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Association of interleukin-10 -1082 A/G (rs1800896) polymorphism with susceptibility to gastric cancer: meta-analysis of 6,101 cases and 8,557 controls

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ABSTRACT – Background – The promoter -1082 A/G (rs1800896) polymorphism of Interleukin-10 (IL-10) gene have been widely reported and considered to have a significant role on gastric cancer risk, but the results are inconsistent. **Objective** – To clarify the association, we conducted a meta-analysis to investigate the associations IL-10 -1082 A/G polymorphism with gastric cancer. **Methods** – Eligible articles were identified by searching databases including PubMed, Web of Science, and Google Scholar up to August 03, 2017. Odds ratios (OR) with corresponding 95% confidence intervals (CIs) were used to assess the association. **Results** – A total of 30 case-control studies with 6,101 cases and 8,557 controls were included in this meta-analysis. Overall, a significant association between IL-10 -1082 A/G polymorphism and gastric cancer risk was observed under the allele model (G vs A: OR=1.305, 95% CI=1.076-1.584; *P*=0.007), heterozygote model and (GA vs AA: OR=1.252, 95% CI=1.252-1.054; *P*=0.011) and dominant model (GG+GA vs AA: OR=1.264, 95% CI=1.053-1.516; *P*=0.012). In the subgroup analysis by ethnicity, increased gastric cancer risk were found in Asians under the allele model (G vs A: OR=1.520, 95% CI=1.172-1.973; *P*=0.002), homozygote model (GG+GA vs AA: OR=1.571, 95% CI=1.023-2.414; *P*= 0.039), heterozygote model (GA vs AA: OR=1.465, 95% CI=1.192-1.801; *P*≤0.001) and dominant model (GG+GA vs AA: OR=1.448, 95% CI=1.152-1.821; *P*=0.002), but not among Caucasian and Latinos populations. **Conclusion** – These results suggested that the IL-10 -1082 A/G (rs1800896) polymorphism might contribute to the gastric cancer susceptibility, especially among Asians.

HEADINGS – Stomach neoplasms. Interleukin-10. Genetic polymorphism. Meta-analysis.

INTRODUCTION

In the recent years, many exciting discoveries regarding the genomics of gastric cancer have been made, but it remains a major health problem as a result of the population growth, ageing, high mortality and poor prognosis for this disease[1-3]. The incidence of gastric cancer varies considerably according to age, gender, socioeconomic conditions and ethnicity, and despite some of the highest risk populations are in Asian countries such as Japan, Korea and China, other Asian countries present relatively low rates[4-6].

To date, the etiology of gastric cancer is still not fully understood[7]. It is well known that environmental factors such as dietary habits, *Helicobacter pylori* (*H. pylori*) infection, tobacco smoking, and alcohol consumption are more important than genetics in the development and progression of gastric cancer[1-3,8]. However, only 1%-5% of individuals with the bacteria actually develop gastric cancer and the pathogenesis is dependent on bacterial strain virulence, host genetic susceptibility and environmental factors[9]. Among human cancers, gastric carcinogenesis appears to be a complex multistep processes. Diverse array of genetics factors including functional polymorphisms, chromosomal instability, microsatellite instability, promoter methylation, and abnormal microRNA expression play important roles in gastric cancer carcinogenesis[10].

Interleukin-10 (IL-10) is an important immunoregulatory cytokine which plays a key role in controlling the balance between cellular and humoral immune responses[11]. Previous studies have presented evidence that IL-10 may inhibit tumor development and progression[12]. It has been reported that the -1082 A/G polymorphism at promoter region of the IL-10 gene may influence this cytokine production and to be associated with the risk of different malignancies including cervical cancer[13], esophageal cancer, nasopharyngeal cancer, oral cancer[14], colon cancer[15], and hepatocellular carcinoma[16]. However, the precise mechanism by which the between IL-10 polymorphisms may modulate cancer progression remains unknown[11,12].

Over the past 2 decades, several epidemiological studies have reported the role of IL-10 -1082 A/G (rs1800896) polymorphism

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in gastric cancer development[17]. However, the results were inconsistent rather than conclusive, as result of the small sample size in the most of studies. While meta-analysis is considered a powerful tool for combining data from all eligible studies with more statistical power and obtaining precise estimates. Therefore, we conducted a meta-analysis of all available case-control studies to derive a more precise estimation of the association between of IL-10 -1082 A/G (rs1800896) polymorphism and gastric cancer risk. In addition, current meta-analysis analyzed available data to explore any role of ethnicity and studies quality on the association of IL-10 -1082 A/G (rs1800896) polymorphism in gastric cancer risk.

METHODS

Study identification and selection

A systematic literature search was performed for the relevant available studies published in PubMed, Web of Science, Chinese Biomedical Literature database, China National Knowledge Infrastructure database and google scholar up to August 1, 2017. The search strategy identified the eligible studies using the following keywords: "Interleukin-10", "IL-10", "-1082 A/G", "rs1800896", "polymorphism", "genotype", "variant", "mutation", "gastric cancer", and "stomach cancer". Additionally, the reference lists of retrieved studies, review articles, clinical trials and previous meta-analyses, were manually searched for collecting more relevant studies that was missed in the electronic search.

