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The -1082A>G polymorphism in promoter region of interleukin-10 and risk of digestive cancer: a meta-analysis

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The -1082A>G polymorphism is located in promoter region of interleukin-10 (IL-10) and it could affect the production of IL-10. Numerous studies have investigated the association between IL-10 -1082A>G and risk of digestive cancer. However, the conclusion is still inconsistent. Here, we have performed a meta-analysis and systematic review to determine the association between the IL-10 -1082A>G and susceptibility to digestive cancer. In this meta-analysis, we identified 40 eligible studies, involving 7195 patients of digestive cancer and 11755 controls. By pooling all eligible studies, we found the variant -1082G allele significantly increased risk of digestive cancer (G vs. A: OR=1.181, 95% CI: 1.057–1.319). Further stratified analysis was performed to evaluate the influence of cancer types, ethnicities, study design, sample size and Hardy–Weinberg equilibrium. Stratified analysis suggested that, the -1082A>G polymorphism was only associated with increased risk for gastric cancer (G vs. A: OR=1.281, 95% CI: 1.102–1.488) and in Asian population (G vs. A: OR=1.399, 95% CI: 1.188–1.646). No significant publication bias was detected. Based on 40 studies and 18950 participants, we found the variant IL-10 -1082G allele significantly increased susceptibility to digestive cancer, especially for gastric cancer and in Asian population.

Cytokines have been investigated for decades and many important cytokines are involved in human diseases, such as interleukin-1 and osteoarthritis[1,2]. In 1989, Mosmann and colleagues[3] first reported a cytokine named "cytokine synthesis inhibiting factor (CISF)", which was secreted by T helper 2 (Th2) clones and inhibited synthesis of interferon-γ (IFN-γ) in Th1 clones. The CISF is now known as interleukin-10 (IL-10).

IL-10 is a cytokine with potent anti-inflammatory activity[4], produced by macropahges, T helper 2 cells and B lymphocytes[5,6]. IL-10 is a multifunctional cytokine involved in both innate and adaptive immune response[4,6]. As an inflammatory cytokine, IL-10 participates in the development of various diseases, such as kidney disease[7], heart failure[8], chronic infection[9,10] and cancer[10]. Although IL-10 has been extensively studied, the exact role of IL-10 in cancer is still elusive, since evidence suggested that IL-10 could mediate both anticancer immune response and immune-mediated rejection of cancer[6].

The gene encoding IL-10 is located on chromosome 1 (1q31-1q32). Three single nucleotide polymorphisms (SNPs) have been confirmed in the promoter region of IL-10: -592C>A (rs1800872), -819C>T (rs1800871), and -1082A>G (rs1800896). Previous studies have shown that the three polymorphisms could affect the expression of IL-10[11,12] and alter the susceptibility to digestive cancers[13–15]. In addition to the elusive role of IL-10 in cancer development, the relationship between functional polymorphisms in IL-10 promoter region and cancer risk is also mysterious. Several meta-analyses have been performed to evaluate the association between IL-10 polymorphisms and cancer risk[16,17]; however, the association between -1082A>G polymorphism and digestive cancer has not been assessed. Thus, this meta-analysis was performed to investigate the association between 1082 polymorphism and digestive cancer and assess the influence of confounding factors.

Methods

Searching strategy. This meta-analysis were conducted and reported in corresponding to the PRISMA guidelines of systematic reviews and meta-analyses (see Supplementary Table S1 online)[18]. Online databases of PubMed, EMBASE, and CNKI were searched. The following terms were used: "Interleukin-10" or "IL10", "polymorphisms, single nucleotide" or "SNPs" and "cancer" or " neoplasm". Both plain text and medical subheadings of above key words were used for searching. No limitation of origin, languages, or other items was placed. To identify additional studies, references of previous meta-analyses and reviews were also manually searched.

Inclusion criteria. Records identified from databases were first screened by titles and abstracts, and then full-text articles were further reviewed. Eligible studies were judged by the following criteria: (1) case-control studies; (2) investigating the association between IL-10 -1082A>G polymorphism and digestive cancer risk; (3) available genotype distribution data. According to the inclusion criteria, 2 authors (LC and TW) extracted eligible studies independently. The two authors reached consensus on each records.

