Associations of common IL-4 gene polymorphisms with cancer risk: A meta-analysis

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Abstract. Cancer incidence is dramatically increasing worldwide, therefore improved prediction and therapeutic methods are needed. Single nucleotide polymorphisms in cytokine genes may contribute to carcinogenesis. Interleukin (IL)-4 gene polymorphisms have been intensively studied with regard to their associations with cancer. However, the results of these previous studies remain inconclusive. The present study, therefore, aimed to conduct a meta-analysis of previously published studies in order to clarify the association of IL-4 with cancer risk. Eligible published articles were searched in Medline, PubMed, Embase and China National Knowledge Infrastructure databases up to March 2016. Odds ratios and 95% confidence intervals were used to identify potential associations between IL-4 genetic polymorphisms and the risk of cancer. A meta-analysis was then performed on 10,873 patients and 14,328 controls for IL-4 rs2243250 polymorphism, 3,970 patients and 5,686 controls for IL-4 rs2070874 polymorphism, and 1,896 patients and 2,526 controls for IL-4 rs79071878 polymorphism. A significant association with cancer risk was observed for rs2243250 and rs79071878 polymorphisms. In the subgroup analysis by cancer type, rs2243250 polymorphism was demonstrated to be associated with an increased risk of gastric cancer and breast cancer, rs2070874 polymorphism was correlated with leukemia and oral carcinoma, and rs79071878 polymorphism was relevant to bladder carcinoma risk. In the subgroup analysis by ethnicity, IL-4 rs2243250 polymorphism was demonstrated to be associated with cancer risk in both Caucasian and Asian populations, rs2070874 was associated with cancer risk in Asian populations, while rs79071878 polymorphism was associated with cancer risk in Caucasian populations. In conclusion, the present results suggested that the IL-4 rs2243250 and rs79071878 polymorphisms were associated with cancer susceptibility. Further subgroup analyses revealed that the effects of IL-4 gene polymorphisms on cancer risk may vary by cancer type and by ethnicity.

Introduction

It was estimated that there were ~14 million new cancer cases in 2012 and the number is expected to rise to 22 million in the next two decades (1). Cancer-associated mortality, meanwhile, was ~8.2 million in 2012 and is predicted to rise to 13 million by 2032 (1). Thus, an improved understanding of the pathogenic mechanisms of cancer is of great importance. At present, it is widely accepted that cancer is a multifactorial and complex disease resulting from interaction between environmental and genetic factors (2).

Single nucleotide polymorphisms (SNPs) are frequently occurring variations in the human genome, and have been extensively investigated in genetic studies of cancer. Recent studies have demonstrated that SNPs of multiple genes may have an important role in cancer occurrence and progression (3). In addition, numerous publications have reported that cytokine gene polymorphisms may affect inflammatory-related pathways, and influence susceptibility to different types of cancer (4,5). Interleukin-4 (IL-4) is a potent regulator of antitumor immune responses with both tumor-promoting and tumor-inhibiting properties, since it has both immunosuppressive and anti-angiogenic functions (6-9). Consequently, certain genetic polymorphisms of IL-4 gene are considered as good candidates for cancer susceptibility prediction. To date, several studies have aimed to assess the potential association of IL-4 polymorphisms rs2243250 [-590C to T, 5'untranslated region (UTR)], rs2070874 (-34C to T, 5' UTR) and rs79071878 (intron-3, 70 bp variable number tandem repeat, VNTR) with cancer risk, but the results remain inconsistent. Therefore, a meta-analysis was performed in the present study in order to better elucidate the roles of IL-4 gene polymorphisms in the occurrence and progression of cancer.

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Materials and methods

Study identification and selection. Potentially relevant articles were independently identified by three investigators from the Medline (http://www.medline.com/), PubMed (https://www.ncbi.nlm.nih.gov/pubmed), Embase (https://www.embase.com) and China National Knowledge Infrastructure databases (http://www.cnki.net/). The searching terms were as follows: (Interleukin-4 OR IL-4 OR Interleukin 4 OR IL 4) AND (polymorphism OR variant OR genotype OR allele) AND (cancer OR tumor OR carcinoma OR neoplasm). In addition, the reference lists of retrieved articles were searched manually for additional eligible studies. Among studies with overlapping data published by the same authors, only the most recent and complete study was included in the present meta-analysis.

Inclusion and exclusion criteria. The following inclusion criteria were used to select eligible articles: i) Case-control study of cancer cases and healthy controls; ii) investigate the relationship between IL-4 gene polymorphisms and cancer risk; iii) provide both genotype and allele distributions inpatients and controls; iv) full text in English or Chinese available. Articles were excluded if: i) The study was duplicated; ii) the analyses were based on linkage considerations; iii) the report was not original (reviews or meta-analyses).

Data extraction and quality assessment. The following information was extracted from all included studies independently by two authors: i) Name of the first author; ii) year of publication; iii) country in which the study was conducted; iv) ethnicity of study population; v) cancer type; vi) allele and genotype frequencies of IL-4 gene polymorphisms in cases and controls; vii) P-value of Hardy-Weinberg equilibrium (HWE) in the control group. The Newcastle-Ottawa quality assessment scale was used to evaluate the quality of all included studies (10). This rating scale has a score range of 0 to 9, and studies with scores >7 were assumed to be of high quality. Two reviewers performed data extraction and quality assessment independently. When necessary, the reviewers wrote to the corresponding authors for extra information or raw data. Disagreements between reviewers were resolved by discussion until a consensus was achieved. The final results were reviewed by a senior reviewer.

Statistical analysis. All statistical analyses were performed with Review Manage version 5.3 (Cochrane, London, United Kingdom). HWE in the control group was estimated using the χ^2test. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to evaluate the strength of the associations between IL-4 gene polymorphisms and cancer susceptibility. In addition, heterogeneity among studies was assessed using the Q test and I^2 statistics. When the probability value (P-value) of Q test was <0.1 or I^2 was >50%, inter-study heterogeneity was considered to be significant, and the random-effects model (REM) was employed for analyses. Otherwise, the fixed-effect model (FEM) was applied for analyses. First, associations based on all study subjects were analyzed, and then subgroup analyses by cancer type and ethnicity were performed to obtain the cancer type-specific effects and the ethnic-specific effects of IL-4 polymorphisms. Sensitivity analyses were conducted by sequentially omitting one individual study each time to assess the stability of the results. Furthermore, the possible publication bias was evaluated by using funnel plots (data not shown).

Results

Characteristics of eligible studies. The literature search identified 1,237 eligible articles. After reading titles and abstracts, a total of 94 articles were selected for further evaluation. Amongst these, 51 articles were excluded based on the inclusion and exclusion criteria, as described in the Methods. Finally, 43 articles (11-53), 33 studies focusing on polymorphism rs2243250, 11 studies onrs2070874, and 10 studies on rs79071878, were included in the meta-analysis. The majority of the articles were published in English, except for three that were published in Chinese. A schematic of the selection process is illustrated in Fig. 1.

IL-4 rs2243250 polymorphism and the risk of cancer. For IL-4 rs2243250 polymorphism, a total of 33 studies including 10,873 cancer cases and 14,328 normal controls were investigated. Deviations from HWE were observed in 9 studies, while the other 24 studies were in accordance with HWE (Table I). As illustrated in Fig. 2, the meta-analysis identified a significant association between IL-4 rs2243250 polymorphism and cancer risk (CT vs. CC/TT: P=0.008, OR=0.88, 95% CI 0.80-0.97) with an overt heterogeneity across studies (I^2=56%). Subgroup analyses were then performed based on cancer type (Table II). The results suggested that the IL-4 rs2243250 polymorphism was significantly associated with an increased risk of gastric cancer (CT vs. TT: P=0.004, OR=0.75, 95% CI 0.61-0.91; CT vs. CC/TT: P=0.002, OR=0.77, 95% CI 0.66-0.91; and C vs. T: P=0.04, OR=1.15, 95% CI 1.01-1.32), breast cancer (CC vs. CT: P=0.05, OR=1.21, 95% CI 1.00-1.46; TT vs. CC: P=0.04, OR=0.56, 95% CI 0.33-0.97; CC vs. CT/TT: P=0.02, OR=1.25, 95% CI 1.04-1.51; and C vs. T: P=0.007, OR=1.25, 95% CI 1.06-1.47), lung cancer (CT vs. CC/TT: P=0.02, OR=0.84, 95% CI 0.75-0.97), prostate cancer (CT vs. TT: P=0.004, OR=1.48, 95% CI 1.14-1.92;TT vs. CC: P=0.0009, OR=0.48, 95% CI 0.31-0.74; CT vs. CC/TT: P=0.02, OR=1.33, 95% CI 1.05-1.69; and TT vs. CC/CT: P=0.0004, OR=0.64, 95% CI 0.50-0.82) and leukemia (CC vs. CT: P=0.005, OR=5.35, 95% CI 1.64-17.47;CC vs. CT/TT: P=0.01, OR=4.67, 95% CI 1.42-15.31; and CT vs. CC/TT: P=0.005, OR=0.19, 95% CI 0.06-0.61). Studies in each cancer subgroup were homogenous. No significant association between IL-4 rs2243250 polymorphism and cancer risk was identified for oral carcinoma, colorectal cancer, skin cancer, hepatocellular carcinoma, lymphoma, bladder cancer, brain tumor, testicular tumor, renal cell carcinoma, and brain tumor (Table II). Subgroup analyses were also conducted by ethnicity. As illustrated in Table II, a significant association between IL-4 rs2243250 polymorphism and cancer risk was identified in both Caucasian (CT vs. TT: P=0.03, OR=0.82, 95% CI 0.68-0.98, I^2=46%; CT vs. CC/TT: P=0.02, OR=0.79, 95% CI 0.66-0.96, I^2=64%) and Asian populations (CT vs. CC/TT: P=0.006, OR=0.89, 95% CI 0.82-0.97, I^2=36%).

