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The Interleukin 10 −819C/T Polymorphism and Cancer Risk: A HuGE Review and Meta-Analysis of 73 Studies Including 15,942 Cases and 22,336 Controls

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Abstract

The aim of the present work was to perform a meta-analysis to evaluate the association between the interleukin 10 (IL-10) −819C/T (rs1800871) polymorphism and cancer risk. A total of 73 studies, including 15,942 cancer cases and 22,336 controls, were identified in this meta-analysis. The odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using the random-effects model. Overall, no significant association was identified between the *IL-10* −819C/T polymorphism and cancer risk. In the subgroup analyses, the T allele and TT genotype were associated with a moderately reduced cancer risk in the Asian population (T allele *vs.* C allele: OR = 0.93, 95%CI: 0.87, 0.99; TT *vs.* CC: OR = 0.86, 95%CI: 0.76, 0.98; TT *vs.* CT/CC: OR = 0.90, 95%CI: 0.82, 0.98). Individuals who were homozygous for the T allele (TT) were found to be associated with significantly reduced gastric cancer risk in the Asian population. The heterozygous variant (CT) and the dominant model (TT/CT *vs.* CC) were associated with an increased risk for cervical and ovarian cancer. However, the *IL-10* −819C/T polymorphism was not significantly associated with breast cancer, colorectal cancer, lung cancer, hepatocellular carcinoma, prostate cancer, lymphoma, or melanoma. The depressed cancer risk of the TT genotype occurred in the studies of hospital-based case-control studies and the studies recruited less than 500 subjects, but no statistically significant results were found in the stratified analyses using genotyping method. The results suggest that the *IL-10* −819TT genotype may be a protective factor for cancer in Asians, especially gastric cancer. In contrast, the CT genotype and the dominant model could be risk factors for cervical and ovarian cancer. The importance of stratifying by ethnicity, cancer type, study design, and sample size needs to be standardized in future studies, together with considering the association between the *IL-10* −819C/T polymorphism and cancer risk. Furthermore, the linkage of −819C/T with other polymorphisms of the *IL-10* gene may help explain the variability in findings.

Introduction

Gene and gene variants

Interleukin-10 (IL-10) is a multifunctional anti-inflammatory cytokine mainly produced by immune cells, such as T cells, monocytes, appropriately stimulated macrophages, some subsets of dendritic cells (DCs), and B cells (Fillatreau et al., 2008; O'Garra and Vieira, 2007; Ryan et al., 2007). Non-immune cell sources of IL-10 also exist, including keratinocytes, epithelial cells, and some tumor cells (Moore et al., 2001; Williams et al., 2004). The human *IL-10* gene is located on chromosome 1q32.1 and contains five exons (Spits and de Waal Malefyt, 1992). Recently, IL-10 has been identified as an important player in the development of immunological and inflammatory responses involving in the pathogenesis of cancer (Chow et al., 2012).

The *IL-10* promoter contains several single-nucleotide polymorphisms (SNPs) (Turner et al., 1997), which may influence *IL-10* gene expression (Liang et al., 2011). A C-to-T single base pair substitution has been identified in the promoter region of the *IL-10* gene −819 base pairs upstream of the transcriptional start site. This single base pair substitution has been named both −819C/T and rs1800871. At this time, a series of seven molecular epidemiological studies and meta-analyses have investigated the association between the *IL-10* −819C/T polymorphism and the susceptibility to different cancer types among different populations (Chen et al., 2010; Persson et al., 2011; Shao et al., 2011; Wei et al., 2011; Xue et al.,

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2012; Zou et al., 2011). However, the results from these studies are inconsistent.

