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Association of the *IL6* polymorphism rs1800796 with cancer risk: a meta-analysis

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ABSTRACT. The human *IL6* [interleukin 6 (interferon, beta 2)] gene encodes IL-6, a cytokine which not only plays regulatory roles in inflammation, but may be also involved in the progression of cancer. Rs1800796 is a single nucleotide polymorphism (SNP) in the promoter region of *IL6*, and is associated with IL-6 production. A number of studies have been carried out to determine whether this SNP is associated with cancer risk. However, the results are inconsistent due to small sample sizes of individual studies and limited statistical power. Therefore, to evaluate the overall effect on all investigated cancer types, we conducted a meta-analysis by combining all available studies. Nineteen eligible case-control studies including 23,030 subjects (9,985 cases and 13,045 controls) were included for this meta-analysis. Our study demonstrates that rs1800796 is significantly associated with cancer risk in three genetic models (allele G *vs* allele C, pooled OR = 1.182, P = 0.009; CG + GG *vs* CC, pooled OR = 1.333, P = 0.006; CG *vs* CC, pooled OR = 1.323, P = 0.007).Our meta-analysis suggests that

polymorphism rs1800796 within the *IL6* gene may be a potential risk factor for cancer.

Key words: rs1800796; Interleukin 6; Cancer risk; Meta-analysis

INTRODUCTION

Inflammation is a fundamental innate immune response that arises due to perturbed tissue homeostasis. There is accumulating evidence which suggest that persistent state of inflammation is associated with progression of cancer (Coussens and Werb, 2002). Cytokines, which are secreted by virtually all immune cells as well as various other nucleated cells, play regulatory roles in the immune response pathways, and are key signaling molecules in inflammation (Lowry, 1993). The relationship between cytokines and cancer has been explored by researchers from various fields. Among those, interleukin-6 (IL-6), which is encoded by the *IL6 (interleukin 6)* gene, has drawn the attention of researchers. Accumulating evidence demonstrate high serum concentration of IL-6 is correlated with negative clinical prognosis in different types of cancer (Lippitz, 2013).

The human *IL6* gene is located on chromosome 7p21, and includes five exons and four introns (Ray et al., 1990). Two single nucleotide polymorphisms (SNPs) on the promoter region of *IL6*, rs1800795 (-174G/C) and rs1800796 (-572C/G), have been identified to be associated with *IL6* production (Fishman et al., 1998). Furthermore, a large number of genetic studies have investigated the association of these two SNPs with risk of cancer. In the case of rs1800795, its association with risk of cancer has been published in a previous meta-analysis (Liu et al., 2012). However, while a number of studies have individually assessed the relationship between rs1800796 (-572G/C, also known as -634G/C) and different types of cancer, no meta-analysis has been published with a compilation of these studies. In the present study, we have conducted a meta-analysis combing all reports together to offer a conclusive assessment on whether rs1800796 increases the risk of cancer.

MATERIAL AND METHODS

This meta-analysis was conducted according to the PRISMA statement (Preferred reporting items for systematic reviews and meta-analyses) and the guidelines presented in “Systematic Reviews of Genetic Association Studies” (Moher et al., 2009; Sagoo et al., 2009) including search strategy, selection criteria, data extraction and data analysis.

Literature Search

The databases PubMed, Elsevier, EMBASE, Web of Knowledge, and Wiley Online Library were searched for all articles with the following search terms: (interleukin 6 OR interleukin-6 OR interleukin6 OR *IL-6* OR *IL6* OR *IL 6*) AND (polymorphism OR polymorphisms) AND (cancer OR tumor or carcinoma), last search update: March, 2015. Publication date and publication language were not restricted in our search. Reference lists were examined manually to further identify potentially relevant studies. Published genome-wide association studies (GWAS) on lung cancer (phs000093.v2.p2), breast cancer (phs000147.v1.p1), and prostate cancer (phs000207.v1.p1) were also examined. If more than one article was published by the same author using the same case series, the study with the most individual investigators was included in our meta-analysis.

Inclusion and Exclusion Criteria

Abstracts of all citations and retrieved studies were reviewed. Studies meeting the following criteria were included: (1) a case–control design was used; (2) association between rs1800796 and cancer was examined; (3) controls were free of autoimmune or inflammatory diseases; (4) available genotype data were provided. Studies were excluded if one of the following was: (1) Study design was based on family or cohort; (2) Genotype frequency was not reported or provided; (3) There was insufficient information for meta-analysis even after requesting from authors.