Data extraction. Name of first author, year of publication, country where the study was carried out, cancer type, ethnicity, the source of control, number of cases and controls, genotype frequency in cases and controls were collected from eligible studies. Ethnicity was simply classified as Asian, Caucasian, and Latino (Table 1). Included studies were defined as hospital-based (HB) and population-based (PB) according to the source of control. Sample size of eligible studies was classified as large (>500) or small (<500). All data were extracted by two authors (LC and TW) independently with a predesigned data-collection form. Two authors reached consensus on each item.

Quality assessment. "Methodological quality assessment scale" (the scale can be found as Supplementary Table S2 online), a quality scale modified form previous meta-analyses[19], was used to evaluate methodological quality of eligible studies. Briefly, the following items were assessed: the representativeness of cases, source of controls, ascertainment of relevant cancer, sample size, quality control of genotyping methods, and Hardy-Weinberg equilibrium (HWE). Quality scores ranged from 0 to 10 (0: the lowest; 10: the highest).

Statistical analysis. Odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated to estimate the association strength between IL-10 -1082A>G polymorphism and digestive cancer risk. Deviation from the Hardy–Weinberg equilibrium (HWE) among controls subjects was tested by a x^2-test and a $P<0.05$ was considered as significant disequilibrium. The pooled ORs were calculated for allele comparison (G vs. A), homozygote comparison (GG vs. AA), heterozygote comparison (GA vs. AA), and dominant models (GG/GA vs. AA, considering the dominant effect of the IL-10 -1082G allele). For some studies only combined genotype (GG/G) data was reported[20,21], thus, only dominant comparison models were conducted for these studies. Heterogeneity between studies were determined by chi-square based on Q test and the random-effects model was used when there was significant heterogeneity ($P<0.1$); otherwise, the fixed-effects model was applied[22]. Sub-group analyses were conducted according to cancer types, ethnicities, source of control, HWE, and sample size. Sub-group analysis was not performed for those subgroups with less than 2 studies. When significant heterogeneity presented, meta-regression was performed to detect the source of heterogeneity. Egger's test and Begg's test were used to test publication bias, and a $p < 0.05$ was significant[23]. Sensitivity analysis was performed to assess individual studies' effect on the pooled results. All meta-analyses were calculated by STATA (version 10.0; Stata Corp, College Station, Texas USA). And all P values are two-side.

Results

Overview of eligible studies. According to our searching strategy, 752 records were retrieved and screened. After primary screening, 38 full-text papers were retrieved for further assessment[13–15,20,21,24–56]. The study reported by Zhou SZ et al was excluded for lacking of detail genotype distribution data[56]. In the studies reported by El-Omar EM[29], Guo W[32], and Savage SA[14], both gastric cancer and