Table I. Characteristics of subjects included in the meta-analysis of interleukin-4 rs2243250 polymorphism and cancer risk.

First author, year	Country	Ethnicity	Cancer type	Case n	Case Genotypes CC/CT/TT	Case Alleles C/T (%)	Control n	Control Genotypes CC/CT/TT	Control Alleles C/T (%)	P-value HWE	NOS score	(Refs.)
Amirzargar, 2005	Iran	Caucasian	Leukemia	30	13/17/0	71.7/28.3	40	5/35/0	56.3/43.7	**<0.001**	7	(42)
Andrie, 2009	Greece	Caucasian	Lymphoma	85	66/17/2	87.6/12.4	85	70/14/1	90.6/9.6	0.753	7	(26)
Chang, 2015	Taiwan	Asian	Lung cancer	358	247/95/16	82.3/17.7	716	439/218/59	76.5/23.5	**<0.001**	7	(35)
Chen, 2016	China	Asian	Prostate cancer	439	46/171/222	30.0/70.0	524	29/173/322	22.0/78.0	0.368	7	(22)
Chu,2012	China	Asian	Bladder cancer	816	39/264/513	21.0/79.0	1140	46/393/701	21.3/78.7	0.322	7	(41)
Chu, 2012	China	Asian	Renal cell carcinoma	620	22/189/409	18.8/81.2	623	36/195/392	21.4/78.6	0.079	7	(18)
Cozar, 2007	Spain	Caucasian	Renal cell carcinoma	127	93/30/4	85.0/15.0	174	123/47/4	84.2/15.8	0.844	7	(19)
Cozar, 2007	Spain	Caucasian	Colorectal cancer	96	68/25/3	83.9/16.1	174	123/47/4	84.2/15.8	0.844	7	(19)
Crusius, 2008	Netherlands	Caucasian	Gastric cancer	242	159/76/7	81.4/18.6	1154	824/305/25	84.6/15.4	0.603	7	(11)
El-omar, 2003	Scotland	Mixed	Esophageal cancer	90	55/28/7	76.7/23.3	209	153/46/10	84.2/15.8	**0.013**	7	(12)
El-omar, 2003	Scotland	Mixed	Gastric cancer	122	78/37/7	79.1/20.9	209	153/46/10	84.2/15.8	**0.013**	7	(12)
Garcia-Gonzalez, 2007	Spain	Caucasian	Gastric cancer	404	283/107/14	83.3/16.7	404	267/123/14	81.3/18.7	0.971	8	(13)
Gaur, 2011	India	Caucasian	Oral carcinoma	140	18/55/67	32.5/67.5	120	9/35/76	22.1/77.9	0.095	8	(28)
Gu, 2014	China	Asian	Lung cancer	500	22/157/321	20.1/79.9	500	15/161/324	19.1/80.9	0.348	7	(34)
Howell, 2003	UK	Caucasian	Skin cancer	153	130/23/0	92.5/7.5	208	165/39/4	88.7/11.3	0.352	8	(25)
Joshi, 2014	India	Caucasian	Breast cancer	163	120/39/4	85.6/14.4	224	144/72/8	80.4/19.6	0.786	8	(20)
Lai, 2005	Taiwan	Asian	Gastric cancer	123	2/38/83	17.1/82.9	162	7/50/105	19.8/80.2	0.736	7	(14)
Li, 2012	China	Asian	Lung cancer	1072	54/280/738	18.1/81.9	1126	94/341/691	23.5/76.5	**<0.001**	7	(33)
Liang, 2010	China	Asian	Gastric cancer	238	10/53/175	15.3/84.7	112	6/28/78	17.9/82.1	0.118	7	(17)
Lu, 2014	China	Asian	Hepatocellular cancer	154	4/39/111	15.3/84.7	170	4/51/115	17.4/82.6	0.055	7	(31)
Monroy, 2011	USA	Mixed	Lymphoma	100	69/27/4	82.5/17.5	100	67/24/9	79.0/21.0	**0.006**	7	(27)
Olson, 2007	USA	Mixed	Prostate cancer	149	101/39/9	80.9/19.1	128	96/26/6	85.2/14.8	**0.026**	7	(23)
Pan, 2014	China	Asian	Gastric cancer	308	39/69/200	23.9/76.1	307	9/100/198	19.2/80.8	0.390	7	(15)
Purdue, 2007	USA	Mixed	Testicular germ cell tumor	506	363/133/10	84.9/15.1	606	450/143/13	86.1/13.9	0.680	8	(40)
Saxena, 2014	India	Caucasian	Hepatocellular carcinoma	59	16/40/3	61.0/39.0	153	58/88/7	66.7/33.3	**<0.001**	7	(32)
Schonfeld, 2010	USA	Mixed	Breast cancer	838	616/206/16	85.8/14.2	1074	750/289/35	83.3/16.7	0.273	8	(21)
Suchy, 2008	Poland	Caucasian	Colorectal cancer	350	225/113/12	80.4/19.6	350	230/107/13	81.0/19.0	0.899	8	(36)
Tsai, 2005	Taiwan	Asian	Oral carcinoma	130	9/21/100	15.0/85.0	105	2/28/75	15.2/84.8	0.741	7	(29)

Table I. Continued.

First author, year	Country	Ethnicity	Cancer type	Case				Control				P-value HWE	NOS score	(Refs.)
				n	Genotypes CC/CT/TT	Alleles C/T (%)		n	Genotypes CC/CT/TT	Alleles C/T (%)				
Vairaktaris, 2008	Greek and German	Caucasian	Oral carcinoma	156	84/46/26	68.6/31.4		162	99/48/15	75.9/24.1		**0.016**	7	(30)
Welsh, 2011	UK	Caucasian	Skin cancer	892	675/197/20	86.6/13.3		801	608/174/19	86.8/13.2		0.126	8	(24)
Wiemels, 2007	USA	Mixed	Glioma	384	278/95/11	84.8/15.2		468	313/144/11	82.3/17.7		0.239	8	(39)
Wilkening, 2008	North Sweden	Caucasian	Colorectal cancer	304	183/104/17	77.3/22.7		582	339/200/43	75.4/24.6		0.079	8	(37)
Yang, 2014	Taiwan	Asian	Oral carcinoma	463	13/148/302	18.8/81.2		623	23/218/382	21.2/78.8		0.233	7	(53)
Yang, 2014	Taiwan	Asian	Pharyngeal carcinoma	129	4/43/82	19.8/80.2		623	23/218/382	21.2/78.8		0.233	7	(53)
Yannopoulos, 2007	Greece	Caucasian	Colorectal cancer	93	73/15/5	86.6/13.4		108	69/30/9	77.8/22.2		**0.041**	7	(38)
Zambon, 2008	Italy	Caucasian	Gastric cancer	40	32/7/1	88.8/11.2		64	45/17/2	83.6/16.4		0.800	7	(16)

Significant associations are denoted in bold font. HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa quality assessment scale.

Table II. Subgroup analyses for interleukin-4 rs2243250 polymorphism and cancer risk.