Data extraction

All data were independently extracted by two reviewers according to the inclusion criteria listed above. Disagreements were resolved by discussion between the two reviewers. The following characteristics were collected from each study: first author, year of publication, country of sample, ethnicity, number of cases and controls, cancer type, gender of samples, genotyping methods, as well as study design and genotyping frequencies in both cases and controls. As environmental data was not available in most of the studies, this meta-analysis was conducted based on unadjusted data.

Statistical analysis

Statistical analysis was conducted using the STATA 11.0 software (Stata Corp LP, College Station, TX, United States). The odds ratio (OR) and 95% confidence interval (CI) were estimated for each study in a random-effects model, or in a fixed-effects model. Heterogeneity among studies was examined with χ^2 -based Q testing and I^2 statistics. $P < 0.1$ was considered significant for the χ^2-based Q testing, and I^2 was interpreted as the proportion of total variation contributed by between-study variation (Higgins and Thompson, 2002). If there was significant heterogeneity ($P < 0.1$), a random-effects model (the DerSimonian and Laird method) was selected to pool the data. Otherwise, a fixed-effects model (the Mantel–Haenszel method) was selected to pool the data. Pooled ORs were calculated for allele frequency comparison (G *vs* C), recessive model (GG *vs* CC + CG), dominant model (CG + GG *vs* CC), co-dominant model of homozygote effect (GG *vs* CC), and co-dominant model of heterozygote effect (CG *vs* CC and GG *vs* CG), respectively. The significance of pooled ORs was determined by Z-test, and $P < 0.05$ was considered statistically significant. Subgroup analyses were also performed based on cancer type, ethnicity, gender, genotyping method, and study design if significant heterogeneity was observed in the meta-analysis.

Hardy-Weinberg Equilibrium (HWE) in the controls was tested by the χ^2 test for goodness of fit using a previous meta-analysis as reference (Verhagen et al. 2010), and $P < 0.01$ was considered as significant deviation from HWE. As deviations from HWE in control subjects may bias the estimates of genetic effects in a meta-analysis (Zintzaras, 2010), sensitivity analysis was conducted by comparing results including studies with significant HWE deviations in control subjects with results excluding these studies. Publication bias was examined with funnel plots, where the presence of publication bias was illustrated in the asymmetric shape of funnel plots (Begg and Mazumdar, 1994). In addition, Egger's tests were also carried with a significance level of 0.05 to further detect publication bias.

RESULTS

Characteristics of studies

A total of 1163 papers were retrieved after the first search. Following our screening procedure, 19 case-control studies fulfilled the inclusion criteria. Genotype information was also checked in three available GWAS databases. However, no additional data was acquired. In total, 9,985 cases and 13,045 controls were included in the analysis. The qualities of studies were considered acceptable for our meta-analysis. A flow chart outlining study selection and reasons for exclusion are presented in Figure 1. The cancer types in the 19 studies included lung cancer (6 studies), prostate cancer (4 studies), gastric cancer (3 studies), colorectal cancer (2 studies), breast cancer (2 studies), esophageal cancer (1 study), and hepatocellular carcinoma (1 study). Among these studies, 12 studies consisted of Asian samples, 5 studies with Caucasian samples, 1 study with both Asian and Caucasian samples, and 1 study with both African and Caucasian samples. The gender breakdown of the studies is as follows: 3 studies were female samples, 6 studies were male samples, and 10 studies were mixed samples. Multiple genotyping methods were used in these studies, including microarray (2 studies), polymerase chain reaction - restriction fragment length polymorphism (PCR-RFLP) (8 studies) and Taqman genotyping (9 studies). Furthermore, 12 studies were hospital-based case-control design while 7 studies were population-based case-control design. Characteristics of all studies included in the meta-analysis are presented in Table 1.