Eligibility criteria

The following inclusion criteria were used in selecting literature for meta-analysis: (a) evaluation of the association between IL-10 -1082 A/G (rs1800896) polymorphism and gastric cancer; (b) studies with case–control or cohort design; (c) sufficient published data for calculating odds ratios (ORs) with their 95% confidence intervals (95% CIs); and (d) publications in English and Chinese. If multiple studies from the same data were available, only the most recent, larger sample size or complete study was selected. The studies were excluded (a) only abstracts, review articles, case reports, letter to editors or editorials; (b) not designed as case-control or cohort studies; (c) not offering essential data; (d) control group not including healthy induvial; (e) duplicate of previous published articles.

Data extraction and quality assessment

The following data of eligible studies were collected by two investigators independently if available: first author, year of publication, country origin, ethnicity, total number of cases and controls, the frequencies of genotypes, genotyping technique, minor allele frequencies (MAFs), *P*-value for Hardy–Weinberg equilibrium (HWE). In case of disagreement, consensus was obtained by discussion, or a third author would assess these articles. The quality of selected studies was tested by the confirmation of HWE in control groups, and studies without the confirmation of HWE in controls were defined as low-quality studies, while studies with the confirmation of HWE in controls were defined as high-quality studies.

Statistical analysis

The strength of the association between the IL-10 -1082 A/G (rs1800896) polymorphism and gastric cancer risk was measured by crude odds ratios (ORs) with 95% confidence intervals (CIs). Pooled estimates of the OR were obtained by calculating a weighted average of OR from each study. The statistical significance of the pooled OR was determined using the Z-test. The meta-analysis examined the IL-10 -1082 A/G (rs1800896) polymorphism association under the allele model (G vs A), the homozygote model (GG vs AA), homozygote model (GA vs AA), heterozygote model and (GA vs AA), dominant model (GG+GA vs AA), and recessive model (GG vs GA+AA). The Q-statistic and the I^2-statistic were used to assess the heterogeneity between studies in the meta-analysis. I^2 was a value describe the degree of heterogeneity between studies, where 0-25% indicated no observed heterogeneity and larger values showed increasing heterogeneity, with 25%-50% regarded as low, 50%-75% as moderate, and 75%–100% as high[18,19]. A *P*-value greater than 0.10 for the Q-statistic indicates a lack of heterogeneity between studies, so the pooled OR estimate of the included studies was calculated by the fixed-effects model (Mantel-Haenszel method)[20]. Otherwise, the random-effects model (the DerSimonian and Laird method) was used[21]. The heterogeneity between studies was adjusted by subgroup analysis, HWE status and meta-regression. Departure from Hardy-Weinberg equilibrium (HWE) in controls was tested by the chi-square test, and a *P*-value <0.05 was considered significant. One-way sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual dataset on the pooled OR. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias[22,23]. To ensure reliability and accuracy of the results, two investigators entered the data into the software independently and reached a consensus. All statistical analyses were performed by using Comprehensive Meta-Analysis software version 2.20 (Stata Corp., College Station, TX, USA). All the *P* values were two-sided, and a *P* value less than 0.05 was considered statistically significant.

RESULTS

Based on the search criteria and manual search of references cited in the published case-control studies and meta-analyses, 67 individual articles were found. After screening the titles and abstracts, 29 articles were excluded because they were not relevant to the association of IL-10 -1082 A/G polymorphism with risk of gastric cancer. After reading the full texts of the remaining 37 articles, we found one article had not sufficient data of genotype for calculating OR and 95% CI, four articles were meta-analyses, and two articles were reviews. Finally, a total of 30 studies[4-7,10-14,16-20,24-39] published from 2002 and 2015 with 6,101 cases and 8,557 controls met our inclusion criteria. The main characteristics of these studies were listed in TABLE 1. Among the 31 case-control studies, there were 21 studies of Asians[24-30,33-46], six studies of Caucasians[47-52], and three studies of Latinos[53,54,32] descendants. The countries of these studies included China, Korea, Japan, Taiwan, India, USA, Italy, Finland, Spain, Romania, Costa Rica, Honduras and Chile. All the genotype distributions of controls were in agreement with HWE for IL-10 -1082 A/G polymorphism except for eleven studies[27,29,30,34,38,41,42,45-47,49]. Twenty of 31 studies were in accordance with HWE and were therefore defined as high-quality studies (TABLE 1).