A, Gastric cancer (n=6[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.47	1.24 (0.69-2.20)	78%	0.0003
CT vs. TT	**0.004**	**0.75 (0.61-0.91)**	0%	0.85
TT vs. CC	0.57	0.81 (0.40-1.66)	63%	0.02
CC vs. CT + TT	0.11	1.42 (0.92-2.20)	68%	0.007
CT vs. CC + TT	**0.002**	**0.77 (0.66-0.91)**	0%	0.62
TT vs. CC + CT	0.63	1.06 (0.85-1.32)	0%	0.95
C vs. T	**0.04**	**1.15 (1.01-1.32)**	21%	0.28

B, Oral carcinoma (n=3[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.43	1.41 (0.60-3.30)	45%	0.14
CT vs. TT	0.68	0.84 (0.37-1.91)	80%	0.007
TT vs. CC	0.67	0.78 (0.25-2.44)	77%	0.01
CC vs. CT + TT	0.45	0.41 (0.58-3.47)	70%	0.04
CT vs. CC + TT	0.90	0.96 (0.54-1.71)	70%	0.03
TT vs. CC + CT	0.83	1.09 (0.50-2.39)	82%	0.004
C vs. T	0.88	1.05 (0.60-1.84)	82%	0.004

C, Colorectal cancer (n=3[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. TT	0.51	1.12 (0.80-1.57)	55%	0.11
CT vs. TT	0.43	1.20 (0.76-1.90)	0%	0.86
TT vs. CC	0.83	1.04 (0.70-1.55)	0%	0.41
CC vs. CT + TT	0.39	1.16 (0.83-1.62)	58%	0.09
CT vs. CC + TT	0.74	0.97 (0.79-1.19)	50%	0.14
TT vs. CC + CT	0.23	0.77 (0.50-1.19)	0%	0.84
C vs. T	0.31	1.15 (0.88-1.52)	56%	0.10

D, Lung cancer (n=3[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.97	0.99 (0.67-1.47)	63%	0.07
CT vs. TT	0.19	0.85 (0.67-1.08)	54%	0.14
TT vs. CC	0.75	0.87 (0.35-2.17)	89%	0.00001
CC vs. CT + TT	0.89	1.05 (0.54-2.01)	88%	0.0002
CT vs. CC + TT	**0.02**	**0.84 (0.75-0.97)**	0%	0.58
TT vs. CC + CT	0.86	0.96 (0.62-1.49)	85%	0.001
C vs. T	0.92	1.02 (0.68-1.54)	92%	0.00001

E, Skin cancer (n=2[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.59	1.06 (0.86-1.31)	0%	0.39
CT vs. TT	0.84	1.07 (0.57-2.00)	23%	0.25
TT vs. CC	0.72	0.89 (0.49-1.64)	44%	0.18
CC vs. CT + TT	0.53	1.07 (0.87-1.31)	33%	0.22
CT vs. CC + TT	0.60	0.94 (0.76-1.17)	0%	0.43
TT vs. CC + CT	0.74	0.90 (0.49-1.65)	41%	0.19
C vs. T	0.45	1.17 (0.77-1.77)	59%	0.12

Table II. Continued.

F, Hepatocellular cancer (n=2[a])

Variable	P-value	OR (95% CI)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.37	0.23 (0.01-5.69)	92%	0.0005
CT vs. TT	0.62	0.88 (0.54-1.44)	0%	0.79
TT vs. CC	0.93	1.05 (0.36-3.04)	10%	0.33
CC vs. CT + TT	0.46	0.51 (0.09-3.03)	80%	0.03
CT vs. CC + TT	0.16	0.55 (0.23-1.27)	84%	0.01
TT vs. CC + CT	0.95	0.99 (0.62-1.58)	36%	0.21
C vs. T	0.28	0.48 (0.13-1.80)	96%	0.00001

G, Lymphoma (n=2[a])

Variable	P-value	OR (95% CI)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.42	0.82 (0.50-1.34)	0%	0.59
CT vs. TT	0.28	1.85 (0.61-5.61)	0%	0.32
TT vs. CC	0.34	0.60 (0.21-1.72)	24%	0.25
CC vs. CT + TT	0.81	0.95 (0.59-1.51)	0%	0.43
CT vs. CC + TT	0.45	1.21 (0.74-1.98)	0%	0.88
TT vs. CC + CT	0.31	0.58 (0.21-1.65)	23%	0.26
C vs. T	0.88	0.95 (0.51-1.76)	54%	0.14

H, Prostate cancer (n=2[a])

Variable	P-value	OR (95% CI)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.87	1.07 (0.48-2.41)	78%	0.03
CT vs. TT	**0.004**	**1.48 (1.14-1.92)**	0%	0.43
TT vs. CC	**0.0009**	**0.48 (0.31-0.74)**	0%	0.43
CC vs. CT + TT	0.52	1.31 (0.57-3.01)	82%	0.02
CT vs. CC + TT	**0.02**	**1.33 (1.05-1.69)**	0%	0.66
TT vs. CC + CT	**0.0004**	**0.64 (0.50-0.82)**	0%	0.90
C vs. T	0.20	1.29 (0.87-1.90)	66%	0.09

I, Breast cancer (n=2[a])

Variable	P-value	OR (95% CI)	I-square (%)	P-value for the heterogeneity
CC vs. CT	**0.05**	**1.21 (1.00-1.46)**	21%	0.26
CT vs. TT	0.18	1.46 (0.84-2.54)	0%	0.61
TT vs. CC	**0.04**	**0.56 (0.33-0.97)**	0%	0.91
CC vs. CT + TT	**0.02**	**1.25 (1.04-1.51)**	7%	0.30
CT vs. CC + TT	0.07	0.84 (0.70-1.02)	21%	0.26
TT vs. CC + CT	0.06	0.60 (0.35-1.02)	0%	0.82
C vs. T	**0.007**	**1.25 (1.06-1.47)**	0%	0.41

J, Bladder cancer (n=1[a])

Variable	P-value	OR (95% CI)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.32	1.26 (0.80-1.99)	NA	NA
CT vs. TT	0.38	0.92 (0.76-1.11)	NA	NA
TT vs. CC	0.51	0.86 (0.56-1.34)	NA	NA
CC vs. CT + TT	0.43	1.19 (0.77-1.85)	NA	NA
CT vs. CC + TT	0.33	0.91 (0.75-1.10)	NA	NA
TT vs. CC + CT	0.54	1.06 (0.88-1.28)	NA	NA
C vs. T	0.81	0.98 (0.84-1.15)	NA	NA

Table II. Continued.

K, Brain tumor (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.06	1.35 (0.99-1.83)	NA	NA
CT vs. TT	0.35	0.66 (0.28-1.58)	NA	NA
TT vs. CC	0.20	1.76 (0.75-4.14)	NA	NA
CC vs. CT + TT	0.08	1.30 (0.97-1.74)	NA	NA
CT vs. CC + TT	0.05	0.74 (0.55-1.00)	NA	NA
TT vs. CC + CT	0.64	1.23 (0.53-2.86)	NA	NA
C vs. T	0.17	1.20 (0.93-1.55)	NA	NA

L, Testicular tumor (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.31	0.87 (0.66-1.14)	NA	NA
CT vs. TT	0.66	1.21 (0.51-2.85)	NA	NA
TT vs. CC	0.91	0.95 (0.41-2.20)	NA	NA
CC vs. CT + TT	0.35	0.88 (0.67-1.15)	NA	NA
CT vs. CC + TT	0.30	1.15 (0.88-1.52)	NA	NA
TT vs. CC + CT	0.84	0.92 (0.40-2.12)	NA	NA
C vs. T	0.43	0.91 (0.72-1.15)	NA	NA

M, Leukemia (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	**0.005**	**5.35 (1.64-17.47)**	NA	NA
CT vs. TT	NA	NA	NA	NA
TT vs. CC	NA	NA	NA	NA
CC vs. CT + TT	**0.01**	**4.67 (1.42-15.31)**	NA	NA
CT vs. CC + TT	**0.005**	**0.19 (0.06-0.61)**	NA	NA
TT vs. CC + CT	NA	1.11 (0.86-1.44)	NA	NA
C vs. T	0.06	1.97 (0.96-4.02)	NA	NA

N, Renal cell carcinoma (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.11	0.63 (0.36-1.11)	NA	NA
CT vs. TT	0.55	0.93 (0.73-1.18)	NA	NA
TT vs. CC	0.06	1.71 (0.99-2.95)	NA	NA
CC vs. CT + TT	0.06	0.60 (0.35-1.03)	NA	NA
CT vs. CC + TT	0.76	0.96 (0.76-1.22)	NA	NA
TT vs. CC + CT	0.26	1.14 (0.91-1.44)	NA	NA
C vs. T	0.10	0.85 (0.70-1.03)	NA	NA

O, Caucasian (n=15[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.85	0.98 (0.75-1.27)	81%	0.00001
CT vs. TT	**0.03**	**0.82 (0.68-0.98)**	46%	0.03
TT vs. CC	0.84	1.03 (0.81-1.30)	0%	0.50
CC vs. CT + TT	0.56	1.07 (0.85-1.34)	77%	0.00001
CT vs. CC + TT	**0.02**	**0.79 (0.66-0.96)**	64%	0.0003
TT vs. CC + CT	0.10	0.83 (0.67-1.04)	4%	0.41
C vs. T	0.84	1.03 (0.80-1.33)	90%	0.00001

Table II. Continued.