Disease

Cancer is currently a major worldwide public health problem. Etiologically, carcinogenesis is a multistep and multifactorial process resulting from complex interactions between genetic and environmental factors (Pharoah et al., 2004). There is convincing evidence that chronic inflammation is a risk factor for tumor development (Chow et al., 2012). Chronic inflammation contributes to the following: (1) cancer initiation by generating genotoxic stress; (2) cancer promotion by inducing cellular proliferation; and (3) cancer progression by enhancing angiogenesis and tissue invasion (Grivennikov et al., 2010). Activated immune cells produce and secrete inflammatory cytokines, chemokines, growth factors, prostaglandins, and reactive oxygen and nitrogen species. All of these factors affect malignant cells (de Visser et al., 2006). However, the exact mechanisms of action of inflammatory cytokines in carcinogenesis are not completely understood, and the associated risk factors must be further elucidated.

The aim of this meta-analysis was to clarify the association of the *IL-10* −819C/T polymorphism with the risk of cancer by integrating published case-control studies.

Materials and Methods

We conducted this systematic review and meta-analysis according to the HuGE review guidelines (http://www.cdc.gov/genomics/hugenet/participate.htm).

Search strategy

We searched the following electronic literature databases: MEDLINE (via PubMed), EMBASE, HuGE Literature Finder, Wanfang Database (China), China National Knowledge Infrastructure (CNKI), and VIP Database (China). Our search identified all relevant articles and used the following search terms: "interleukin 10", "interleukin-10", "IL-10", "IL10," and "cancer" or the same group of interleukin-10 based search terms and "polymorphism". One author (Zhibin Yu) identified relevant studies up to May 14, 2012. The search was without restriction with regard to language or publication date, but it was limited to studies conducted on human subjects. All of the studies identified by the search were retrieved, and their references were checked for other relevant publications. Review articles were also searched to find eligible studies. Only the most recent or complete study was selected when studies involved examination of the same population by different investigators or overlapping data by the same authors.

Inclusion/exclusion criteria

Two authors (Zhibin Yu and Yinnan Sun) reviewed all titles or abstracts of the identified studies to select those for inclusion. Studies included in our meta-analysis were required to meet the following criteria: (1) involve the evaluation of the association of the −819C/T polymorphism in the *IL-10* gene and cancer risk, (2) have a case-control or cohort study design, and (3) contain sufficient published data for estimating an odds ratio (OR) with a 95% confidence interval (CI). Studies were excluded if one of the following conditions was met: (1) the study was not relevant to the *IL-10* −819C/T polymorphism or cancer risk, (2) the study design was based on family or sibling pairs, (3) the study did not contain a report of genotype frequencies or number, and (4) the study was a review or an abstract.

Data extraction

The data extracted from each eligible publication included the following information: first author's name, year of publication, original country, subjects' ethnicity, sample size, cancer type, genotyping method, source of controls, and genotype numbers for cases and controls. The different ethnic origins were categorized as European, Asian, or African. If a study did not state the ethnic origin, or if it was not possible to separate participants according to such phenotypes, the group was termed "mixed." For studies including subjects from different ethnic groups, data were extracted separately for each ethnic group whenever possible. Meanwhile, studies investigating more than one type of cancer were counted as individual data sets only in subgroup analyses by cancer type. In addition, if more than one cancer type was included in a study in the meta-analysis, it was termed "mixed cancer". The data were extracted and independently entered into two databases by two authors (Zhibin Yu and Yinnan Sun). Any discrepancy between these two investigators was resolved by a third author (Chen Huang).

Statistical analysis

The presence of control population selective bias was evaluated using a chi-squared goodness-of-fit test to determine whether the genotype distribution of the control subjects of each individual reported population conformed to Hardy-Weinberg equilibrium (HWE; $p < 0.05$ was considered significant). The frequencies of the T and C alleles in various ethnic groups were estimated using the studies with control groups that were in HWE ($p < 0.05$).