Quantitative data synthesis

The main results of this meta-analysis were listed in TABLE 2

TABLE 1. Main characteristics of studies included in this meta-analysis

First author	Country (Ethnicity)	Case	Control	Cases					Controls					MAFs	HWE
				Genotypes			Allele		Genotypes			Allele			
-1082A/G (rs1800896)		6101	8557	AA	AG	GG	A	G	AA	AG	GG	A	G		
Wu 2002[37]	China (Asian)	150	220	135	14	1	284	16	208	11	1	427	13	0.029	0.057
Wu 2003[38]	China (Asian)	220	230	195	23	2	413	27	217	11	2	445	15	0.032	0.002
El-Omar 2003[48]	USA (Caucasian)	314	210	120	133	61	373	255	59	103	48	221	199	0.473	0.812
Savage 2004[34]	China (Asian)	84	382	4	20	60	28	140	20	81	284	120	644	0.842	≤0.001
Lee 2005[28]	Korea (Asian)	122	120	104	17	1	225	19	101	18	1	220	20	0.083	0.842
Lu 2005[30]	China (Asian)	250	300	201	43	6	445	55	268	29	3	565	35	0.058	0.037
Guo 2005[42]	China (Asian)	179	443	93	56	3	285	73	267	164	12	698	188	0.212	0.023
Zambon 2005[52]	Italy (Caucasian)	120	644	48	56	25	141	99	232	326	86	790	498	0.386	0.087
Alpízar-Alpízar 2005[53]	Costa Rica (Latinos)	45	44	45	0	0	90	0	43	1	0	87	1	0.011	0.939
Morgan 2006[32]	Honduras (Latinos)	170	162	121	42	7	284	56	101	49	11	253	71	0.220	0.145
Kamangar 2006[51]	Finland (Caucasian)	112	208	38	47	27	123	101	72	96	37	244	172	0.414	0.613
Sugimoto 2007[36]	Japan (Asian)	105	168	78	26	0	184	26	134	34	0	302	34	0.101	0.144
García 2007[50]	Spain (Caucasian)	404	404	123	204	77	450	358	133	189	82	455	353	0.436	0.322
Bai 2008[40]	China (Asian)	111	111	89	22 (AG+GG)		-	-	104	7 (AG+GG)		-	-	-	-
Forte 2008[49]	Italy (Caucasian)	42	185	21	16	5	58	26	83	66	36	235	135	0.364	≤0.001
Kang 2009[44]	Korea (Asian)	335	335	281	49	4	613	57	289	35	0	634	36	0.054	0.304
Ko 2009[25]	Korea (Asian)	84	336	67	12	1	153	15	276	35	1	632	40	0.059	0.921
Xiao 2009[39]	China (Asian)	220	624	176	41	3	393	47	593	31	0	1208	40	0.032	0.524
Zhou 2008[46]	China (Asian)	150	150	29	62	59	120	180	52	53	45	157	143	0.476	≤0.001
Shin 2011[35]	Korea (Asian)	632	237	534	91	7	1159	105	199	38	0	436	38	0.080	0.179
Liu 2011[29]	China (Asian)	234	243	189	39	6	417	51	217	23	3	457	29	0.059	0.014
He 2012[43]	China (Asian)	196	248	154	42	0	350	42	194	54	0	442	54	0.108	0.054
Zeng 2012[45]	China (Asian)	151	153	27	60	64	114	188	48	53	52	149	157	0.513	≤0.001
Kim 2012[23]	Korea (Asian)	495	495	416	72	7	904	86w	435	56	1	932	58	0.058	0.564
Chand-Bhayal 2012[41]	India (Asian)	100	132	47	35	18	129	71	40	50	42	130	134	0.507	0.005
Pan 2013[33]	China (Asian)	308	308	263	41	4	567	49	264	41	3	596	47	0.076	0.329
Kuo 2014[27]	Taiwan (Asian)	358	358	235	101	22	571	145	281	67	10	629	87	0.121	0.019
Hormazabal 2014[54]	Chile (Latinos)	147	172	79	54	14	212	82	88	71	13	247	97	0.282	0.799
Burada 2010[47]	Romania (Caucasian)	63	78	9	54	0	72	54	12	66	0	90	66	0.423	≤0.001
Kumar 2015[26]	India (Asian)	200	250	74	96	30	244	156	85	122	43	464	36	0.071	0.945

MAF: minor allele frequencie; HWE: Hardy–Weinberg equilibrium.

TABLE 2. The meta-analysis of IL-10 -1082 A/G polymorphism and gastric cancer risk