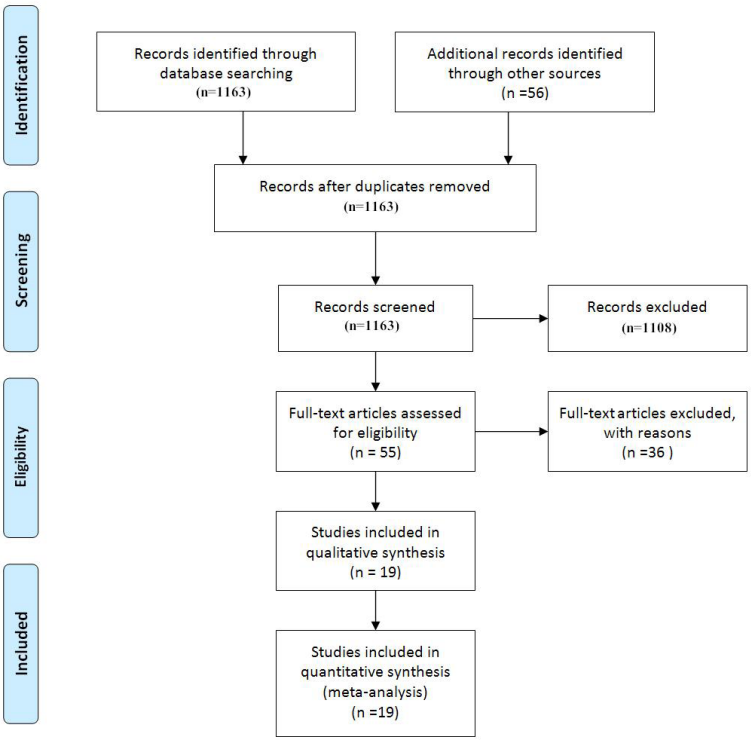

Figure 1. Flow chart of study selection and specific reasons for exclusion.

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

References	Cancer type	Country	Ethnic group	Genotyping method	Gender	Study design	N (Case)				N (Control)				HWE
							Total	CC	CG	GG	Total	CC	CG	GG	
He et al., (2011)	Breast cancer	China	Asian	PCR-RFLP	Female	HCC	176	85	83	8	200	138	59	3	0.236
Slattery et al., (2008)	Breast cancer	USA	Caucasian	TaqMan	Female	PCC	1175	153	1022[a]		1329	141	1188[a]		NA
Slattery et al., (2008)	Breast cancer	USA	Mixed	TaqMan	Female	PCC	575	242	333[a]		726	320	406[a]		NA
Tsilidis et al., (2009)	Colorectal cancer	USA	Caucasian	TaqMan	Mixed	PCC	201	2	19	180	362	3	30	329	0.019
Slattery et al., (2007)	Colorectal cancer	USA	Caucasian	TaqMan	Mixed	HCC	2373	27	311	2035	2982	34	366	2582	<0.01
Tang et al., (2007)	Esophageal cancer	China	Asian	PCR-RFLP	Mixed	HCC	118	74	40	4	130	89	38	3	0.652
Hwang et al., (2003)	Gastric cancer	USA	Caucasian	PCR-RFLP	Mixed	HCC	30	3	16	11	30	5	7	18	0.02
Hwang et al., (2003)	Gastric cancer	Mixed	Asian	PCR-RFLP	Mixed	HCC	30	16	13	1	30	16	13	1	0.394
Xing et al., (2006)	Gastric cancer	China	Asian	Microarray	Mixed	PCC	130	4	118	8	142	22	112	8	<0.01
Kang et al., (2009)	Gastric cancer	Korea	Asian	PCR-RFLP	Mixed	PCC	284	154	113	17	278	140	123	15	0.069
Bai et al., (2013)	Lung cancer	China	Asian	TaqMan	Mixed	HCC	193	86	89	18	210	125	69	16	0.145
Chen et al., (2013)	Lung cancer	China	Asian	PCR-RFLP	Mixed	HCC	1237	682	474	81	1252	630	515	107	0.904
Liang et al., (2013)	Lung cancer	China	Asian	PCR-RFLP	Mixed	HCC	138	100	29	9	138	105	30	3	0.625
Lim et al., (2011)	Lung cancer	Singapore	Asian	PCR-RFLP	Female	HCC	298	163	123	12	718	449	231	38	0.25
Seow et al., (2006)	Lung cancer	Singapore	Asian	PCR-RFLP	Female	HCC	124	70	46	8	162	97	55	10	0.56
Kiyohara et al., (2014)	Lung cancer	Japan	Asian	TaqMan	Mixed	HCC	462	259	175	28	379	250	116	13	0.919
Sun et al., (2004)	Prostate cancer	Sweden	Caucasian	Microarray	Male	PCC	1337	2	109	1226	753	4	74	675	0.211
Bao et al., (2008)	Prostate cancer	China	Asian	TaqMan	Male	HCC	136	50	39	47	120	65	27	28	<0.01
Pierce et al., (2009)	Prostate cancer	USA	Caucasian	TaqMan	Male	PCC	175	0	19	156	1934	2	192	1740	0.161
Pierce et al., (2009)	Prostate cancer	USA	African	TaqMan	Male	PCC	40	1	2	37	300	1	46	253	0.47
Wang et al., (2009)	Prostate cancer	USA	Caucasian	TaqMan	Male	PCC	253	1	19	233	280	0	25	255	0.434
Liu et al., (2012)	Hepatocellular carcinoma	China	Asian	TaqMan	Male	HCC	500	315	169	16	590	399	173	18	0.886

PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism; HCC = hospital-based case-control; PCC = population-based case-control; HWE = Hardy-Weinberg equilibrium; NA = not applicable. [a] = CG+GG is provided in this study.

Overall analysis

The association of rs1800796 in the *IL6* gene with cancer was investigated in 19 studies with a total of 9985 cases and 13,045 controls. As shown in Table 2,Table 3, Figure 2, Figure 3 and Figure 4, significant association was observed under three genetic models (allele G *vs* allele C, pooled OR = 1.182, P = 0.009; CG+GG *vs* CC, pooled OR = 1.333, P = 0.006; CG *vs* CC, pooled OR = 1.323, P = 0.007). Significant heterogeneity was also observed with P < 0.1. However, no significant association was observed in other genetic model in the overall analysis (Table 2).

Subgroup analysis

Results of subgroup meta-analysis and heterogeneity test are shown in Table 2 and Table 3.

When studies were stratified according to cancer types, the results indicated that rs1800796 was significantly associated with prostate cancer under two genetic models (allele G *vs* allele C, pooled OR = 1.324, P = 0.023; GG *vs* CG + CC, pooled OR = 1.263, P = 0.034). Neither significant heterogeneity (P > 0.1) nor significant association was observed in other genetic models. In other cancer types, no significant association was found between rs1800796 and cancer risk.

When studies were stratified according to the ethnicity of samples, the results showed that significant associations were observed in Asians under four genetic models (allele G *vs* allele C, pooled OR = 1.258, P = 0.006; CG + GG *vs* CC, pooled OR = 1.380, P = 0.005; GG *vs* CC, pooled OR = 1.465, P = 0.036; CG *vs* CC, pooled OR = 1.35, P = 0.007). However, significant heterogeneity was observed under all four genetic models with P < 0.1. There was no significant association observed in other ethnic subgroups.

Table 2. Results of meta- and subgroup analysis.

