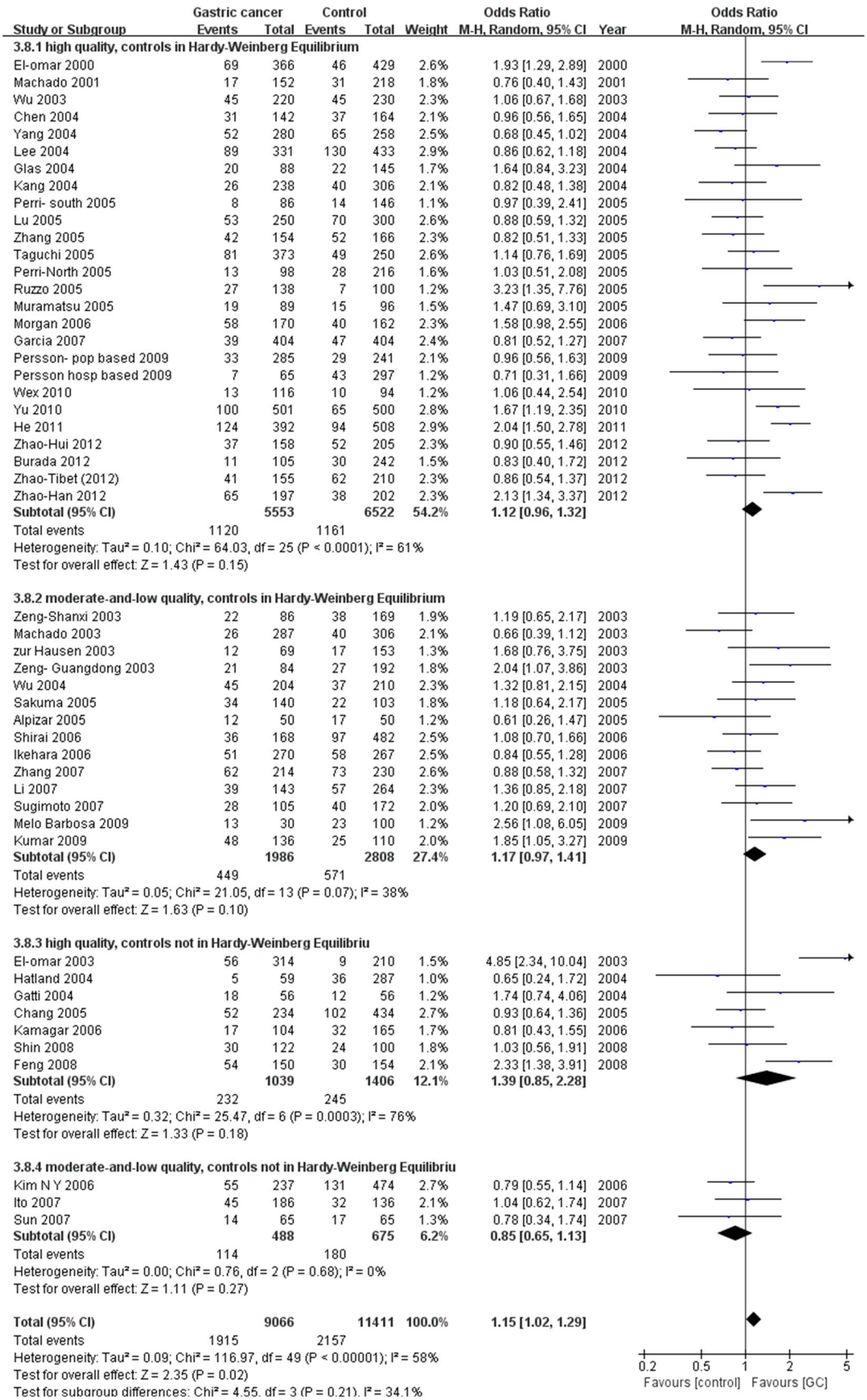
With respect to ethnicity, Asian populations were found to show a positive relation between the presence of the IL-1β-511 T allele and the risk of stomach carcinoma in overall and HWE satisfying studies, which is inconsistent with the findings of three previous meta-analyses [10, 12, 13] that found no such relation. In the present meta-analysis, ten recently published Asian studies were included and five Caucasian studies were excluded because healthy individuals and patients with premalignant lesions such as ulcer, MALToma, and gastritis were not differentiated in control populations. In this regard, the large size of Asian populations included in the present study and the process used for selecting control populations probably affected the results.