Subgroup	Study number	Genetic model	Type of model	Heterogeneity		Odds ratio				Publication Bias	
				I^2 (%)	P_H	OR	95% CI	Z_{test}	P_{OR}	P_{Beggs}	P_{Eggers}
Overall	29	G vs. A	Random	85.89	≤0.001	1.305	1.076-1.584	2.701	0.007	0.398	0.393
	25	GG vs. AA	Random	52.67	0.001	1.225	0.925-1.622	1.416	0.157	0.107	0.118
	29	GA vs. AA	Random	67.95	≤0.001	1.252	1.252-1.054	2.555	0.011	0.338	0.438
	30	GG+GA vs. AA	Random	74.13	≤0.001	1.264	1.053-1.516	2.517	0.012	0.253	0.483
	25	GG vs. GA+ AA	Random	39.20	0.024	1.150	0.929-1.425	1.281	0.200	0.107	0.071
By ethnicity											
Caucasian	6	G vs. A	Fixed	27.54	0.228	0.975	0.867-1.096	-0.427	0.669	1.000	0.911
	5	GG vs. AA	Fixed	44.94	0.123	0.975	0.767-1.239	-0.208	0.835	1.000	0.814
	6	GA vs. AA	Fixed	13.69	0.327	0.915	0.759-1.104	-0.929	0.353	0.425	0.867
	6	GG+GA vs. AA	Fixed	32.65	0.191	0.975	0.817-1.164	-0.280	0.780	0.452	0.916
	5	GG vs. GA+ AA	Random	52.81	0.076	1.048	0.847-1.297	0.434	0.664	1.000	0.995
Asian	21	G vs. A	Random	87.13	≤0.001	1.520	1.172-1.973	3.152	0.002	0.770	0.860
	18	GG vs. AA	Random	53.70	0.004	1.571	1.023-2.414	2.063	0.039	0.225	0.198
	20	GA vs. AA	Random	67.76	≤0.001	1.465	1.192-1.801	3.645	≤0.001	0.314	0.272
	21	GG+GA vs. AA	Random	76.34	≤0.001	1.448	1.152-1.821	3.173	0.002	0.349	0.400
	18	GG vs. GA+ AA	Random	40.62	0.038	1.290	0.934-1.781	1.547	0.122	0.129	0.056
Latinos	3	G vs. A	Fixed	0.00	0.375	0.843	0.651-1.091	-1.298	0.194	1.000	0.665
	2	GG vs. AA	Fixed	36.06	0.211	0.862	0.460-1.613	-0.466	0.641	NA	NA
	3	GA vs. AA	Fixed	0.00	0.766	0.774	0.553-1.083	-1.494	0.135	0.296	0.442
	3	GG+GA vs. AA	Fixed	0.00	0.609	0.786	0.572-1.078	-1.493	0.135	1.000	0.604
	2	GG vs. GA+ AA	Fixed	33.01	0.222	0.944	0.512-1.743	-0.183	0.855	NA	NA
By studies quality											
High quality	18	G vs. A	Random	88.61	≤0.001	1.336	1.016-1.756	2.071	0.038	0.129	0.361
	16	GG vs. AA	Random	43.12	0.034	1.225	0.892-1.683	1.253	0.210	0.052	0.021
	19	GA vs. AA	Random	71.94	≤0.001	1.187	0.962-1.465	1.596	0.110	0.441	0.699
	21	GG+GA vs. AA	Random	73.11	≤0.001	1.150	0.929-1.424	1.286	0.198	0.263	0.570
	16	GG vs. GA+ AA	Fixed	29.33	0.130	1.060	0.890-1.263	0.656	0.512	0.052	0.015
Low quality	10	G vs. A	Random	79.54	≤0.001	1.260	0.968-1.641	1.721	0.085	0.755	0.790
	10	GG vs. AA	Random	66.60	0.001	1.268	0.754-2.134	0.894	0.371	0.720	0.554
	11	GA vs. AA	Random	54.98	0.014	1.460	1.121-1.902	2.806	0.005	0.436	0.848
	12	GG+GA vs. AA	Random	76.86	≤0.001	1.449	1.033-2.033	2.150	0.032	0.450	0.854
	10	GG vs. GA+ AA	Random	52.26	0.026	1.109	0.770-1.597	0.555	0.579	0.858	0.932

and FIGURE 1A, 1B. Overall, there was a significant association between IL-10 -1082 A/G polymorphism and gastric cancer in overall under the allele model (G vs A: OR=1.305, 95% CI=1.076-1.584; *P*=0.007, FIGURE 1A), the heterozygote model (GA vs AA: OR=1.252, 95% CI=1.252-1.054; *P*=0.011) and the dominant model (GG+GA vs AA: OR=1.264, 95% CI=1.053-1.516; *P*=0.012, FIGURE 1B), but not under the homozygote model (GG vs AA: OR=1.225, 95% CI=0.925-1.622; *P*=0.157) and the recessive model (GG+GA vs AA: OR=1.150, 95% CI=0.929-1.425; *P*=0.200).

Subgroup analysis of Asians showed that there was a significant association between IL-10 -1082 A/G polymorphism and increased risk of gastric cancer under the allele model (G vs A: OR=1.520, 95% CI=1.172-1.973; *P*=0.002), the homozygote model (GG vs AA: OR=1.571, 95% CI=1.023-2.414; *P*=0.039), the heterozygote model and (GA vs AA: OR=1.465, 95% CI=1.192-1.801; *P*≤0.001) and the dominant model (GG+GA vs AA: OR=1.448, 95% CI=1.152-1.821; *P*=0.002). However, subgroup analysis of Caucasians and Latinos showed that there was no association between IL-10 -1082 A/G polymorphism and increased risk of gastric cancer in the Caucasians and Latinos populations (TABLE 2).