Group	N[a]	Allele G *vs* allele C		GG *vs* CC + CG		CG + GG *vs* CC		GG *vs* CC		CG *vs* CC		GG *vs* CG	
		OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value	OR (95%CI)	P value
Overall	20	1.182(1.042-1.339)	0.009	1.028(0.902-1.171)	0.678	1.333(1.088-1.634)	0.006	1.321(0.988-1.765)	0.06	1.323(1.08-1.622)	0.007	0.974(0.868-1.094)	0.657
Cancer type													
Breast	1	2.017(1.417-2.870)	<0.001	1.007(0.698-1.453)	0.969	2.383(1.564-3.63)	<0.001	4.329(1.118-16.77)	0.034	2.284(1.487-3.509)	<0.001	1.896(0.483-7.447)	0.36
Colorectal	2	0.936(0.814-1.077)	0.357	0.928(0.798-1.078)	0.328	0.988(0.606-1.612)	0.963	0.979(0.6-1.596)	0.931	1.061(0.638-1.763)	0.82	0.923(0.789-1.079)	0.316
Gastric	4	1.018(0.808-1.281)	0.882	0.866(0.523-1.433)	0.575	1.583(0.652-3.845)	0.311	1.516(0.66-3.483)	0.327	1.821(0.674-4.921)	0.237	0.771(0.372-1.599)	0.485
Lung	6	1.203(0.945-1.533)	0.134	1.095(0.74-1.62)	0.651	1.266(0.941-1.702)	0.119	1.238(0.769-1.994)	0.38	1.255(0.941-1.674)	0.123	0.922(0.677-1.255)	0.605
Prostate	5	1.324(1.039-1.688)	0.023	1.263(1.018-1.568)	0.034	1.267(0.46-3.491)	0.647	1.323(0.476-3.676)	0.592	0.928(0.271-3.179)	0.906	1.174(0.937-1.471)	0.162
Esophageal	1	1.253(0.796-1.972)	0.329	1.485(0.325-6.779)	0.609	1.291(0.763-2.183)	0.341	1.604(0.348-7.394)	0.545	1.266(0.737-2.174)	0.392	1.267(0.266-6.036)	0.767
Hepatocellular carcinoma	1	1.169(0.943-1.449)	0.155	1.051(0.53-2.082)	0.888	1.227(0.955-1.576)	0.109	1.126(0.565-2.244)	0.736	1.237(0.956-1.602)	0.106	0.91(0.449-1.843)	0.793
Ethnic group													
Asian	14	1.258(1.067-1.483)	0.006	1.177(0.913-1.518)	0.21	1.380(1.105-1.725)	0.005	1.465(1.025-2.092)	0.036	1.35(1.087-1.677)	0.007	0.956(0.784-1.164)	0.652
Caucasian	6	0.991(0.872-1.126)	0.887	0.936(0.793-1.105)	0.433	1.089(0.701-1.691)	0.705	1.032(0.663-1.606)	0.889	1.198(0.758-1.894)	0.439	0.97(0.781-1.204)	0.779
African	1	1.652(0.579-4.711)	0.348	2.291(0.678-7.738)	0.182	0.130(0.008-2.127)	0.153	0.146(0.009-2.389)	0.177	0.043(0.002-0.977)	0.048	3.364(0.783-14.442)	0.103
Gender													
Female	3	1.381(0.981-1.944)	0.064	0.955(0.733-1.244)	0.734	1.557(1.055-2.298)	0.026	1.367(0.6-3.114)	0.457	1.58(1.118-2.233)	0.01	0.832(0.46-1.504)	0.542
Mixed	11	1.088(0.928-1.275)	0.299	0.966(0.79-1.181)	0.736	1.242(0.948-1.627)	0.115	1.298(0.892-1.889)	0.173	1.246(0.952-1.631)	0.109	0.924(0.808-1.055)	0.243
Male	6	1.272(1.066-1.519)	0.008	1.242(1.011-1.526)	0.039	1.402(0.849-2.316)	0.187	1.386(0.722-2.661)	0.327	1.286(0.731-2.262)	0.383	1.147(0.925-1.422)	0.211
Genotyping methods													
PCR-RFLP	9	1.123(0.908-1.388)	0.285	0.954(0.671-1.356)	0.793	1.201(0.919-1.569)	0.181	1.082(0.741-1.581)	0.683	1.203(0.917-1.579)	0.182	0.889(0.628-1.259)	0.509
TaqMan	9	1.216(1.012-1.462)	0.037	1.028(0.888-1.19)	0.71	1.405(1.131-1.746)	0.002	1.376(0.989-1.913)	0.058	1.38(1.102-1.728)	0.005	0.965(0.844-1.103)	0.6
Microarray	2	1.301(1.044-1.622)	0.019	1.26(0.942-1.687)	0.12	5.014(1.998-12.582)	0.001	4.62(1.535-13.909)	0.006	4.768(1.891-12.024)	0.001	1.206(0.897-1.622)	0.216
Study design													
HCC	13	1.226(1.445-0.015)	0.015	1.073(1.358-0.555)	0.555	1.351(1.666-0.005)	0.005	1.322(0.963-1.815)	0.084	1.345(1.099-1.646)	0.004	0.917(0.791-1.062)	0.246
PCC	7	1.092(1.264-0.242)	0.242	1.017(1.174-0.813)	0.813	1.2(3.078-0.704)	0.704	1.266(0.551-2.91)	0.578	1.093(0.398-2.997)	0.863	1.127(0.915-1.389)	0.259

[a]Number of studies. CI = confidence interval; OR = odds ratio.

Table 3. Heterogeneity tests for each genotype in the overall and subgroup analysis.