Table 1 | Baseline Characteristics of Eligible Studies

Author	Year	Cancer Type	Country	Ethnicity	Study Design	Sample Size	Cases	Controls	HWE
Alpízar-Alpízar W	2005	GC	Costa Rica	Latinos	PB	Small	45	44	Y
Bai XL	2008	GC	China	Asians	HB	Small	104	111	NA
Bouzgarrou N	2009	HCC	Tunisia	African	HB	Small	58	145	Y
Cacev T	2008	CRC	Croatia	Caucasian	PB	Small	160	160	N
Cozar JM	2007	CRC	Spain	Caucasian	HB	Small	96	176	Y
Crivello A	2006	CRC	Italy	Caucasian	PB	Small	62	124	Y
Crusius JB	2008	GC	European	Caucasian	PB	Large	235	1134	N
El-Omar EM(EC)	2003	EC	USA	Mixed	PB	Small	161	210	Y
El-Omar EM(GC)	2003	GC	USA	Mixed	PB	Large	314	210	Y
Forte GI	2008	GC	Italy	Caucasian	HB	Small	42	185	N
García-González MA	2007	GC	Spain	Caucasian	PB	Large	404	404	Y
Guo W (EC)	2005	EC	China	Asians	PB	Large	203	443	N
Guo W (GC)	2005	GC	China	Asians	PB	Large	152	443	N
He B	2012	GC	China	Asians	HB	Small	196	248	Y
Heneghan MA	2003	HCC	China	Asians	HB	Small	98	175	Y
Kamangar F	2006	GC	Finland	Caucasian	PB	Small	112	205	Y
Kang JM	2009	GC	Korea	Asians	HB	Large	334	335	Y
Kim J	2012	GC	Korea	Asians	HB	Large	495	495	Y
Ko KP	2009	GC	Korea	Asians	PB	Small	80	336	Y
Lee JY	2005	GC	Korea	Asians	HB	Small	122	120	Y
Liu J	2011	GC	China	Asians	HB	Small	234	243	N
Lu W	2005	GC	China	Asians	PB	Large	250	300	N
Macarthur M	2005	CRC	UK	Caucasian	PB	Large	257	408	Y
Migita K	2005	HCC	Japan	Asians	HB	Small	48	188	N
Morgan DR	2006	GC	Honduras	Latinos	HB	Small	170	161	Y
Nieters A	2005	HCC	China	Asians	HB	Small	249	250	NA
Ognjanovic S	2009	HCC	USA	Caucasian	PB	Small	118	230	NA
Pan XF	2013	GC	China	Asians	HB	Large	308	308	Y
Savage SA (EC)	2004	EC	China	Asians	HB	Large	115	385	N
Savage SA (GC)	2004	GC	China	Asians	HB	Small	84	385	N
Scola L	2009	PC	Italy	Caucasian	PB	Small	48	131	Y
Shin CM	2011	GC	Korea	Asians	HB	Large	632	237	Y
Shin HD	2003	HCC	Korea	Asians	HB	Large	230	792	Y
Sugimoto M	2007	GC	Japan	Asians	HB	Small	104	168	Y
Wu MS	2002	GC	China	Asians	HB	Small	150	220	Y
Xiao H	2009	GC	China	Asians	HB	Large	220	624	Y
Yin YQ	2012	GC	China	Asians	HB	Small	75	75	N
Zambon CF	2005	GC	Italy	Caucasian	HB	Large	129	644	Y
Zeng X	2012	GC	China	Asians	PB	Small	151	153	N
Zhou Y	2011	GC	China	Asians	PB	Small	150	150	N

CRC: Colorectal Cancer; EC: Esophageal Cancer; GC: Gastric Cancer; HCC: Hepatocellular Carcinoma; PC: Pancreatic Cancer; HB: hospital-based; PB: population-based; Large: >500 participants; Small: <500 participants; HWE: Hardy-Weinberg equilibrium; Y: agreement with HWE; N: disagreement with HWE; NA: unable to estimate.

esophageal cancer were reported and the data were presented independently, and each kind of the cancer was treated as a separate study. Thus, 40 eligible studies were included in this meta-analysis[13–15,20,21,24–55]. The process of study selection was shown in Figure 1.

Of the 40 eligible studies, 7195 patients of digestive cancer and 11755 controls were enrolled. Baseline characteristics of those studies were shown in Table 1. Most studies were performed among Asian population (24 studies) and Caucasian population (11 studies).

Methodological quality of eligible studies was assessed by a quality scale reported by previous studies. Generally, quality of eligible studies was acceptable, with an average score of 7.3. Of 40 analyzed studies, 23 were hospital-based and 17 studies were population based. As for HWE, 24 studies were in agreement with HWE, 13 studies were in disagreement with HWE and it was unable to test in 3 studies[20,21,44] due to combined data (Table 2). Since no genotyping error was reported, all studies were included in quantitative synthesis, and stratified analysis was performed to assess the influence of disagreement of HWE.

Meta-analysis Results. By pooling all eligible studies, compared with the wild -1082A allele, we found the variant IL-10 -1082G allele was associated with significantly increased risk of digestive cancer in all four comparison models (G vs. A: OR=1.181, 95% CI: 1.057–1.319; Heterogeneity, P<0.001; Figure 2 and Figure 3; Table 2).