Subgroup analysis of studies with high quality showed that there was a significant association between IL-10 -1082 A/G polymorphism and increased risk of gastric cancer only under the allele model (OR=1.336, 95% CI=1.016-1.756, *P*=0.038, TABLE 2). However, in the subgroup analysis of studies with low quality, there was still a significant association between IL-10 -1082 A/G polymorphism and increased risk of gastric cancer under heterozygote model (GA vs AA: OR=1.460, 95% CI=1.121-1.902; *P*=0.005) and dominant model (GG+GA vs AA: OR=1.449, 95% CI=1.033-2.033; *P*=0.032) (TABLE 2).

Test of heterogeneity and sensitivity analysis

The heterogeneity test showed that there was significant between-study heterogeneity in terms of the IL-10 -1082 A/G polymorphism in all five genetic models (TABLE 2). Then, we used a meta-regression analysis to explore the source of heterogeneity by Ethnicity and quality of studies. Results showed that ethnicity contribute to substantial heterogeneity. Furthermore, we performed sensitivity analyses to assess the influence of each individual study on the pooled ORs by sequential omission of individual studies, such as the study that did not conform to HWE. However, the corresponding pooled ORs were not materially altered by removing any individual study. Moreover, in all tests the I^2 value for heterogeneity did not reduced. Therefore, the sensitivity analysis confirmed that the results of this meta-analysis were statistically reliable and stable.

Study name	Odds ratio	Lower limit	Upper limit	Z-Value	*P*-Value	Relative weight
Wu 2002[37]	1.850	0.877	3.906	1.615	0.106	2.62
Wu 2003[38]	1.939	1.017	3.697	2.012	0.044	2.91
El-Omar 2003[48]	0.759	0.592	0.974	-2167	0.030	4.02
Savage 2004[34]	0.932	0.594	1.461	-0.308	0.758	3.49
Lee 2005[28]	0.929	0.483	1.788	-2.221	0.825	2.88
Lu 2005[30]	1.995	1.283	3.103	3.066	0.002	3.52
Guo 2005[42]	0.951	0.702	1.288	-0.325	0.745	3.89
Zambon 2005[52]	1.114	0.841	1.474	0.753	0.451	3.95
Alpízar-Alpízar 2005[53]	0.322	0.013	8.018	-0.690	0.490	0.33
Morgan 2006[32]	0.703	0.476	1.037	-1778	0.075	3.67
Kamangar 2006[51]	1.165	0.839	1.616	0.913	0.361	3.83
Sugimoto 2007[36]	1.255	0.730	2.159	0.821	0.412	3.22
García 2007[50]	1.025	0.730	2.159	0.821	0.412	4.12
Forte 2008[49]	0.780	0.469	1.298	-0.956	0.339	3.32
Kang 2009[44]	1.638	1.063	2.522	2.239	0.025	3.54
Ko 2009[25]	1.549	0.834	2.877	1.385	0.166	2.99
Xiao 2009[39]	3.612	2.334	5.590	5.763	0.000	3.53
Zhou 2008[46]	1.647	1.192	2.276	3.022	0.003	3.84
Shin 2011[35]	1.039	0.706	1.531	0.196	0.845	3.67
Liu 2011[29]	1.927	1.199	3.089	2.709	0.007	3.42
He 2012[43]	0.982	0.641	1.505	-8.082	0.934	3.56
Zeng 2012[45]	1.565	1.133	2.162	2.717	0.007	3.84
Kim 2012[23]	1.529	1.082	2.159	2.409	0.016	3.78
Chand-Bayal 2012[41]	0.534	0.366	0.778	-3262	0.001	3.70
Pan 2013[33]	1.046	0.690	1.587	0.213	0.832	3.59
Kuo 2014[27]	1.836	1.375	2.451	4.121	0.000	3.93
Hormazabal 2014[54]	0.985	0.696	1.393	-0.086	0.932	3.78
Burada 2010[47]	1.023	0.636	1.644	0.093	0.926	3.42
Kumar 2015[26]	8.240	5.556	12.222	10.488	0.000	3.65
	1.305	1.076	1.584	2.701	0.007	

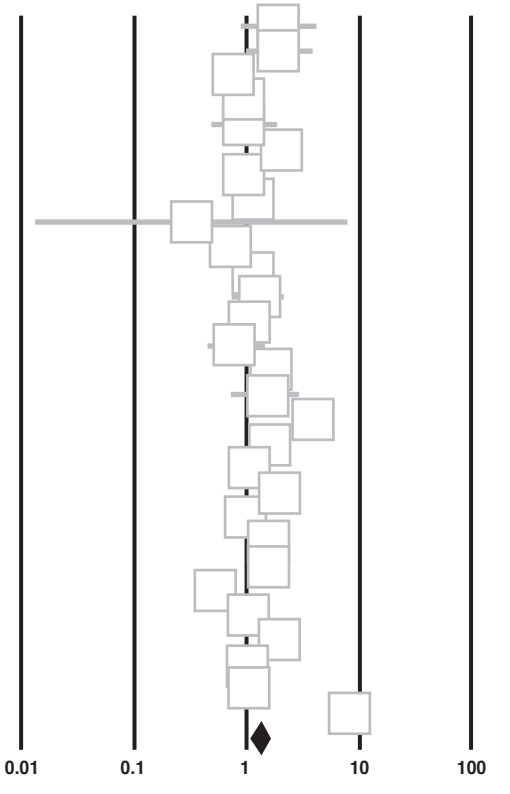

FIGURE 1A. Forest plot of gastric cancer risk associated with the IL-10 -1082 A/G (rs1800896) polymorphism. **A.** Allele model (G vs A) and **B.** Dominant model (GG+GA vs. AA). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