P, Asian (n=12[a])

Variable	P-value	OR (95% CI)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.26	1.22 (0.87-1.72)	71%	0.00001
CT vs. TT	0.11	0.90 (0.79-1.02)	47%	0.04
TT vs. CC	0.38	0.83 (0.54-1.27)	80%	0.00001
CC vs. CT + TT	0.34	1.19 (0.83-1.72)	77%	0.00001
CT vs. CC + TT	**0.006**	**0.89 (0.82-0.97)**	36%	0.11
TT vs. CC + CT	0.62	1.04 (0.89-1.21)	66%	0.0007
C vs. T	0.90	1.01 (0.87-1.18)	80%	0.00001

[a]Number of articles. Significant associations are denoted in bold font. OR, odds ratio; CI, confidence interval; NA, not applicable.
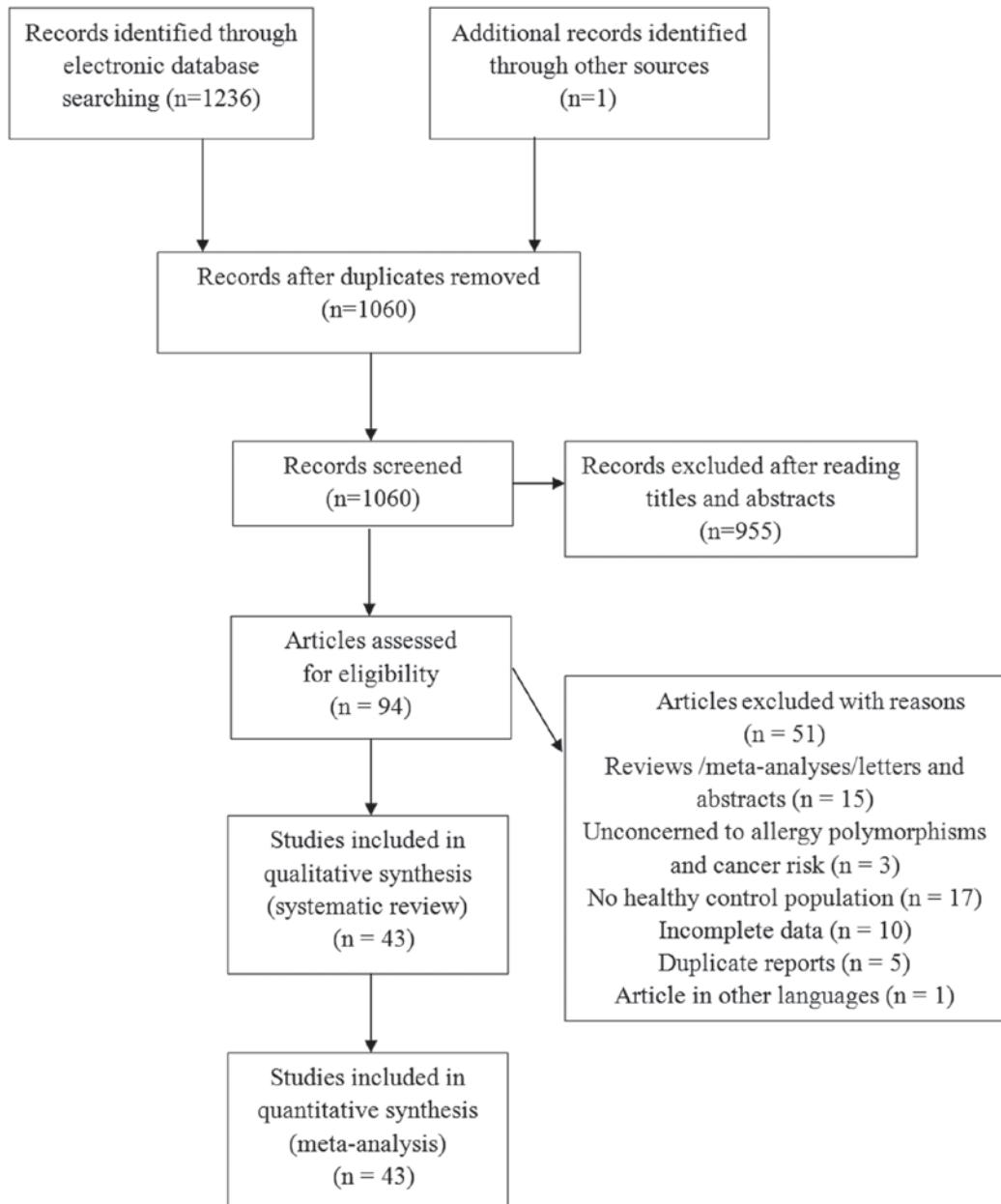

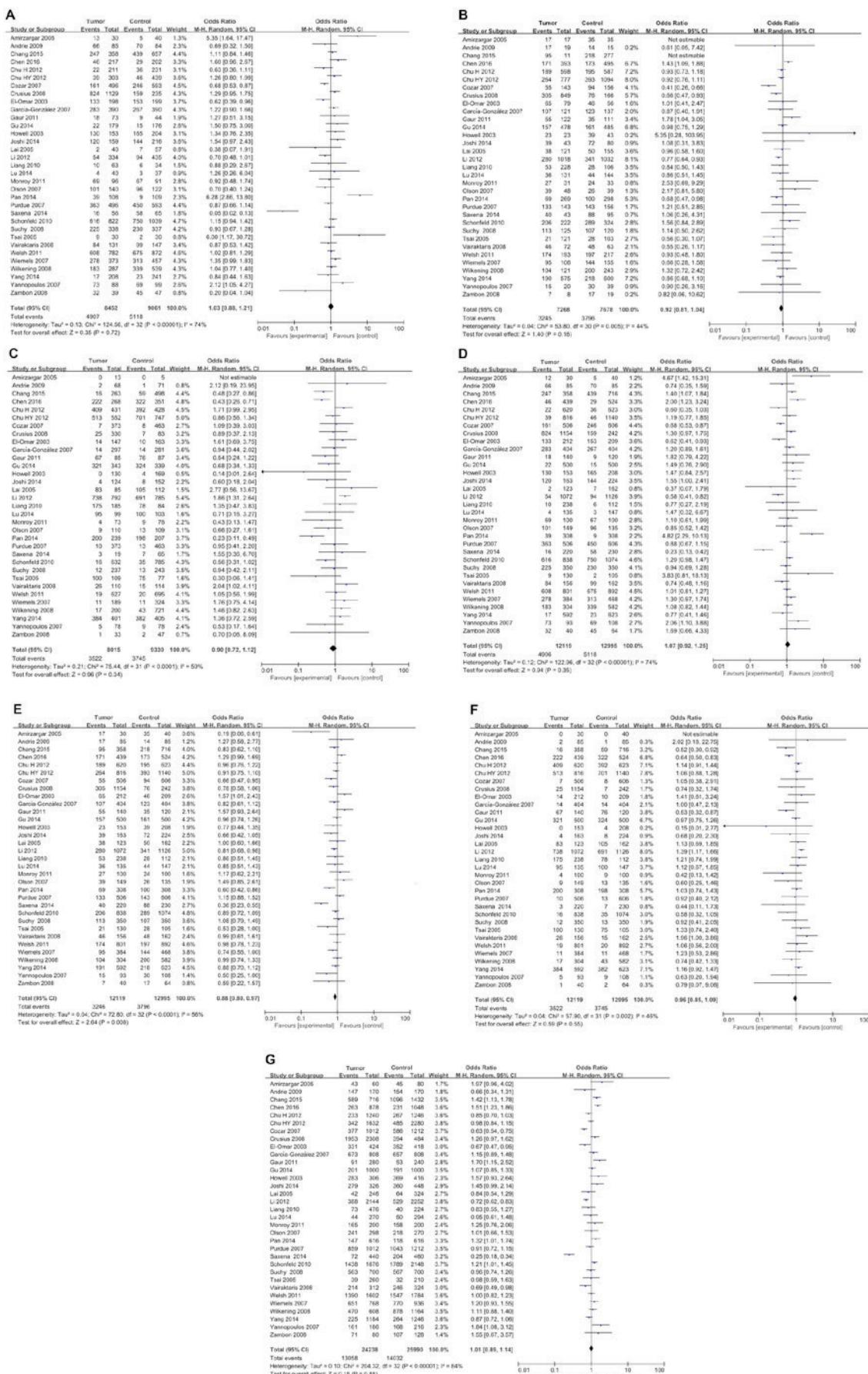Figure 1. Flow diagram of included/excluded studies for the meta-analysis.

Figure 2. Forest plots of association between IL-4 rs2243250 polymorphism and cancer risk for all genetic models. (A) CC vs. CT. (B) CT vs. TT. (C) TT vs. CC. (D) CC vs. CT. (E) CT vs. CC/TT. (F) TT vs. CC/CT. (G) C vs. T. 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. IL, interleukin; OR, odds ratio; CI, confidence interval.

Table III. Characteristics of subjects included in the meta-analysis of inteleukin-4 rs2070874 polymorphism and cancer risk.