Further sub-group analyses were conducted to assess the effects of potential confounding factors. When stratified by cancer types, we found the variant G allele only increased risk of gastric cancer (G vs. A: OR= 1.281, 95% CI: 1.102–1.488; Heterogeneity, P<0.001) but did not alter the risk of colorectal cancer (G vs. A: OR= 0.937, 95% CI: 0.805–1.090; Heterogeneity, P=0.710), hepatocellular carcinoma (G vs. A: OR= 1.104, 95% CI: 0.797–1.530; Heterogeneity, P=0.283) or esophageal cancer (G vs. A: OR= 0.982, 95% CI: 0.820–1.175; Heterogeneity, P=0.591). As for ethnicities, significant association was only found among Asians (G vs. A: OR= 1.399, 95% CI: 1.188–1.646; Heterogeneity, P<0.001), while the -1082 polymorphism did not alter digestive cancer risk in Caucasians (G vs. A: OR= 1.016, 95% CI: 0.930–1.111; Heterogeneity, P=0.796). HWE also significantly affected the pooled analysis. In the sub-groups classified according to source of control and sample size, meta-analysis results were quite consistent.

Heterogeneity and publication bias. Notably, significant heterogeneity was observed in most comparisons. Thus, meta-regression

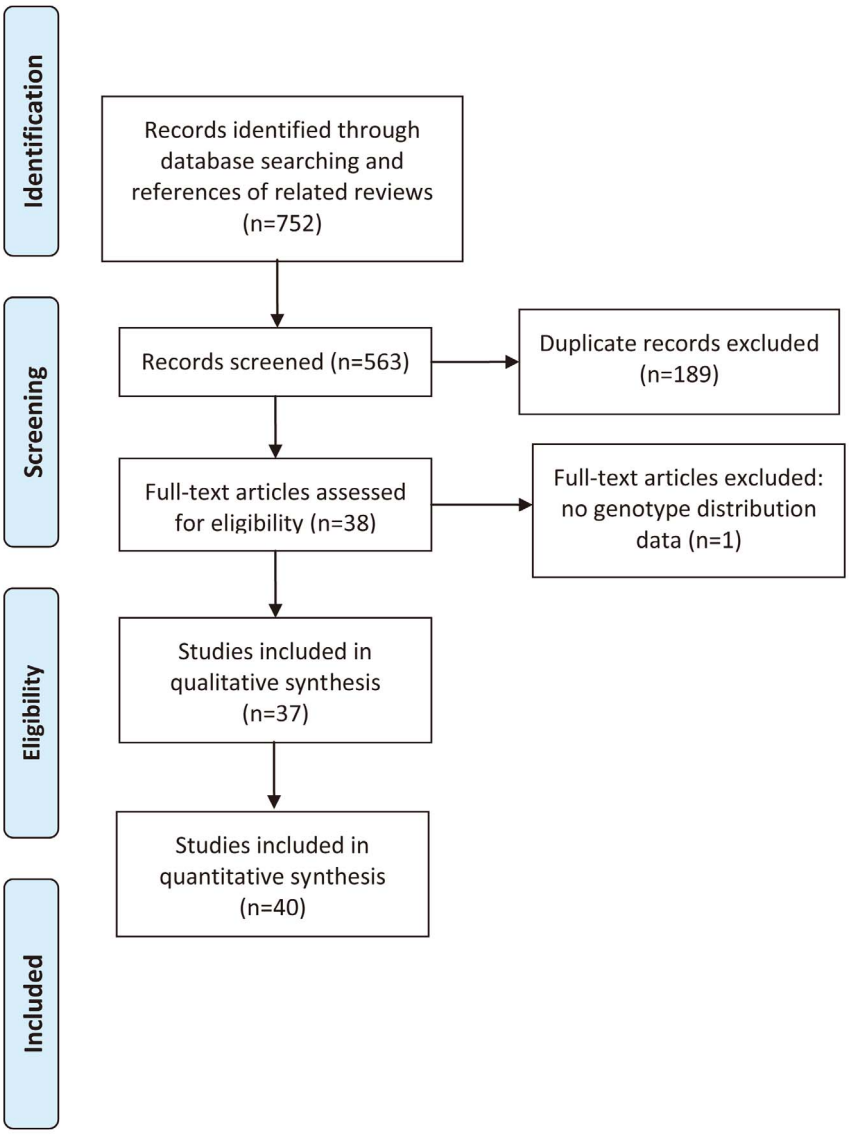

Figure 1 | Flow Chart of Study Selection. Both gastric cancer and esophageal cancer were reported in 3 studies, and each kind of cancer was treated as a separate study. Thus, 37 studies were included in qualitative synthesis and 40 studies were included in quantitative synthesis.

Table 2 | Meta-analysis Results

	G vs. A			GG vs. AA			GA vs. AA			GGGA vs. AA		
	Studies	OR (95% CI)	P_{heter}	Studies	OR (95% CI)	P_{heter}	Studies	OR (95% CI)	P_{heter}	Studies	OR (95% CI)	P_{heter}