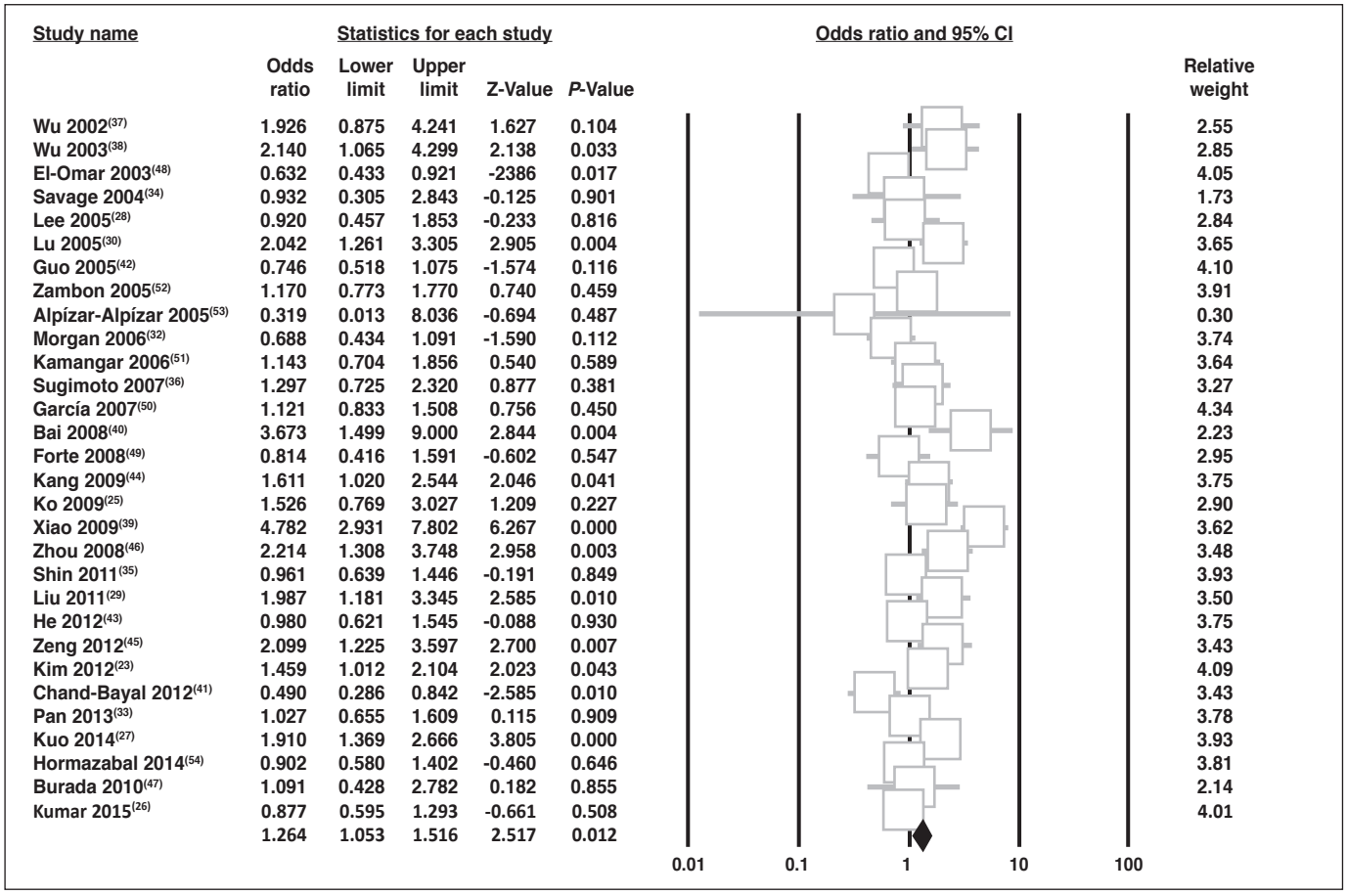

FIGURE 1B. Forest plot of gastric cancer risk associated with the IL-10 -1082 A/G (rs1800896) polymorphism. **A.** Allele model (G vs A) and **B.** Dominant model (GG+GA vs. AA). The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

Publication bias

Begg's funnel plot and Egger's test were used to assess the potential publication bias in the literature. However, the shape of funnel plots did not reveal any evidence of funnel plot asymmetry (FIGURE 2A, 2B). Then, the Egger's test was used to provide statistical evidence for funnel plot symmetry. The results also provided statistical evidence for the absence of publication bias.