The random-effects model was used to estimate the summary odds ratio (ORs) and the corresponding 95% confidence intervals (CIs) for each association from the studies (DerSimonian and Laird, 1986). The meta-analysis assessed the association between allele T and cancer risk compared with allele C (T *vs.* C), as well as using TT versus CC (co-dominant model, homozygote effect), CT versus CC (co-dominant model, heterozygote effect), TT versus CT, TT/CT versus CC (dominant model), TT versus CT/CC (recessive model), and TT/CC versus CT (complete overdominant model). Between-study heterogeneity was measured using a Q-statistic test and the I^2 statistic with its corresponding 95% confidence (uncertainty) interval (Higgins et al., 2003; Ioannidis et al., 2007). The I^2 takes values between 0% and 100%, where higher values indicate higher levels of heterogeneity ($I^2 < 25\%$: no heterogeneity; $I^2 = 25\%$–50%: moderate heterogeneity; $I^2 = 50\%$–75%: large heterogeneity; $I^2 = 75\%$–100%: extreme heterogeneity). If $p < 0.10$ for the Q statistic or $I^2 > 25\%$, the between-study heterogeneity was considered to be significant. The statistical significance of the summary OR was determined with a Z test, for which $p < 0.05$ was considered significant.

Subgroup analyses were also performed based on ethnicity, cancer type, study design, sample size, and genotyping method if a subgroup contained at least three individual studies. Additionally, sensitivity analyses were performed by

including or excluding studies not in HWE. Cumulative meta-analysis was also conducted via the assortment of studies by publication time. Publication bias among the included studies was assessed graphically using a Begg's funnel plot and Egger's linear regression test (Sterne et al., 2000).

Statistical analyses were performed with SPSS for Windows (version 11.0; SPSS, Inc., Chicago, IL) and Stata software (version 11.0; Stata Corporation, College Station, TX).

Assessment of cumulative evidence

The cumulative evidence for the association between *IL-10* −819C/T and cancer risk was assessed according to the Venice interim guidelines (Ioannidis et al., 2008) and was graded based on three categories: (1) the amount of evidence (grade "A" was assigned when the total number of minor alleles of cases and controls combined in the meta-analyses exceeded 1000, "B" when it was between 100 and 1000, and "C" when it was less than 100); (2) the replication consistency (grade A was assigned for $I^2 < 25\%$, B for $I^2 = 25\%–50\%$, and C for $I^2 > 50\%$); (3) protection from bias (grade A was assigned if there was no observable bias, grade B was assigned if bias could be present or could explain the presence of the association; grade C was assigned if bias was considerable and had an effect in either the presence or absence of the association). The composite epidemiological credibility was rated as "strong" if three A grades were assigned, "moderate" if at least one B grade but no C grades were assigned, and "weak" if a C grade in any of the three assessment criteria was assigned.

Results

Characteristics of studies

As shown in Figure 1, 807 published records were retrieved based on the search criteria. A total of 73 studies from 68 eligible articles, involving 15,942 cancer cases and 22,336 controls, were identified that had investigated the association between the *IL-10* −819C/T polymorphism and the risk for cancer (Ahirwar et al., 2009; Alonso et al., 2005; Alpizar-Alpizar et al., 2005; Amirzargar et al., 2005; Ando et al., 2009; Basturk et al., 2005; Bushley et al., 2004; Cacev et al., 2008; Castro et al., 2009; Colakogullari et al., 2008; Cozar et al., 2007; Crivello et al., 2006; Crusius et al., 2008; da Silva et al., 2007;