Overall	37	1.181 (1.057–1.319)*	<0.001	33	1.305 (1.044–1.631) *	<0.001	37	1.168 (1.015–1.344) *	<0.001	40	1.153 (1.005–1.323) *	<0.001
Cancer Types												
CRC	4	0.937 (0.805–1.090)	0.71	4	0.873 (0.638–1.195)	0.737	4	0.914 (0.709–1.179)	0.572	4	0.903 (0.709–1.149)	0.552
EC	3	0.982 (0.820–1.175)	0.591	3	0.872 (0.559–1.361)	0.864	3	1.113 (0.850–1.456)	0.761	3	1.070 (0.825–1.387)	0.656
GC	25	1.281 (1.102–1.488) *	<0.001	22	1.575 (1.146–2.164) *	<0.001	25	1.277 (1.067–1.527) *	<0.001	26	1.275 (1.056–1.538) *	<0.001
HCC	4	1.104 (0.797–1.530)	0.283	3	1.355 (0.587–3.124)	0.757	4	1.022 (0.714–1.463)	0.335	6	0.912 (0.739–1.126)	0.431
Ethnicity												
Asian	22	1.399 (1.188–1.646) *	<0.001	19	2.072 (1.446–2.971) *	0.068	22	1.397 (1.161–1.680) *	<0.001	24	1.351 (1.108–1.649) *	<0.001
Caucasian	10	1.016 (0.930–1.111)	0.796	10	1.055 (0.880–1.264)	0.649	10	0.973 (0.786–1.205)	0.044	11	1.010 (0.881–1.159)	0.386
Control Source												
PB	16	1.151 (1.001–1.324) *	<0.001	15	1.336 (0.973–1.835)	<0.001	16	1.118 (0.915–1.364)	0.001	17	1.153 (0.964–1.379)	0.001
HB	21	1.212 (1.014–1.449) *	<0.001	18	1.246 (0.940–1.650)	0.38	21	1.216 (0.992–1.489)	<0.001	23	1.153 (0.935–1.422)	<0.001
Sample Size												
Small	22	1.151 (1.010–1.312) *	0.016	18	1.291 (1.010–1.649) *	0.191	22	1.170 (0.973–1.406)	0.026	25	1.109 (0.927–1.327)	0.001
Large	15	1.214 (1.013–1.456) *	<0.001	15	1.388 (0.944–2.040)	<0.001	15	1.164 (0.938–1.444)	<0.001	15	1.208 (0.974–1.498)	<0.001
HWE												
YES	24	1.125 (0.982–1.288)	<0.001	20	1.045 (0.871–1.253)	0.412	24	1.069 (0.896–1.275)	<0.001	24	1.103 (0.931–1.308)	<0.001
NO	13	1.280 (1.063–1.541) *	<0.001	13	1.553 (1.018–2.367) *	<0.001	13	1.386 (1.121–1.714) *	0.04	13	1.428 (1.151–1.772) *	0.012