DISCUSSION

To date, several case-control studies have been reported to evaluate the association between IL-10 -1082 A/G polymorphism and gastric cancer. However, the results were inconsistent and most studies in Caucasian and Latinos populations failed to identify an association with gastric cancer. The current study was not the first

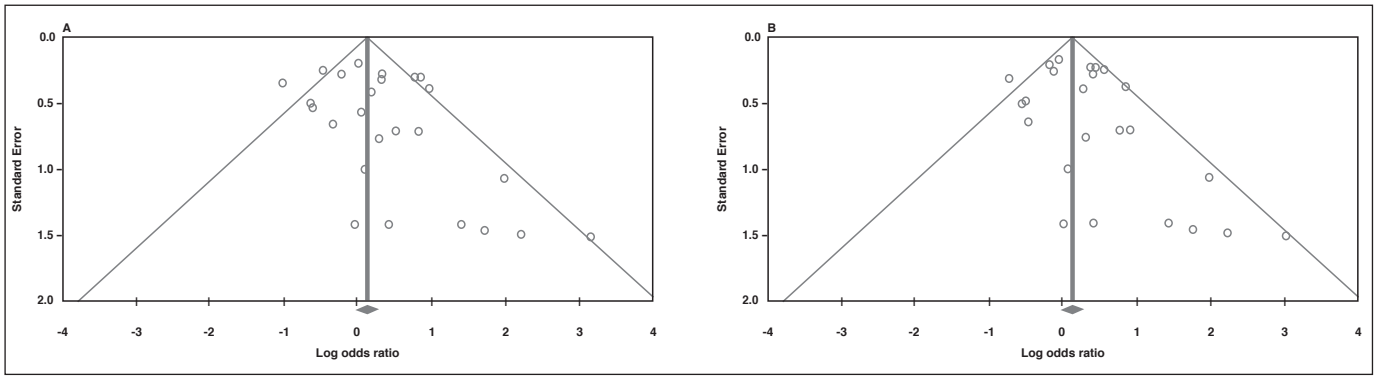

FIGURE 2. Begg's funnel plot of publication bias test. **A**. The homozygote model (GG vs AA), **B**. The recessive model (GG vs Ga+ AA). Each point representes a separete study for the indicated association. Log (OR),natural logarithm of OR. Horizontal line, mean effect size.

meta-analysis aimed to evaluate the associations between IL-10 -1082 A/G polymorphism and gastric cancer. However, the current meta-analysis was the most comprehensive assessment of the association between IL-10 -1082 A/G polymorphism and gastric cancer, which extended the previous meta-analyses with a larger sample size and different subgroups. Additionally, we believe the current meta-analysis is most accurate meta-analysis on the association due to the subgroup analysis by studies quality according to the Hardy–Weinberg equilibrium (HWE) status.

A total of 30 studies with a total of 6431 controls and 3631 cases were eligible for the meta-analysis of IL-10 -1082 A/G polymorphism and gastric cancer. In this meta-analysis, a significant association of the of IL-10 -1082 A/G polymorphism with gastric cancer risk was found under the allele model (G vs A: OR=1.305, 95% CI=1.076-1.584; *P*=0.007), heterozygote model and (GA vs AA: OR=1.252, 95% CI=1.252-1.054; *P*=0.011), dominant model (GG+GA vs AA: OR=1.264, 95% CI=1.053-1.516; *P*=0.012), and in Asians. The inconsistent results between Asians and other ethnicity (Caucasians and Latinos) on subgroup analysis partly may be caused by genetic diversity in different ethnicities. Furthermore, as gastric cancer is a multifactorial disease, except genetic factors, environmental factors play important roles in the pathogenesis of gastric cancer.

We found that the results of our meta-analysis are consistent with a meta-analysis of 20 case-control studies with a total of 3631 cases and 6431 controls published in 2012 by Ni et al. to examine the relationship between IL-10 -1082 A/G polymorphism and gastric cancer[17]. They have found that the IL-10 -1082 A/G polymorphism was associated with susceptibility to gastric cancer infection in Asians. However, their study had some limitations should be mentioned. First, they wrongly not included a study by Bai et al., 2008 because they reported only the number of combined group GG+GA rather than the number of genotype GG and GA. Second, they have excluded all studies that deviated from HWE, which it seems publication bias have been occurred at the start of their meta-analysis. However, meta-analyses should report both the magnitude and the statistical significance of deviation from HWE[40]. There is currently no consensus for whether to select eligible studies according to HWE status. In the current meta-analysis the results was different by HWE status or studies quality, it is suggested that the analysis with studies departed from HWE may be more reliable. Third, they have performed some subgroup analyses by sample size and publication before or after 2005, which we suggested unnecessary to do these subgroup analyses. Fourth, their results reliability and the number of studies are considerably smaller than that needed to receive the robust conclusions.