		G *vs* C		GG *vs* CC + CG		CG + GG *vs* CC		GG *vs* CC		CG *vs* CC		GG *vs* CG	
Group	N[a]	I^2	P value	I^2	P value	I^2	P value	I^2	P value	I^2	P value	I^2	P value
Overall	20	65.70%	<0.001	29.90%	0.107	67.00%	<0.001	34.10%	0.084	65.00%	<0.001	14.70%	0.282
Cancer type													
Breast	1	NA	NA	69.30%	0.039	NA	NA	NA	NA	NA	NA	NA	NA
Colorectal	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gastric	4	0.00%	0.747	27.00%	0.254	0.00%	0.633	0.00%	1	34.20%	0.219	57.90%	0.093
Lung	6	81.60%	<0.001	50.70%	0.071	81.60%	<0.001	65.00%	0.014	78.50%	<0.001	22.10%	0.268
Prostate	5	0.00%	0.601	0.00%	0.494	40.40%	0.169	38.30%	0.182	51.70%	0.102	5.20%	0.367
Esophageal	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hepatocellular carcinoma	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Ethnic group													
Asian	14	76.20%	<0.001	26.80%	0.189	76.70%	<0.001	48.40%	0.036	73.20%	<0.001	0.00%	0.599
Caucasian	6	0.60%	0.403	44.70%	0.107	0.00%	0.558	0.00%	0.568	0.00%	0.471	45.00%	0.122
African	1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Gender													
Female	3	71.30%	0.031	43.20%	0.134	67.60%	0.046	54.00%	0.114	56.30%	0.101	16.00%	0.304
Mixed	11	71.30%	0.001	39.00%	0.108	69.10%	0.001	45.20%	0.067	64.90%	0.004	20.50%	0.261
Male	6	0.00%	0.758	0.00%	0.641	22.10%	0.274	17.70%	0.302	39.70%	0.157	0.00%	0.46
Genotyping methods													
PCR-RFLP	9	72.70%	<0.001	31.20%	0.169	73.60%	<0.001	33.30%	0.151	72.20%	<0.001	25.80%	0.214
TaqMan	9	15.10%	0.315	18.20%	0.281	21.70%	0.264	1.90%	0.41	34.90%	0.162	0.00%	0.604
Microarray	2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Study design													
HCC	13	76.00%	<0.001	39.40%	0.086	75.20%	<0.001	48.40%	0.036	71.90%	<0.001	15.90%	0.292
PCC	7	0.00%	0.469	21.20%	0.261	0.60%	0.412	0.00%	0.43	18.80%	0.291	0.00%	0.538

[a]number of studies.

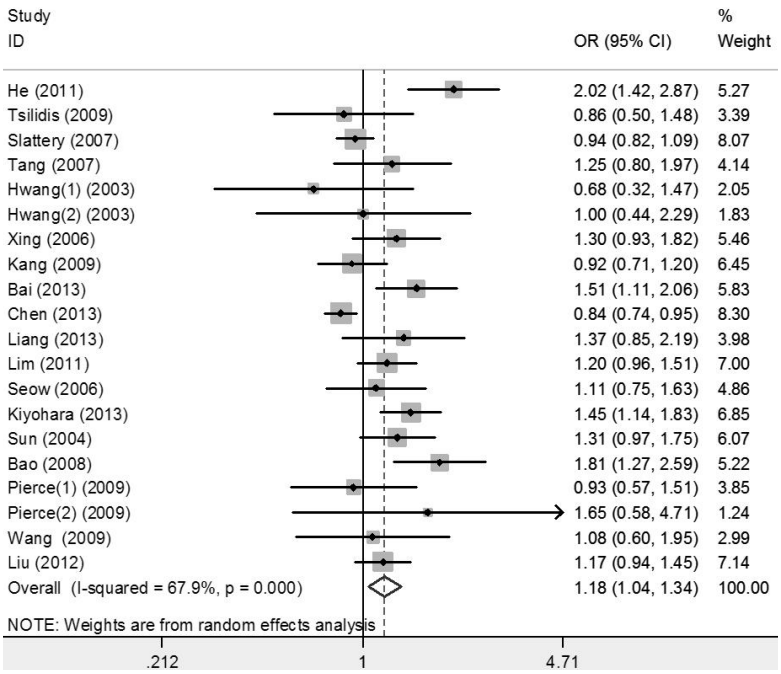

Figure 2. Forest plots of association between rs1800796 and cancer risk (allele G *vs* allele C).