*Significant association; OR: odds ratio; CI: confident intervals; CRC: Colorectal Cancer; EC: Esophageal Cancer; GC: Gastric Cancer; HCC: Hepatocellular Carcinoma; HB: hospital-based; PB: population-based; Large: >500 participants; Small: <500 participants; HWE: Hardy-Weinberg equilibrium; YES: agreement with HWE; NO: disagreement with HWE.

was performed to detect the source of heterogeneity. The results indicated that sample size (P<0.001), HWE (P<0.001), source of control (P<0.001), and cancer types (P=0.03) contributed heterogeneity, while ethnicity (P=0.207) did not. Publication bias was detected by Egger's test and Begg's test, and no evidence of publication bias was found (P=0.133 for Begg's test and P= 0.524 for Egger's test; Figure 4). As shown in Figures 2–4, the study reported by Alpizar-Alpizar W[24] was an outlier. Thus, sensitivity analysis was performed to assess individual study's effect by omitting one study each time. Sensitivity analysis revealed that the pooled results were not affected by the study by Alpizar-Alpizar W et al or any other studies (see supplementary Figure S3 online), indicating our results were stable and reliable.

Discussion

In this meta-analysis, we identified 40 eligible studies, including 7195 cases and 11755 controls. By pooling all eligible studies, we found the variant IL-10 -1082G allele significantly increased the susceptibility to digestive cancer, especially to gastric cancer and among Asian population.

By pooling all eligible studies, we found the IL-10 -1082A>G polymorphism was associated with significantly increased risk of digestive cancer in all comparison models. Then stratified analysis showed that the increased risk was mostly contributed by gastric cancer, since significant association was observed only in gastric cancer and ORs in the sub-groups of gastric cancer were similar with those in overall analysis. It has been proposed that inflammation is a risk factor of tumorigenesis[57]. In the process of chronic gastric inflammation, different types of cytokines are secreted by activated neutrophils and mononuclear cells and altered cytokine levels have been observed[36]. Thus, it is biological plausible that IL-10 polymorphism increased risk of gastric cancer. Sub-group analysis revealed that the IL-10 -1082A>G polymorphism was only associated with gastric cancer and no association was found for other digestive cancers, indicating that the role of IL-10 varied among cancers.

During sub-group analysis for ethnicities, we found ethnicity significantly affect the association between IL-10 -1082A>G polymorphism and digestive cancer risk. Since the variant -1082G allele was only associated with increased risk in Asian population and no significant association was found in Caucasian population. This ethnicity difference is common for meta-analysis and may be explained by different environmental exposure, life style, and genetic background. Of note, since the incidence of gastric cancer was higher in Asian population, most Asian studies were about gastric cancer (19 of 24 studies, as shown in table 1). The higher prevalence of gastric cancer in Asian population might be another explanation for the ethnicity difference.

In the process of statistical analysis, we found the study reported by Alpizar-Alpizar W[24] and colleagues was an outlier. This could be explained by ethnicity difference, since the study was conducted among Latinos. Additionally, the frequency of IL-10 -1082G allele was very low in Alpizar-Alpizar's study[24]. Specifically, the GG and GA genotype was not detected in cases while the GG was not detected in controls and only one participants carried the heterozygote GA genotype in controls (0% in cases and 1.14% in controls), which would led to relatively wide confidence intervals as shown in Figure 2 and Figure 3. It should also be highlighted that this study was conducted in high-risk population, which might be also related with the low frequency of G allele.

In this meta-analysis, we included 40 studies with 18950 participants. The sample size was large enough to provide enough statistical power. Additionally, no publication bias was detected by Egger's test and Begg's test, suggesting our results were unbiased. On the other hand, limitation of this meta-analysis should also be also highlighted. Firstly, heterogeneity was significant in this meta-analysis. Due to the