In subgroup analysis of *H. pylori* carriers, it was shown that *H. pylori* infection reinforces the relation between IL-1β-511 T allele with susceptibility to gastric cancer in both overall and HWE satisfying studies. It provides support for the mechanism that IL-1β contributes to chronic inflammation by producing hypochlorhydria. Close attention should be paid to the fact that East Asian populations have generally high *H. pylori* infection rate and that Asian exhibited the strongest relationship between the IL-1β-511 C/T SNP and gastric cancer in our study. As explained above, IL-1β-511 C/T SNP makes IL-1β to be overexpressed, which suppresses acid secretion and thus creates favorable conditions for *H. pylori* proliferation. These findings suggest that Asian populations, which are particularly vulnerable to *H. pylori* infection, would have a strong relationship between the IL-1β-511 C/T SNP and gastric cancer.

In addition, the relationship between stomach carcinoma and the IL-1β-511 C/T SNP was noteworthy in studies that employed PCR–RFLP genotyping methods. Of the various genotyping methods used, PCR–RFLP method was employed most frequently (25 of the 50 population data sets). The PCR–RFLP method was the first DNA-profiling technique which was used for genetic fingerprinting, evaluating the risk of genetic disorders, and analyzing samples from crime scenes. The large pool of cases analyzed in previous studies using PCR–RFLP supports the validity of the method. In addition, the sensitivity of PCR–RFLP has been verified in many studies. Accordingly, the reliability and validity of this method support the observed relation between IL-1β-511 T allele and risk of gastric cancer.

A subgroup analysis according to study quality scores showed a positive association between the IL-1β-511 T allele and the risk of stomach carcinoma. Quality analysis was carried out utilizing the scale proposed by Thakkinstian et al. [7] and refined by Camargo et al. [12] and Xue et al. [13]. High-score studies were elaborated by designating the source of control groups, confirming the representativeness of cases, using reliable methods to confirm the presence of stomach carcinoma and to conduct genotyping. Classifying studies by quality reduced study heterogeneity because it ensured the reliabilities of control sources and case populations.

In the present study, only recessive model (TT vs. CT+CC) results are presented, but recessive model results are consistent with those of other models. In the additive model (TT vs. CC), pooled ORs (95 % CI) were 1.20 (1.00–1.45) for overall studies and 1.24 (1.02–1.57) for