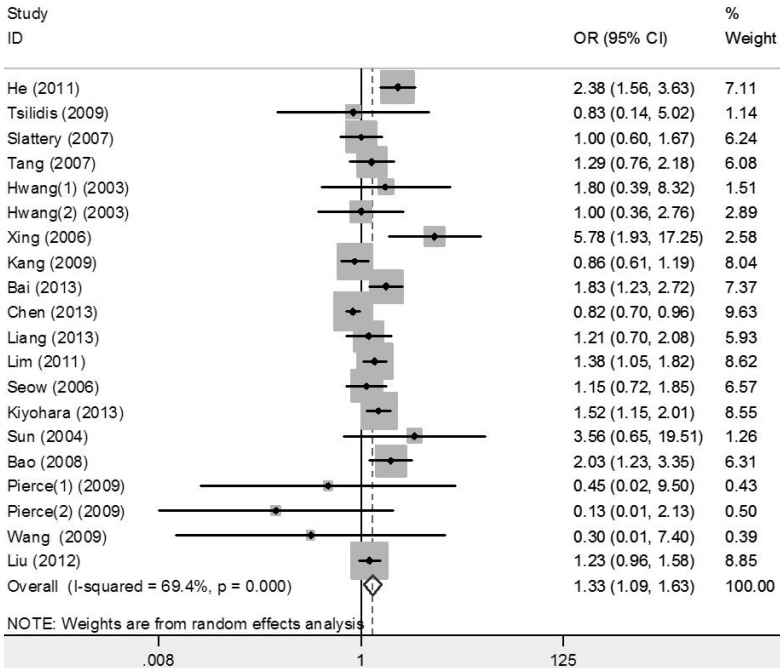

Figure 3. Forest plots of association between rs1800796 and cancer risk (CG + GG *vs* CC).

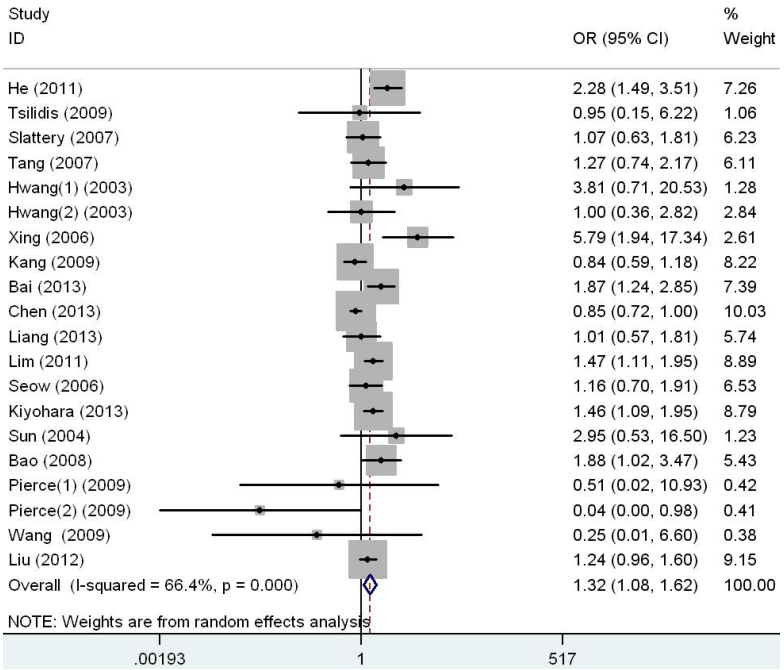

Figure 4. Forest plots of association between rs1800796 and cancer risk (CG *vs* CC).

When studies were stratified according to gender of subjects, the results showed that significant associations were observed in both male (allele G *vs* allele C, pooled OR = 1.272, P = 0.008; GG *vs* CG + CC, pooled OR = 1.242, P = 0.039) and female samples (CG + GG *vs* CC, pooled OR = 1.557, P = 0.026; CG *vs* CC, pooled OR = 1.58, P = 0.01). No significant heterogeneity was observed in male samples (P > 0.1), while significant heterogeneity was observed in female samples with (P < 0.1). No significant association was observed in mixed samples.

When studies were stratified according to genotyping methods, significant associations were observed in both studies using Taqman technology (allele G *vs* allele C, pooled OR = 1.216, P = 0.037; CG + GG *vs* CC, pooled OR = 1.405, P = 0.002; CG *vs* CC, pooled OR=1.38, P = 0.005) and studies using microarray (allele G *vs* allele C, pooled OR = 1.182, P = 0.019; CG + GG *vs* CC, pooled OR = 5.014, P = 0.001; GG *vs* CC, pooled OR = 4.62, P = 0.006; CG *vs* CC, pooled OR = 4.768, P = 0.001). No significant heterogeneity was observed with either microarray (all genetic models) or Taqman (dominant and recessive model) genotyping methods (P > 0.1). Lastly, no significant association was observed in studies using PCR-RFLP.