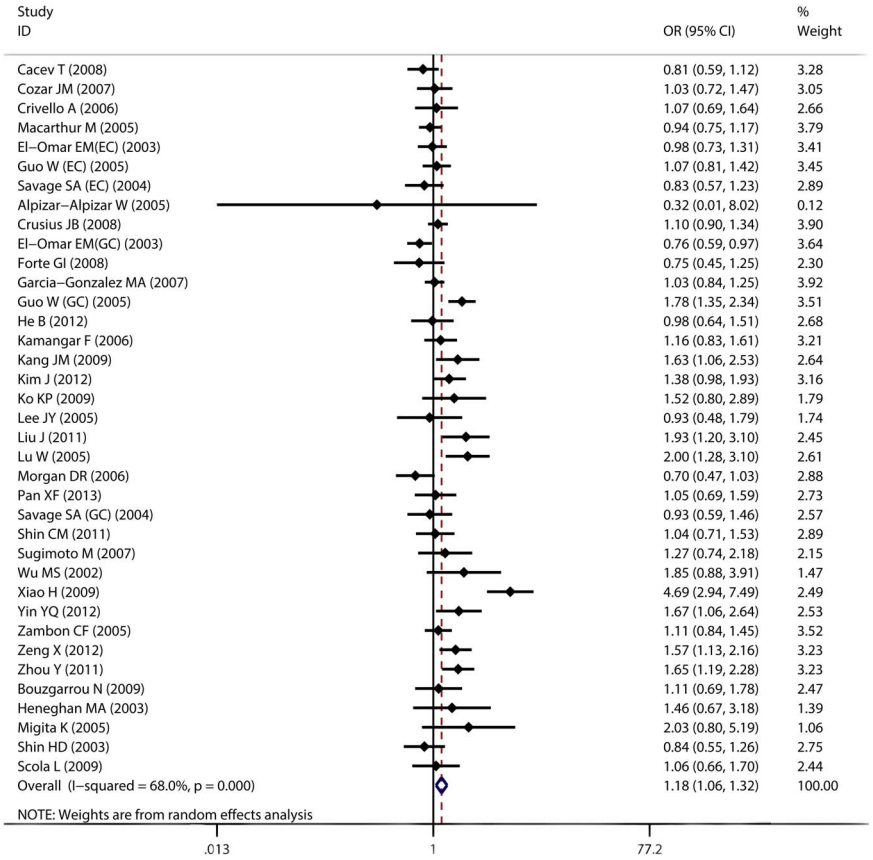

Figure 2 | Forest plot of IL-10 -1082A>G polymorphism and risk of digestive cancer, G vs. A.