First author, year	Country	Ethnicity	Cancer type	Case			Control				NOS score	(Ref.)
				n	Genotypes CC/CT/TT	Alleles C/T (%)	n	Genotypes CC/CT/TT	Alleles C/T (%)	P-value HWE		
Amirzargar, 2005	Iran	Caucasian	Leukemia	30	20/5/5	75.0/25.0	40	22/18/0	77.5/22.5	0.066	7	(42)
Chang, 2015	Taiwan	Asian	Lung cancer	358	238/101/19	80.6/19.4	716	453/223/40	78.8/21.2	0.075	7	(35)
Crusius, 2008	Netherlands	Caucasian	Gastric cancer	243	159/77/7	81.3/18.7	1160	839/296/25	85.1/14.9	0.853	8	(11)
Gaur, 2011	India	Caucasian	Oral carcinoma	140	20/61/59	36.1/63.9	120	11/38/71	25.0/75.0	0.088	8	(28)
Gu, 2008	USA	Mixed	Skin cancer	217	160/52/5	85.7/14.3	214	165/43/6	87.1/12.9	0.132	8	(45)
Lu, 2010	China	Asian	Gastric cancer	1042	27/271/744	15.6/84.4	1099	24/332/743	17.3/82.7	0.062	7	(44)
Lu, 2014	China	Asian	Hepatocellular cancer	135	8/43/84	21.9/78.1	147	4/45/98	18.0/82.0	0.664	7	(31)
Purdue, 2007	USA	Mixed	Testicular germ cell tumor	501	364/128/9	85.4/14.6	598	447/139/12	86.4/13.6	0.757	8	(40)
Schonfeld, 2010	USA	Mixed	Breast cancer	818	600/206/12	85.9/14.1	1081	763/288/30	83.9/16.1	0.654	7	(21)
Shamran, 2014	Iraq	Caucasian	Brain tumor	100	71/26/3	84.0/16.0	40	22/13/5	71.3/28.7	0.191	8	(43)
Wiemels, 2007	USA	Mixed	Brain tumor	386	281/93/12	84.8/15.2	471	328/134/9	83.9/16.1	0.267	8	(39)

Significant associations are denoted in bold font. HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa quality assessment scale.

Table IV. Subgroup analyses for interleukin-4 rs2070874polymorphism and cancer risk.

A, Gastric cancer (n=3[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.91	1.03 (0.60-1.76)	59%	0.09
CT vs. TT	0.07	0.85 (0.71-1.01)	0%	0.52
TT vs. CC	0.67	0.91 (0.59-1.41)	25%	0.26
CC vs. CT + TT	0.94	1.02 (0.60-1.74)	60%	0.08
CT vs. CC + TT	0.85	1.04 (0.72-1.49)	75%	0.85
TT vs. CC + CT	0.11	1.15 (0.97-1.36)	5%	0.35
C vs. T	0.35	0.90 (0.72-1.12)	53%	0.12

B, Brain tumor (n=2[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.10	1.27 (0.95-1.70)	0%	0.55
CT vs. TT	0.86	1.17 (0.19-7.13)	75%	0.05
TT vs. CC	0.62	0.59 (0.07-4.70)	82%	0.02
CC vs. CT + TT	0.11	1.25 (0.95-1.65)	41%	0.19
CT vs. CC + TT	0.30	0.52 (0.15-1.77)	78%	0.03
TT vs. CC + CT	0.67	0.65 (0.09-4.74)	81%	0.02
C vs. T	0.29	1.42 (0.74-2.73)	75%	0.05

C, Leukemia (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	**0.05**	**3.27 (1.02-10.45)**	NA	NA
CT vs. TT	**0.02**	**0.03 (0.00-0.57)**	NA	NA
TT vs. CC	0.10	12.07 (0.63-232.12)	NA	NA
CC vs. CT + TT	0.33	1.64 (0.61-4.37)	NA	NA
CT vs. CC + TT	**0.02**	**0.24 (0.08-0.77)**	NA	NA
TT vs. CC + CT	0.06	17.47 (0.93-329.53)	NA	NA
C vs. T	0.73	0.87 (0.40-1.91)	NA	NA

D, Lung cancer (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.30	1.16 (0.87-1.54)	NA	NA
CT vs. TT	0.88	0.95 (0.53-1.73)	NA	NA
TT vs. CC	0.73	0.90 (0.51-1.60)	NA	NA
CC vs. CT + TT	0.30	1.15 (0.88-1.50)	NA	NA
CT vs. CC + TT	0.32	0.87 (0.66-1.15)	NA	NA
TT vs. CC + CT	0.85	0.95 (0.54-1.66)	NA	NA
C vs. T	0.35	1.11 (0.89-1.39)	NA	NA

E, Oral carcinoma (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.77	1.13 (0.49-2.62)	NA	NA
CT vs. TT	**0.02**	**1.93 (1.13-3.29)**	NA	NA
TT vs. CC	0.06	0.46 (0.20-1.03)	NA	NA
CC vs. CT + TT	0.21	1.65 (0.76-3.60)	NA	NA
CT vs. CC + TT	**0.05**	**1.67 (1.00-2.77)**	NA	NA
TT vs. CC + CT	**0.006**	**0.50 (0.31-0.82)**	NA	NA
C vs. T	**0.007**	**1.69 (1.16-2.48)**	NA	NA

Table IV. Continued.

F, Breast cancer (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.37	1.10 (0.89-1.35)	NA	NA
CT vs. TT	0.10	1.79 (0.89-3.58)	NA	NA
TT vs. CC	0.05	0.51 (0.26-1.00)	NA	NA
CC vs. CT + TT	0.18	1.15 (0.94-1.41)	NA	NA
CT vs. CC + TT	0.47	0.93 (0.75-1.14)	NA	NA
TT vs. CC + CT	0.06	0.52 (0.27-1.03)	NA	NA
C vs. T	0.08	1.17 (0.98-1.40)	NA	NA

G, Testicular tumor (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.38	0.88 (0.67-1.17)	NA	NA
CT vs. TT	0.65	1.23 (0.50-3.01)	NA	NA
TT vs. CC	0.85	0.92 (0.38-2.21)	NA	NA
CC vs. CT + TT	0.43	0.90 (0.69-1.18)	NA	NA
CT vs. CC + TT	0.38	1.13 (0.86-1.49)	NA	NA
TT vs. CC + CT	0.80	0.89 (0.37-2.14)	NA	NA
C vs. T	0.53	0.93 (0.73-1.18)	NA	NA

H, Skin cancer (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.35	0.80 (0.51-1.27)	NA	NA
CT vs. TT	0.56	1.45 (0.41-5.08)	NA	NA
TT vs. CC	0.81	0.86 (0.26-2.87)	NA	NA
CC vs. CT + TT	0.42	0.83 (0.54-1.29)	NA	NA
CT vs. CC + TT	0.33	1.25 (0.79-1.98)	NA	NA
TT vs. CC + CT	0.74	0.82 (0.25-2.72)	NA	NA
C vs. T	0.54	0.88 (0.60-1.31)	NA	NA

I, Caucasian (n=4[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.48	1.25 (0.67-2.33)	66%	0.03
CT vs. TT	0.78	1.16 (0.41-3.29)	70%	0.02
TT vs. CC	0.67	0.78 (0.24-2.51)	72%	0.01
CC vs. CT + TT	0.40	1.30 (0.71-2.38)	70%	0.02
CT vs. CC + TT	0.92	0.97 (0.55-1.73)	73%	0.01
TT vs. CC + CT	0.68	0.80 (0.28-2.27)	73%	0.01
C vs. T	0.45	1.23 (0.71-2.13)	83%	0.0006

J, Asian (n=3[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
CC vs. CT	0.12	1.22 (0.95-1.56)	0%	0.77
CT vs. TT	0.07	0.86 (0.72-1.01)	0%	0.49
TT vs. CC	0.35	0.83 (0.57-1.22)	0%	0.54
CC vs. CT + TT	0.15	1.19 (0.94-1.51)	0%	0.58
CT vs. CC + TT	**0.03**	**0.85 (0.73-0.98)**	0%	0.61
TT vs. CC + CT	0.17	1.12 (0.95-1.32)	15%	0.17
C vs. T	0.81	1.03 (0.83-1.26)	54%	0.11

[a]Number of articles. Significant associations are denoted in bold font. OR, odds ratio; CI, confidence interval; NA, not applicable.