Gastric cancer
Control
Odds Ratio
Odds Ratio
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
3.8.1 high quality, controls in Hardy-Weinberg Equilibrium
El-omar 2000 69 366 46 429 2.6% 1.93 [1.29, 2.89] 2000
Machado 2001 17 152 31 218 1.8% 0.76 [0.40, 1.43] 2001
Wu 2003 45 220 45 230 2.3% 1.06 [0.67, 1.68] 2003
Chen 2004 31 142 37 164 2.1% 0.96 [0.56, 1.65] 2004
Yang 2004 52 280 65 258 2.5% 0.68 [0.45, 1.02] 2004
Lee 2004 89 331 130 433 2.9% 0.86 [0.62, 1.18] 2004
Glas 2004 20 88 22 145 1.7% 1.64 [0.84, 3.23] 2004
Kang 2004 26 238 40 306 2.1% 0.82 [0.48, 1.38] 2004
Perri- south 2005 8 86 14 146 1.1% 0.97 [0.39, 2.41] 2005
Lu 2005 53 250 70 300 2.6% 0.88 [0.59, 1.32] 2005
Zhang 2005 42 154 52 166 2.3% 0.82 [0.51, 1.33] 2005
Taguchi 2005 81 373 49 250 2.6% 1.14 [0.76, 1.69] 2005
Perri-North 2005 13 98 28 216 1.6% 1.03 [0.51, 2.08] 2005
Ruzzo 2005 27 138 7 100 1.2% 3.23 [1.35, 7.76] 2005
Muramatsu 2005 19 89 15 96 1.5% 1.47 [0.69, 3.10] 2005
Morgan 2006 58 170 40 162 2.3% 1.58 [0.98, 2.55] 2006
Garcia 2007 39 404 47 404 2.4% 0.81 [0.52, 1.27] 2007
Persson- pop based 2009 33 285 29 241 2.1% 0.96 [0.56, 1.63] 2009
Persson hosp based 2009 7 65 43 297 1.2% 0.71 [0.31, 1.66] 2009
Wex 2010 13 116 10 94 1.2% 1.06 [0.44, 2.54] 2010
Yu 2010 100 501 65 500 2.8% 1.67 [1.19, 2.35] 2010
He 2011 124 392 94 508 2.9% 2.04 [1.50, 2.78] 2011
Zhao-Hui 2012 37 158 52 205 2.3% 0.90 [0.55, 1.46] 2012
Burada 2012 11 105 30 242 1.5% 0.83 [0.40, 1.72] 2012
Zhao-Tibet (2012) 41 155 62 210 2.3% 0.86 [0.54, 1.37] 2012
Zhao-Han 2012 65 197 38 202 2.3% 2.13 [1.34, 3.37] 2012
Subtotal (95% CI) 5553 6522 54.2% 1.12 [0.96, 1.32]
Total events 1120 1161
Heterogeneity: Tau² = 0.10; Chi² = 64.03, df = 25 (P < 0.0001); I² = 61%
Test for overall effect: Z = 1.43 (P = 0.15)
3.8.2 moderate-and-low quality, controls in Hardy-Weinberg Equilibrium
Zeng-Shanxi 2003 22 86 38 169 1.9% 1.19 [0.65, 2.17] 2003
Machado 2003 26 287 40 306 2.1% 0.66 [0.39, 1.12] 2003
zur Hausen 2003 12 69 17 153 1.3% 1.68 [0.76, 3.75] 2003
Zeng- Guangdong 2003 21 84 27 192 1.8% 2.04 [1.07, 3.86] 2003
Wu 2004 45 204 37 210 2.3% 1.32 [0.81, 2.15] 2004
Sakuma 2005 34 140 22 103 1.8% 1.18 [0.64, 2.17] 2005
Alpizar 2005 12 50 17 50 1.2% 0.61 [0.26, 1.47] 2005
Shirai 2006 36 168 97 482 2.5% 1.08 [0.70, 1.66] 2006
Ikehara 2006 51 270 58 267 2.5% 0.84 [0.55, 1.28] 2006
Zhang 2007 62 214 73 230 2.6% 0.88 [0.58, 1.32] 2007
Li 2007 39 143 57 264 2.3% 1.36 [0.85, 2.18] 2007
Sugimoto 2007 28 105 40 172 2.0% 1.20 [0.69, 2.10] 2007
Melo Barbosa 2009 13 30 23 100 1.2% 2.56 [1.08, 6.05] 2009
Kumar 2009 48 136 25 110 2.0% 1.85 [1.05, 3.27] 2009
Subtotal (95% CI) 1986 2808 27.4% 1.17 [0.97, 1.41]
Total events 449 571
Heterogeneity: Tau² = 0.05; Chi² = 21.05, df = 13 (P = 0.07); I² = 38%
Test for overall effect: Z = 1.63 (P = 0.10)
3.8.3 high quality, controls not in Hardy-Weinberg Equilibriu
El-omar 2003 56 314 9 210 1.5% 4.85 [2.34, 10.04] 2003
Hatland 2004 5 59 36 287 1.0% 0.65 [0.24, 1.72] 2004
Gatti 2004 18 56 12 56 1.2% 1.74 [0.74, 4.06] 2004
Chang 2005 52 234 102 434 2.7% 0.93 [0.64, 1.36] 2005
Kamagar 2006 17 104 32 165 1.7% 0.81 [0.43, 1.55] 2006
Shin 2008 30 122 24 100 1.8% 1.03 [0.56, 1.91] 2008
Feng 2008 54 150 30 154 2.1% 2.33 [1.38, 3.91] 2008
Subtotal (95% CI) 1039 1406 12.1% 1.39 [0.85, 2.28]
Total events 232 245
Heterogeneity: Tau² = 0.32; Chi² = 25.47, df = 6 (P = 0.0003); I² = 76%
Test for overall effect: Z = 1.33 (P = 0.18)
3.8.4 moderate-and-low quality, controls not in Hardy-Weinberg Equilibriu
Kim N Y 2006 55 237 131 474 2.7% 0.79 [0.55, 1.14] 2006
Ito 2007 45 186 32 136 2.1% 1.04 [0.62, 1.74] 2007
Sun 2007 14 65 17 65 1.3% 0.78 [0.34, 1.74] 2007
Subtotal (95% CI) 488 675 6.2% 0.85 [0.65, 1.13]
Total events 114 180
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 2 (P = 0.68); I² = 0%
Test for overall effect: Z = 1.11 (P = 0.27)
Total (95% CI) 9066 11411 100.0% 1.15 [1.02, 1.29]
Total events 1915 2157
Heterogeneity: Tau² = 0.09; Chi² = 116.97, df = 49 (P < 0.00001); I² = 58%
Test for overall effect: Z = 2.35 (P = 0.02)
Test for subgroup differences: Chi² = 4.55, df = 3 (P = 0.21), I² = 34.1%
0.2 0.5 1 2 5
Favours [control] Favours [GC]