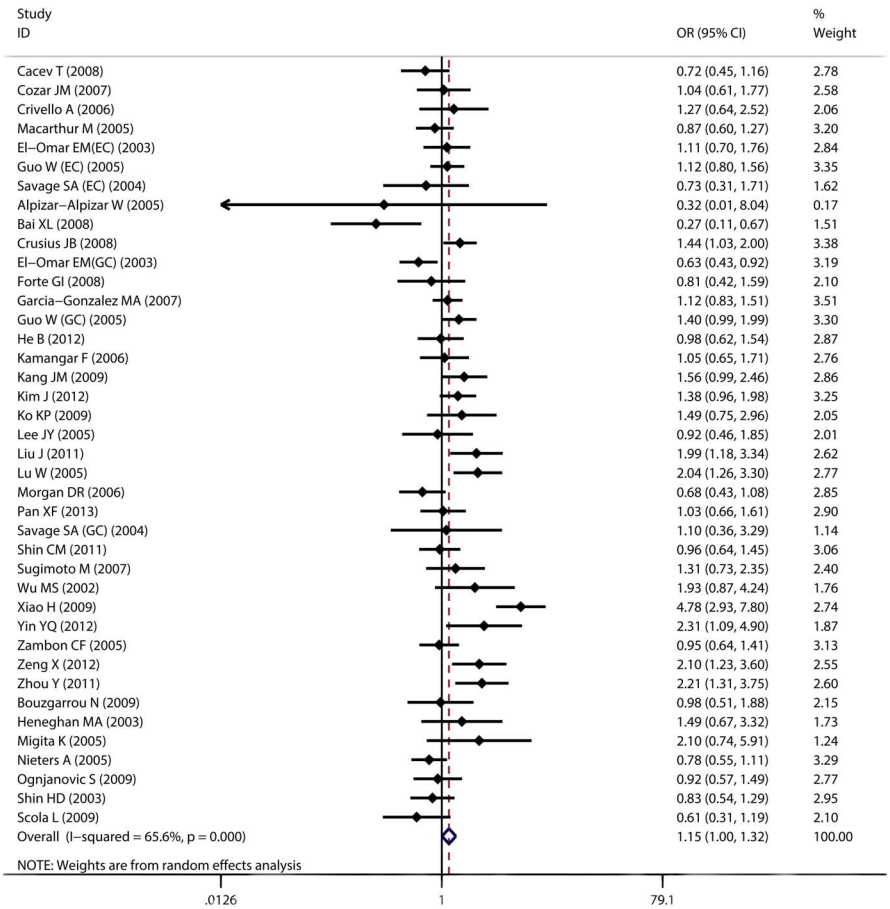

Figure 3 | Forest plot of IL-10 -1082A>G polymorphism and risk of digestive cancer, GGGA vs. AA.

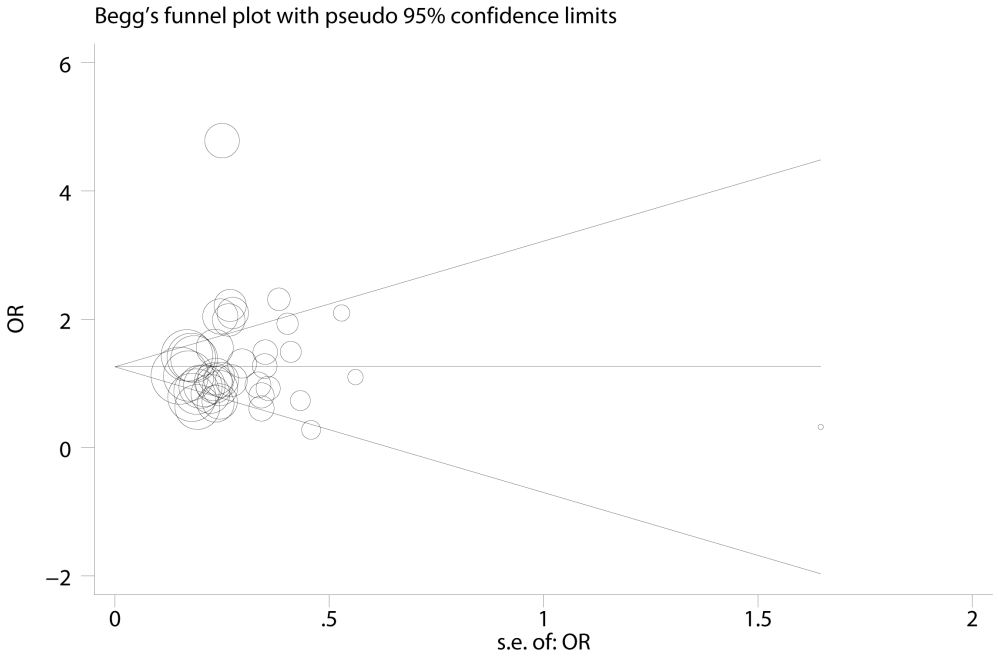

Figure 4 | Funnel plot of IL-10 -1082A>G polymorphism and risk of digestive cancer, G vs. A. Circles represent the weight of studies.

significant heterogeneity, we used random-effects model to calculate the pooled ORs, which could provide stable results. To identify the source of heterogeneity, meta-regression was conducted and revealed that sample size, HWE, source of control, and cancer types were the sources. And stratified analyses were also performed to evaluate the influence of these confounding factors. Secondly, individual data were missed and we could not assess the effects of other factors, like environmental factors, life habit, and family history.

In summary, in this meta-analysis of 40 studies and 18950 participants, we found the variant IL-10 -1082G allele significantly increased susceptibility to digestive cancer, especially for gastric cancer and in Asian population.

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C.L., W.T. and B.L. designed this study; A.Z. and F.L. searched databases and collected full-text papers; C.L., W.T. and B.L., extracted and analyzed data; C.L., W.T., B.L., A.Z. and F.L. wrote the manuscript.

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