Table V. Characteristics of subjects included in the meta-analysis of interleukin-4 rs79071878 polymorphism and cancer risk.
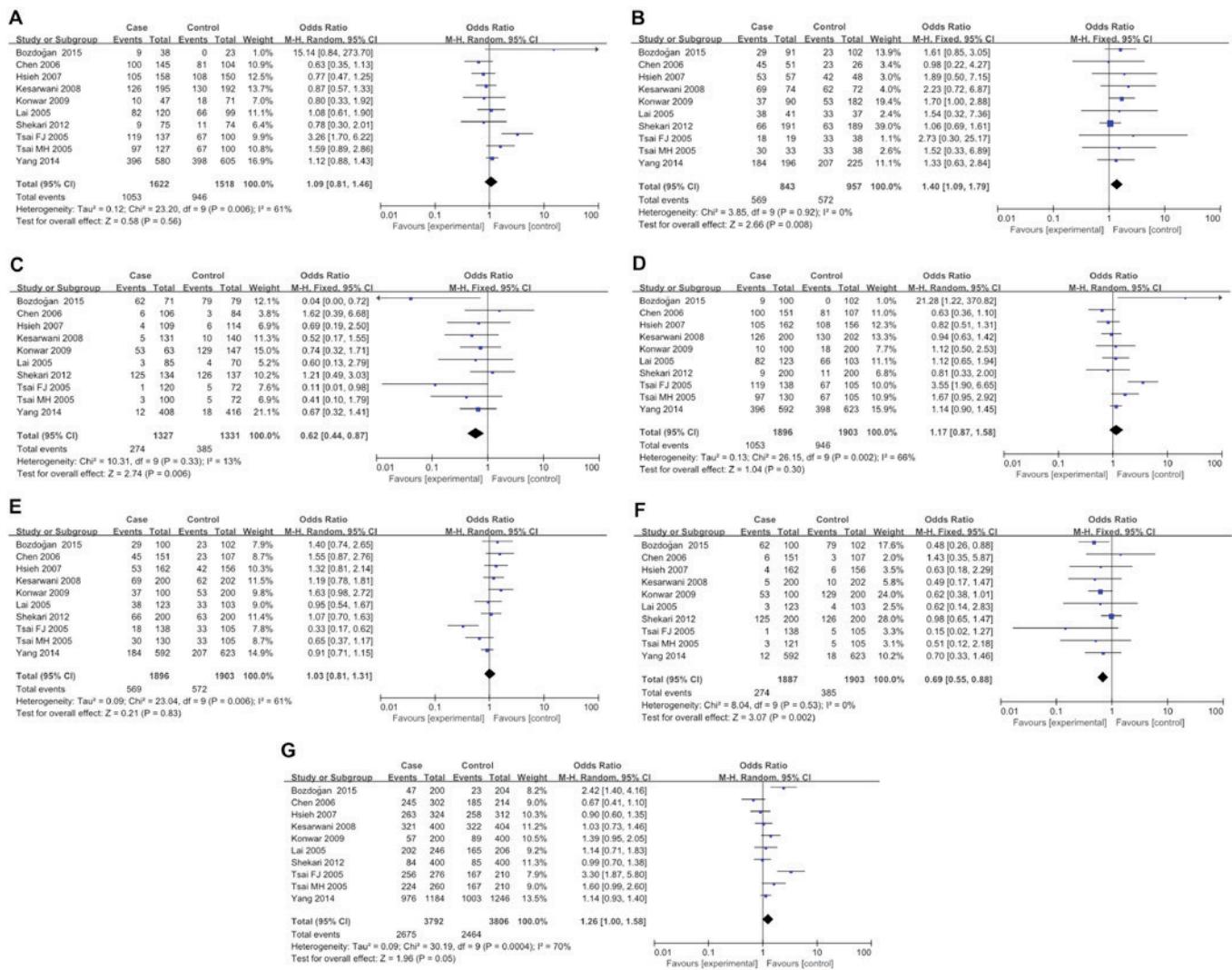
First author, year	Country	Ethnicity	Cancer type	Case			Control				NOS score	(Refs.)
				n	Genotypes RP1.1/RP1.2/RP2.2	Alleles RP1.1/RP2.2 (%)	n	Genotypes RP1.1/RP1.2/RP2.2	Alleles RP1.1/RP2.2 (%)	P-value HWE		
Bozdoğan, 2015	Turkey	Caucasian	Bladder cancer	100	9/29/62	40.0/60.0	102	0/23/79	38.7/61.3	0.199	7	(48)
Chen, 2006	China	Asian	Gastric cancer	151	100/45/6	81.1/18.9	107	81/23/3	86.4/13.6	0.393	7	(46)
Hsieh, 2007	Taiwan	Asian	Leiomyoma	162	105/53/4	81.2/18.8	156	108/42/6	82.7/17.3	0.458	8	(27)
Kesarwani, 2008	India	Caucasian	Prostate cancer	200	126/69/5	80.3/19.7	202	130/62/10	79.7/20.3	0.465	8	(52)
Konwar, 2009	India	Caucasian	Breast cancer	100	10/37/53	28.5/71.5	200	18/53/129	22.3/77.7	**0.001**	7	(51)
Lai, 2005	Taiwan	Asian	Gastric cancer	123	82/38/3	82.1/17.9	103	66/33/4	80.1/19.9	0.961	7	(14)
Shekari, 2012	India	Caucasian	Cervical cancer	200	9/66/125	21.0/79.0	200	11/63/126	21.3/78.7	0.405	8	(50)
Tsai, 2005	Taiwan	Asian	Bladder cancer	138	119/18/1	92.8/7.2	105	67/33/5	79.5/20.5	0.720	7	(47)
Tsai, 2005	Taiwan	Asian	Oral carcinoma	121	97/30/3	88.8/11.2	105	67/33/5	47.7/52.3	0.720	7	(29)
Yang, 2014	Taiwan	Asian	Oral carcinoma	463	309/145/9	82.4/17.6	623	398/207/18	80.5/19.5	0.146	8	(53)
Yang, 2014	Taiwan	Asian	Pharyngeal carcinoma	129	87/39/3	82.6/17.4	623	398/207/18	80.5/19.5	0.146	8	(53)

Significant associations are denoted in bold font. Alleles of two and three repeats were designated as RP1 and RP2, respectively. Genotypes were designated as RP1.1=RP1/RP1, RP1.2=RP1/RP2 and RP2.2=RP2/RP2. RP, repeat; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa quality assessment scale.

Figure 3. Forest plot of association between IL-4 rs2070874 polymorphism and cancer risk for all genetic models. (A) CC vs. CT. (B) CT vs. TT. (C) TT vs. CC. (D) CC vs. CT/TT. (E) CT vs. CC/TT. (F) TT vs. CC/CT. (G) C vs. T. 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. IL, interleukin; OR, odds ratio; CI, confidence interval.
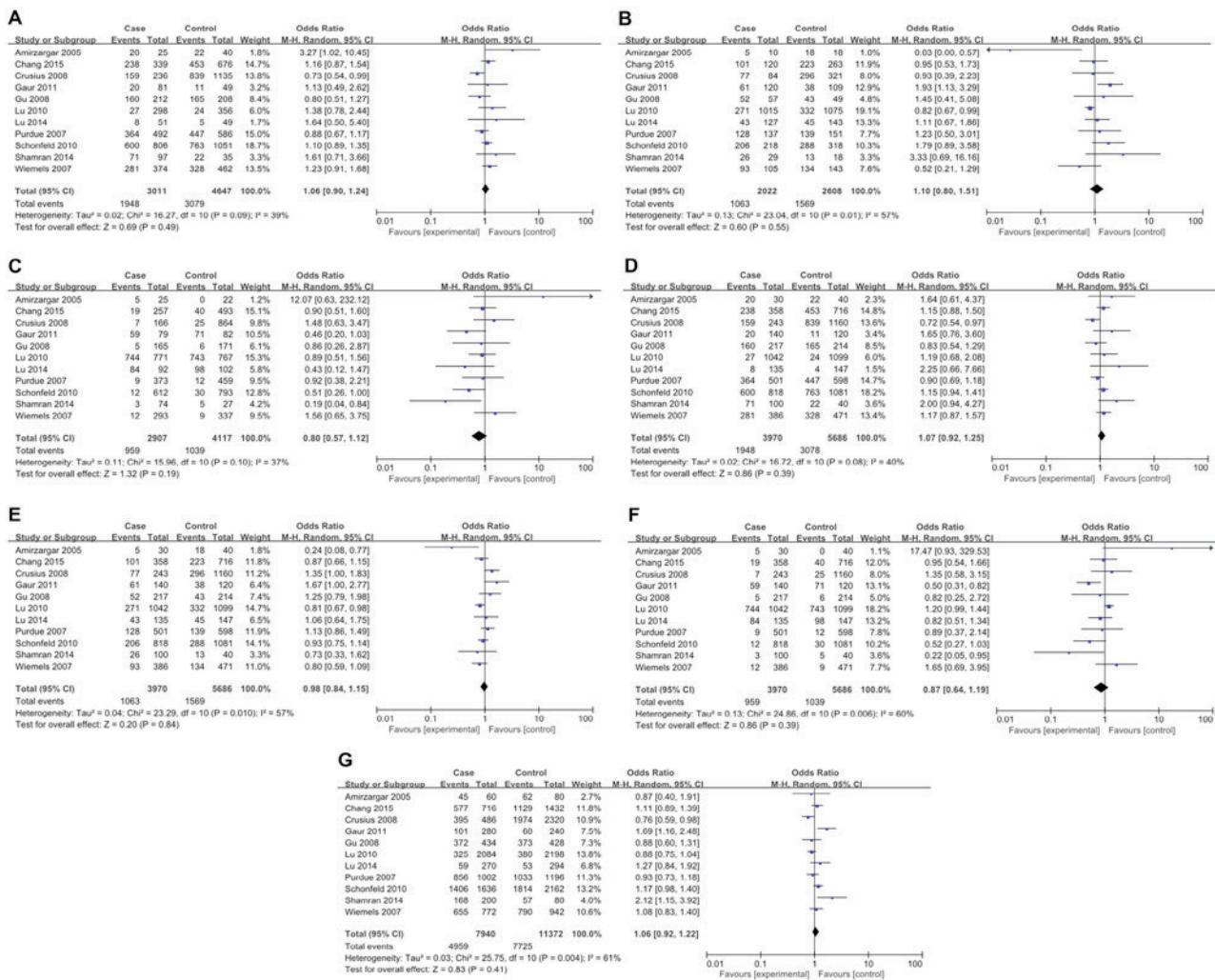
IL-4 rs2070874 polymorphism and the risk of cancer. For IL-4 rs2070874 polymorphism, 11 studies involving 3,970 patients and 5,686 controls were included. All relevant studies were in agreement with HWE (Table III). Inter-study heterogeneity was obvious in all comparisons and thus REMs were used for analyses. No significant association between IL-4 rs2070874 polymorphism and cancer risk was observed in all genetic models (Fig. 3). Further stratification analyses by cancer type revealed a significant association with leukemia (CC vs. CT: P=0.05, OR=3.27, 95% CI1.02-10.45; CT vs. TT: P=0.02, OR=0.03, 95% CI 0.00-0.57; and CT vs. CC/TT: P=0.02, OR=0.24, 95% CI 0.08-0.77), and oral carcinoma (CT vs. TT: P=0.02, OR=1.93, 95% CI1.13-3.29; CT vs. CC/TT: P=0.05, OR=1.67, 95% CI 1.00-2.77; TT vs. CC/CT: P=0.006, OR=0.50, 95% CI 0.31-0.82; and C vs. T: P=0.007, OR=1.69, 95% CI 1.16-2.48) (Table II). Nevertheless, no association was observed between rs2070874 polymorphism and other tumor types (Table III). In the subgroup analyses by ethnicity, a significant association was found in Asian populations (CT vs. CC/TT: P=0.03, OR=0.85, 95% CI 0.73-0.98), but not in Caucasian populations (Table IV).