◀**Fig. 7** A forest plot of the stomach carcinoma risk of relevance to the interleukin-1β-511 C/T polymorphism (TT vs. CC+CT) according to the study quality subgroup based on the Hardy–Weinberg equilibrium. The *areas* of the *squares* indicate the relative weights of the specific studies. *Bars* represent 95 % confidence intervals, and "GC," gastric cancer

HWE satisfying studies. In addition, the dominant model (TT+CT vs. TT) produced insignificant results for overall studies (OR = 1.10; 95 % CI 0.97–1.24), but the susceptibility of IL-1β-511 T carriers for HWE satisfying studies (OR = 1.14; 95 % CI 1.01–1.27) (data not shown). A similar pattern was observed for ethnicity analysis. Caucasian populations showed no relationship for any model: TT+CT versus CC (overall: OR = 1.13; 95 % CI 0.89–1.42; HWE: OR = 1.12; 95 % CI 0.87–1.44) and TT versus CC (overall: OR = 1.23; 95 % CI 0.86–1.75; HWE: OR = 1.18; 95 % CI 0.87–1.62), whereas Asian in HWE satisfying studies showed statistical significance in all models: TT+CT vs. CC (OR = 1.15; 95 % CI 1.00–1.34) and TT versus CC (OR = 1.26; 95 % CI 1.04–1.54).

This meta-analysis has several limitations that should be considered. Although we evaluated publication bias comprehensively using a funnel plot, Egger's test, and Begg's test, the tendency not to publish negative results may have produced this bias. In addition, future research should provide updated systematic analysis on the relationship between gastric cancer and haplotypes of the gene family cluster on chromosome 2q, IL-1β-31 C, IL-1β +3954, and IL1RN, because a polymorphism in one gene is often accompanied instability of a nearby gene.

In summary, the results of this refined and updated meta-analysis verify the relationship between the IL-1β-511 T allele carrier and stomach carcinoma susceptibility. It also confirms that Asian ethnicity strengthens this relationship. In addition, the coexistence of IL-1β-511 C/T SNP and *H. pylori* infection was found to increase susceptibility to stomach carcinoma. The most reliable genotyping technique appears to be PCR–RFLP, which suggests that it should be used to analyze the relationship between the IL-1β-511 C/T SNP and the risk of stomach carcinoma.