When studies were stratified according to study design, both significant associations and significant heterogeneity (P < 0.1) were observed in studies with hospital-based design (allele G *vs* allele C, pooled OR = 1.226, P = 0.015; GG *vs* CG + CC, pooled OR = 1.351, P = 0.005; CG *vs* CC, pooled OR = 1.345, P = 0.004). However, no significant association was observed in studies with population-based design.

Sensitivity analysis

To determine whether a specific variable would affect the overall results, we compared the data before and after removing studies with significant deviation from the HWE (Slattery et al. 2007). It was determined that deviations from the HWE do not affect the overall analysis, which indicated that the results of the meta-analysis were not biased by studies with significant deviation from HWE (See **Table S1** and **Table S2**). For subgroup analysis, removal of studies with significant deviation from HWE resulted in a loss of association rs1800796 and prostate cancer, while no significant difference was observed in other subgroup analyses (See **Table S1** and **Table S2**).

Publication bias

Funnel plot and Egger's test were performed to assess the publication bias of the literature (See **Figure S1**). No significant publication bias was observed under all studied models (Allele G *vs* allele C, P = 0.055; GG *vs* CG + CC, P = 0.085; GG + CG *vs* CC, P = 0.217; GG *vs* CC, P = 0.148; CG *vs* CC, P = 0.279; GG *vs* CG, P = 0.345).

DISCUSSION

Our meta-analysis demonstrated significant association between rs1800796 of *IL6* and cancer risk, with the allele G as a risk allele. It has been previously reported that rs1800796 is associated with different levels of *IL6* production (Fishman et al., 1998), and there are strong positive correlations between serum interleukin-6 concentrations and tumor size, tumor stage, or disease progression in various cancer patients (Lippitz, 2013). Our results supported previous studies, and indicated that individuals with genetic variants that give rise to reduced IL-6 production

may be at greater risk for cancer. *IL-6* is involved in the recruitment of neutrophils, and promotes the migration and proliferation of T lymphocytes into the affected tissue (Romano et al., 1997). Findings also show that IL-6 provides a key signal during Th17 cell development, while blocking the differentiation of CD4+ cells into Treg cells (Bettelli et al., 2006). Increasing evidence suggest that the balance between Th17 and Treg cells may be involved in the development or progression of cancer (Chi et al., 2010). It is possible that the association of IL-6 with cancer risk may be due to modulation of Th17 and Treg differentiation.

In subgroup analysis, significant association was observed in Asians but not in Caucasian. In this study, a significant difference was observed in the frequency of allele G (rs1800796) between Asians (23.9%) and Caucasians (93.8%). The statistical power achieved in the Asian samples was 0.995 with the observed odds ratio of 1.258 and sample size of 8,173; however, due to different allele frequencies, when setting the odds ratio at 1.258, under the current sample size of 10,710, the statistical power in the Caucasian samples was 0.758. Under this allele frequency, the sample size required to gain sufficient statistical power (power > 0.9) in Caucasians is 15,809, indicating that insignificant association in the Caucasian population may be due to the limited sample size. Future studies with a sample size larger than 15,000 subjects are needed for further verification. Subgroup analysis using cancer types showed significant results only in prostate cancer, which is consistent with a previous study (Magalhaes et al., 2013). For individual cancers, sample size may still a limiting factor for statistical analysis.

Some limitations in this study are as follows: 1) in some cases, heterogeneity was still present after subgroup analysis, indicating that we were not able to detect all heterogeneous factors; 2) control subjects included in this study were not all subjected to the same study design. Controls from population-based studies and hospital-based studies might be under different psychical conditions, which might be a potential confounder; 3) this meta-analysis was based on unadjusted data, and a more precise analysis could be performed if individual data were available.

In conclusion, as the first meta-analysis investigating the association between rs1800796 of *IL6* and overall cancer risk, our study observed that rs1800796 was significantly associated with cancer risk, with the allele G as a risk allele, indicating that *IL6* may be a risk gene for cancer. Larger and well-designed studies based on different ethnic groups are needed to confirm our results.

Supplementary material

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