IL-4 rs79071878 polymorphism and the risk of cancer. A total of 10 studies with 1,896 patients and 2,526 controls were involved in the present analyses for IL-4 rs79071878 polymorphism and cancer risk. HWE test revealed that only one study deviated from HWE (Table V). IL-4 VNTR is a 70 bp repeat. Alleles of two and three repeats were designated as repeat 1 (RP1) and repeat 2 (RP2), respectively, and genotypes of RP1/RP1, RP1/RP2 and RP2/RP2 were designated as RP1.1, RP1.2 and RP2.2, respectively. For RP1.2 vs. RP2.2, RP2.2 vs. RP1.1 and RP2.2 vs. RP1.1/RP1.2, FEMs were selected for analyses since only mild inter-study heterogeneity was observed. In contrast, for RP1.1 vs. RP1.2, RP1.1 vs. RP1.2/RP2.2, RP1.2 vs. RP1.1/RP2.2 and RP1 vs. RP2, REMs were used because heterogeneity between studies was significant. The results demonstrated an apparent correlation between IL-4 rs79071878 polymorphism and cancer risk (RP1.2 vs. RP2.2: P=0.008, OR=1.40, 95% CI 1.09-1.79; RP2.2 vs. RP1.1: P=0.006, OR=0.62, 95% CI0.44-0.87, RP2.2 vs. RP1.1/RP1.2: P=0.002, OR=0.69, 95% CI 0.55-0.88; and RP1.1 vs. RP2.2: P=0.05, OR=1.26, 95% CI 1.00-1.58; Fig. 4). Further analyses by cancer type subgroup revealed that the

Figure 4. Forest plot of association between IL-4 rs79071878 polymorphism and cancer risk for all genetic models. (A) RP1.1 vs. RP1.2. (B) RP1.2 vs. RP2.2. (C) RP2.2 vs. RP1.1. (D) RP1.1 vs. RP1.2/RP2.2. (E) RP1.2 vs. RP1.1/RP2.2. (F) RP2.2 vs. RP1.1/RP1.2. (G) RP1 vs. RP2. 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. Alleles of two and three repeats were designated as RP1 and RP2, respectively. Genotypes were designated as RP1.1=RP1/RP1, RP1.2=RP1/RP2 and RP2.2=RP2/RP2. IL, interleukin; RP, repeat; OR, odds ratio; CI, confidence interval.

rs79071878 polymorphism was associated with an increased risk of bladder cancer (RP1.1 vs. RP1.2: P<0.0001, OR=3.78, 95% CI 2.03-7.05; RP2.2 vs. RP1.1: P=0.002, OR=0.07, 95% CI 0.01-0.38; RP1.1 vs. RP1.2/RP2.2: P<0.0001, OR=4.28, 95% CI 2.35-7.81; and RP2.2 vs. RP1.1/RP1.2: P=0.004, OR=0.42, 95% CI 0.24-0.76) and breast cancer (RP1.2 vs. RP2.2: P=0.05, OR=1.70, 95% CI 1.00-2.88) (Table VI). However, no significant association was observed in other types of cancer. Furthermore, stratified analysis by ethnicity yielded a significant association for the IL-4 rs79071878 polymorphism with cancer risk in the Asian ethnicity (RP1.2 vs. RP2.2: P=0.03, OR=1.38, 95% CI 1.04-1.83; and RP2.2 vs. RP1.1/RP1.2: P=0.01, OR=0.71, 95% CI 0.54-0.93). However, no evidence for any associations between IL-4 rs79071878 polymorphism and cancer risk was detected in the Caucasian ethnicity (Table VI).

Sensitivity analysis and publication bias. Sensitivity analyses were performed by removing one individual study from the analysis at a time. For IL-4 rs2243250 polymorphism, when

the study of Chen *et al* (22) was omitted, the comparison in CT vs. TT yielded positive result (P=0.03, OR=0.88, 95% CI 0.79-0.98). For IL-4 rs2070874 and rs79071878 polymorphisms, however, removing individual studies did not impact the overall results. Publication bias was evaluated with funnel plots, and visual inspection of the funnel plots for all investigated polymorphisms indicated that there was no significant publication bias in the present meta-analysis.

Discussion

Cancer is a major public health problem with extremely high morbidity and mortality. Certain cytokine gene polymorphisms may serve crucial roles in cancer pathogenesis. Among these, IL-4 rs2243250, rs2070874 and rs79071878 polymorphisms are three intensively studied variants. Previous studies have demonstrated that the T allele of IL-4 rs2243250 and rs2070874 polymorphisms can increase binding of nuclear transcription factors to the promoter region of the IL-4 gene, and thus lead to increased transcription of

Table VI. Subgroup analyses for inteleukin-4 rs79071878polymorphism and cancer risk.

A, Bladder cancer (n=2[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.56	1.09 (0.81-1.46)	8%	0.30
RP1.2 vs. RP2.2	**0.008**	**1.40 (1.09-1.79)**	0%	0.65
RP2.2 vs. RP1.1	**0.006**	**0.62 (0.44-0.87)**	0%	0.57
RP1.1 vs. RP1.2/ RP2.2	0.30	1.17 (0.87-1.58)	35%	0.21
RP1.2 vs. RP1.1/RP2.2	0.83	1.03 (0.81-1.13)	90%	0.002
RP2.2 vs. RP1.1/ RP1.2	**0.002**	**0.69 (0.55-0.88)**	6%	0.30
RP1 vs. RP2	**0.005**	**1.26 (1.00-1.58)**	0%	0.44

B, Gastric cancer (n=2[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.36	0.83 (0.49-1.40)	40%	0.20
RP1.2 vs. RP2.2	0.73	1.21 (0.42-3.50)	0%	0.68
RP2.2 vs. RP1.1	0.94	1.04 (0.38-2.85)	0%	0.35
RP1.1 vs. RP1.2/RP2.2	0.55	0.84 (0.48-1.48)	52%	0.15
RP1.2 vs. RP1.1/RP2.2	0.35	1.21 (0.81-1.81)	30%	0.23
RP2.2 vs. RP1.1/RP1.2	0.97	0.98 (0.36-2.69)	0%	0.43
RP1 vs. RP2	0.63	0.88 (0.52-1.47)	57%	0.13

C, Leiomyoma (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.29	0.77 (0.47-1.25)	NA	NA
RP1.2 vs. RP2.2	0.35	1.89 (0.50-7.15)	NA	NA
RP2.2 vs. RP1.1	0.57	0.69 (0.19-2.50)	NA	NA
RP1.1 vs. RP1.2/RP2.2	0.40	0.82 (0.51-1.31)	NA	NA
RP1.2 vs. RP1.1/RP2.2	0.26	1.32 (0.81-2.14)	NA	NA
RP2.2 vs. RP1.1/RP1.2	0.49	0.63 (0.18-2.29)	NA	NA
RP1 vs. RP2	0.62	0.90 (0.60-1.35)	NA	NA