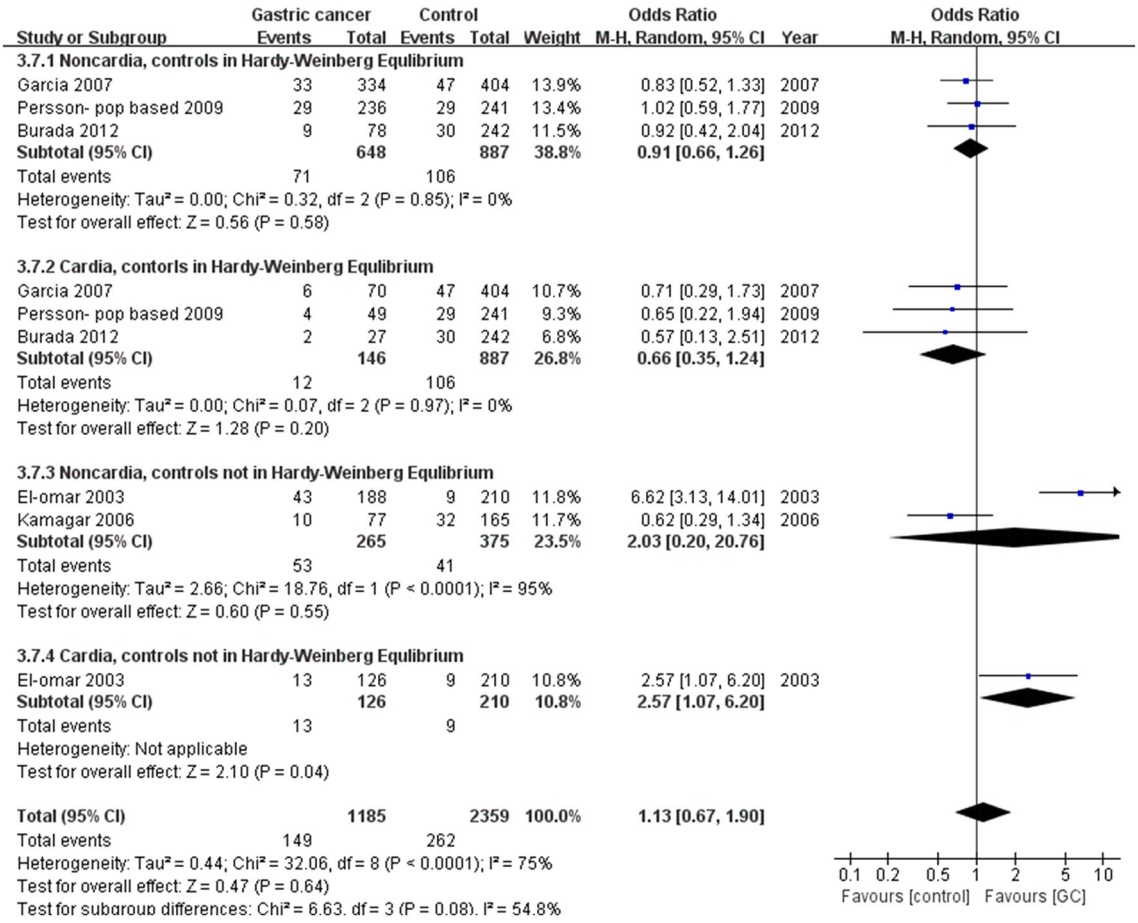


Fig. 8 A forest plot of the stomach carcinoma risk of relevance to the interleukin-1β-511 C/T polymorphism (TT vs. CC+CT) according to histology subgroups based on the Hardy–Weinberg equilibrium. The *areas* of the *squares* indicate the relative weights of the specific studies. *Bars* represent 95 % confidence intervals, and "GC," gastric cancer

Thorough screening of eligible studies and the adoption of a strict study selection procedure based on the elimination of selection bias for control groups may explain reported inconsistencies across ethnic subgroups.

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