Between-study heterogeneity is inevitable in a meta-analysis[55]. Thus, one of the most important goals of the meta-analysis is to identify the source of heterogeneity[56]. Basically, between-studies variability and variability due to sampling error are main sources of heterogeneity in a set of studies in a meta-analysis[19,31,55,56]. The between-study heterogeneity in the current meta-analysis existed in overall under all genetic models and subgroup analyses in Asians. There was no significant heterogeneity after subgroup analyses among Caucasians and Latinos population. Moreover, after removing the study deviating from HWE, the heterogeneity did not disappear. Thus, the results revealed that studies in Asians may be the major source of heterogeneity in overall models.

The current meta-analysis had several strengths. Most importantly, this is the biggest and most recent meta-analysis of the association between IL-10 -1082 A/G polymorphism and gastric cancer. Therefore, this was more powerful than previous meta-analysis. In addition, a subgroup analysis among mixed population and HWE status was conducted and demonstrated that the IL-10 -1082 A/G polymorphism not significantly associated with gastric cancer risk in Caucasian and mixed populations. Third, we did not detect any publication bias indicating that the whole pooled results should be unbiased.

Despite the clear strength of our study including large sample sizes, some limitations of this meta-analysis should be acknowledged. Second, the overall OR was based on individual unadjusted ORs, and some important confounding factors, such as age, gender, dietary, *Helicobacter pylori* (*H. pylori*) infection, tobacco smoking, and alcohol consumption, gastric cancer site (cardia and noncardia) and histological type must be adjusted for. Third, although the funnel plots and Egger's tests showed that publication bias did not affect our results, only published studies published in English or Chinese with sufficient data were included, thus, publication bias may have occurred at the start of current meta-analysis. Finally, lack of original data from origin data in the including studies limited our evaluation of potential gene-gene and gene-environment interactions and even different polymorphic loci of the same gene which may modulate the gastric cancer susceptibility.

In conclusion, this meta-analysis suggests that IL-10 -1082 A/G (rs1800896) polymorphism may be associated with increased gastric cancer risk. Moreover, further studies estimating the effect of gene-gene and gene-environment interactions are necessary to better understanding of the association between the IL-10 -1082 A/G (rs1800896) polymorphism and risk of gastric cancer.

Authors' contributions

Namazi A, Forat-Yazdi M and Abolbaghaei SM conceived and research design. Farahnak S, Nasiri R, and Foroughi E selected the articles. Neamatzadeh H and Jafari M performed data analysis. The manuscript was drafted by Namazi A, Forat-Yazdi M and Neamatzadeh H critically reviewed and discussed with the other co-authors. All the authors read and approved the final manuscript.

Namazi A, Forat-Yazdi M, Jafari M, Farahnak S, Nasiri R, Foroughi E, Abolbaghaei SM, Neamatzadeh H. Associação de interleucina-10-1082 A/polimorfismo G (rs1800896) com suscetibilidade a câncer gástrico: meta-análise de 6.101 casos e 8.557 controles. Arq Gastroenterol. 2018;55(1):33-40.

RESUMO – **Contexto** – O promotor-1082 A/polimorfismo G (rs1800896) do gene da interleucina-10 (IL-10) é amplamente relatado e considerado por ter um papel significativo no risco de câncer gástrico, porém os resultados são inconsistentes. **Objetivo** – Para esclarecer melhor esta associação, realizou-se uma meta-análise para investigar as associações de IL-10-1082 A/polimorfismo G com câncer gástrico. **Métodos** – Artigos elegíveis foram identificados através de pesquisa de bases de dados PubMed, Web of Science e Google Scholar até 3 de agosto de 2017. Razões de possibilidades (OR) com intervalo de confiança de 95% correspondente (CIs) foram usados para avaliar a associação. **Resultados** – Um total de 30 estudos de caso-controle, 6.101 casos e com 8.557 controles foram incluídos nesta meta-análise. Em geral, uma associação significativa entre IL-10-1082 A/G polimorfismo e risco de câncer gástrico foi observada sob o modelo de alelo (G vs A: OR=1.305, 95% CI=1.076-1.584; *P*=0.007), no modelo heterozigoto (GA vs AA: OR=1.252, 95% CI=1.252-1.054; *P*=0.011) e modelo dominante (GG+GA vs AA: OR=1.264, 95% CI=1.053-1.516; *P*=0.012). Na análise de subgrupo pela etnia, foi encontrado risco aumentado de câncer gástrico em asiáticos sob o modelo de alelo (G vs A: OR=1.520, 95% CI=1.172-1.973; *P*=0.002), modelo heterozigoto (GG+GA vs AA: OR=1.571, 95% CI=1.023-2.414; *P*= 0.039), e modelo dominante (GG+GA vs AA: OR=1.448, 95% CI=1.152-1.821; *P*=0.002), mas não entre a população caucasiana e latina. **Conclusão** – Estes resultados sugeriram que a IL-10-1082 A/polimorfismo G (rs1800896) pode contribuir para a suscetibilidade de câncer gástrico, especialmente entre os asiáticos.

DESCRITORES – Neoplasias gástricas. Interleucina-10. Polimorfismo genético. Metanálise.

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