D, Oral carcinoma (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.12	1.59 (0.89-2.86)	NA	NA
RP1.2 vs. RP2.2	0.59	1.52 (0.33-6.89)	NA	NA
RP2.2 vs. RP1.1	0.24	0.41 (0.10-1.79)	NA	NA
RP1.1 vs. RP1.2/RP2.2	0.07	1.67 (0.95-2.92)	NA	NA
RP1.2 vs. RP1.1/RP2.2	0.15	0.65 (0.37-1.17)	NA	NA
RP2.2 vs. RP1.1/RP1.2	0.36	0.51 (0.12-2.18)	NA	NA
RP1 vs. RP2	0.06	1.60 (0.99-2.60)	NA	NA

E, Prostate cancer (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.52	0.87 (0.57-1.33)	NA	NA
RP1.2 vs. RP2.2	0.16	2.23 (0.72-6.87)	NA	NA
RP2.2 vs. RP1.1	0.24	0.52 (0.17-1.55)	NA	NA
RP1.1 vs. RP1.2/RP2.2	0.78	0.94 (0.63-1.42)	NA	NA
RP1.2 vs. RP1.1/RP2.2	0.42	1.19 (0.78-1.81)	NA	NA
RP2.2 vs. RP1.1/RP1.2	0.20	0.49 (0.17-1.47)	NA	NA
RP1 vs. RP2	0.85	1.03 (0.73-1.46)	NA	NA

Table VI. Continued.

F, Cervical cancer (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.61	0.78 (0.30-2.01)	NA	NA
RP1.2 vs. RP2.2	0.80	1.06 (0.69-1.61)	NA	NA
RP2.2 vs. RP1.1	0.68	1.21 (0.49-3.03)	NA	NA
RP1.1 vs. RP1.2/RP2.2	0.65	0.81 (0.33-2.00)	NA	NA
RP1.2 vs. RP1.1/RP2.2	0.75	1.07 (0.70-1.63)	NA	NA
RP2.2 vs. RP1.1/RP1.2	0.92	0.98 (0.65-1.47)	NA	NA
RP1 vs. RP2	0.93	0.99 (0.70-1.38)	NA	NA

G, Breast cancer (n=1[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.61	0.80 (0.33-1.92)	NA	NA
RP1.2 vs. RP2.2	**0.05**	**1.70 (1.00-2.88)**	NA	NA
RP2.2 vs. RP1.1	0.48	0.74 (0.32-1.71)	NA	NA
RP1.1 vs. RP1.2/RP2.2	0.78	1.12 (0.50-2.53)	NA	NA
RP1.2 vs. RP1.1/RP2.2	0.06	1.63 (0.98-2.72)	NA	NA
RP2.2 vs. RP1.1/RP1.2	0.06	0.62 (038-1.01)	NA	NA
RP1 vs. RP2	0.09	1.39 (0.95-2.05)	NA	NA

H, Caucasian (n=4[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.74	0.94 (0.67-1.33)	24%	0.26
RP1.2 vs. RP2.2	**0.03**	**1.38 (1.04-1.83)**	1%	0.39
RP2.2 vs. RP1.1	0.05	0.61 (0.37-1.01)	49%	0.12
RP1.1 vs. RP1.2/RP2.2	0.64	1.08 (0.78-1.50)	40%	0.17
RP1.2 vs. RP1.1/RP2.2	0.06	1.26 (0.99-1.59)	0%	0.63
RP2.2 vs. RP1.1/RP1.2	**0.01**	**0.71 (0.54-0.93)**	37%	0.19
RP1 vs. RP2	0.13	1.30 (0.92-1.82)	66%	0.03

I, Asian (n=6[a])

Variable	P-value	OR (95% Cl)	I-square (%)	P-value for the heterogeneity
RP1.1 vs. RP1.2	0.41	1.17 (0.81-1.71)	72%	0.003
RP1.2 vs. RP2.2	0.14	1.46 (0.88-2.42)	0%	0.98
RP2.2 vs. RP1.1	0.05	0.62 (0.38-1.01)	0%	0.48
RP1.1 vs. RP1.2/RP2.2	0.31	1.22 (0.83-1.81)	76%	0.0009
RP1.2 vs. RP1.2/RP2.2	0.46	0.87 (0.61-1.25)	70%	0.006
RP2.2 vs. RP1.1/RP1.2	0.07	0.64 (0.40-1.04)	0%	0.67
RP1 vs. RP2	0.23	1.23 (0.88-1.74)	76%	0.0008

[a]Number of articles. Significant associations are denoted in bold font. Alleles of two and three repeats were designated as RP1 and RP2, respectively. Genotypes were designated as RP1.1=RP1/RP1, RP1.2=RP1/RP2 and RP2.2=RP2/RP2. RP, repeat; OR, odds ratio; CI, confidence interval; NA, not applicable.

IL-4 (32,43). In addition, the rs79071878 polymorphism may also affect the transcription activity of IL-4 (54). However, despite the identifications of these potential mechanisms, the results concerning the association of IL-4 gene polymorphisms and cancer risk remain controversial. Thus, in order to clarify this association, a meta-analysis was performed in the present study to estimate the correlation between IL-4 gene polymorphisms (rs2243250, rs2070874 and rs79071878) and cancer susceptibility.

For IL-4 rs2243250 polymorphism, the present data suggested that this polymorphism was significantly associated with cancer risk. In subgroup analyses by cancer type,

rs2243250 was demonstrated to be associated with a higher risk of gastric cancer and breast cancer. The CT/TT genotype carriers were at a lower risk of developing gastric cancer or breast cancer compared with individuals with the CC genotype. Furthermore, the CT genotype was demonstrated to be associated with an increased risk of prostate cancer compared with the CC/TT genotypes. These results suggested that this polymorphism may serve different roles in different types of malignancies. Further subgroup analysis by ethnicity revealed that the IL-4 rs2243250 polymorphism was correlated with an increased cancer risk in both Asian and Caucasian populations. The overall analysis for the IL-4 rs2070874 polymorphism yielded no significant association with general cancer risk. In the cancer-type subgroup analysis, a significant association of IL-4 rs2070874 polymorphism with leukemia and oral carcinoma was identified, with patients carrying the CT genotype or the C allele being more likely to develop oral carcinoma. By contrast, for leukemia the CT genotype carriers were at a lower risk of developing leukemia. It is worth noting that these results should be interpreted with caution, since our estimations regarding leukemia and oral carcinoma were based on one single study. Additionally, in ethnicity sub-analysis, the results indicated a significant association with cancer susceptibility among Asian populations under the recessive genetic model. Finally, the IL-4 rs79071878 polymorphism was overtly associated with a higher risk of cancer under the allelic model. The results of subgroup analyses indicated that IL-4 rs79071878 polymorphism was significantly associated with bladder cancer and breast cancer in certain genetic models, and an association between IL-4 rs79071878 polymorphism and cancer susceptibility was only observed among Caucasians, but not Asians. Overall, from general and subgroup analyses, it can be concluded that IL-4 gene polymorphisms may be important in the pathogenesis of certain types of cancer, and their effects on cancer risk may be ethnic specific. Nevertheless, the amount of relevant studies is not sufficient to draw a safe conclusion, and further well-designed studies with larger patient sample size will be required in the future to validate the present results.

Heterogeneity is one of the most important issues when performing meta-analysis. In the present meta-analysis, heterogeneity between studies existed in almost all comparisons. Therefore, we attempted to detect the source of heterogeneity by dividing included studies into different subgroups according to cancer type and ethnicity. The heterogeneity was drastically decreased in most subgroups, suggesting that these two factors contribute to a significant portion of heterogeneity in the present meta-analysis.

When interpreting the results of the present meta-analysis, several limitations should be considered. Firstly, the numbers of relevant studies were limited, and studies regarding several particular types of cancer were extremely lacking. Secondly, although funnel plots did not reveal any publication bias, the possibility of publication bias cannot be completely eliminated, since only published studies were included. Thirdly, the present results were based on unadjusted estimates, while a more precise analysis should have been adjusted by other factors, including smoking, age, and environmental factors. Finally, the present analyses did not consider the possibility of gene-gene or SNP-SNP interactions or the possibility of linkage disequilibrium between polymorphisms. Taking all these limitations into consideration, the results reported by the current study should be interpreted with caution.

In summary, the present results suggest that the IL-4 rs2243250 and rs79071878 polymorphisms were associated with cancer susceptibility. Further subgroup analyses revealed that the effects of IL-4 gene polymorphisms on cancer risk may vary depending on the cancer type and the ethnicity. However, given that the present results were based on limited number of case-control studies, further multi-center studies with larger sample size from different populations are warranted to confirm our results.

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