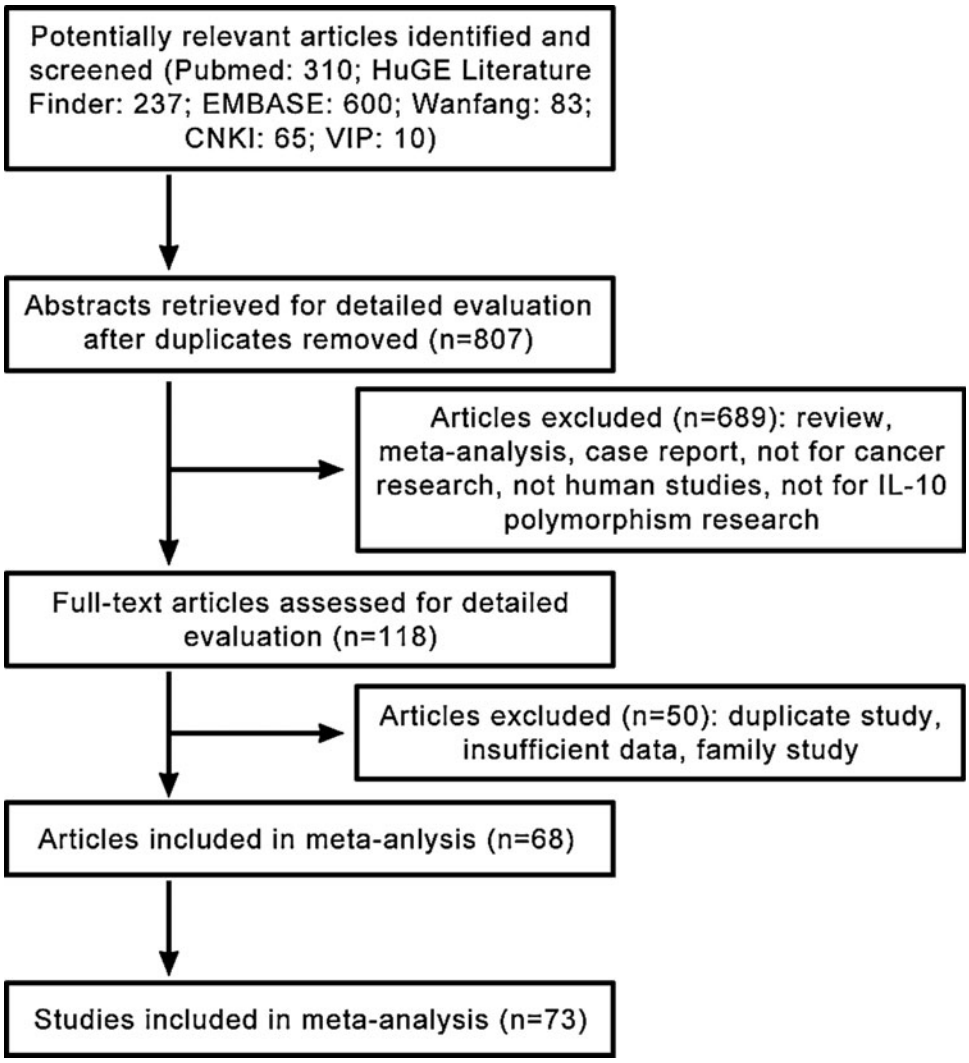

FIG. 1. Flow chart depicting the procedures for the identification of studies, including the inclusion and exclusion criteria.

Table 1. Characteristics of Studies Included in the Meta-Analysis

First author	Year	Cancer type	Study location	Ethnic group	Genotyping method	Study design	Case	Control	HWE
Guey	2010	bladder	Spain	European	GoldenGate, TaqMan	HCC	1017	1062	0.52
Ahirwar	2009	bladder	India	Asian	AS-PCR	HCC	214	385	0.00
Kong	2010	breast	China	Asian	PCR-RFLP	HCC	315	322	0.01
Schonfeld	2010	breast	USA	Mixed	TaqMan	PCC	829	1059	0.40
Scola	2006	breast	Italy	European	PCR-RFLP	HCC	84	106	0.06
Guzowski	2005	breast	USA	Mixed	DHPLC	HCC	50	25	0.62
Singh	2009	cervical	India	Asian	PCR-RFLP	HCC	150	162	0.04
Zoodsma	2005	cervical	Netherlands	European	TaqMan	PCC	654	606	0.20
Roh	2002	cervical	Korea	Asian	sequencing	HCC	144	179	0.72
Cacev	2008	colorectal	Croatia	European	PCR-RFLP	PCC	160	160	0.26
Cozar	2007	colorectal	Spain	European	TaqMan	HCC	95	175	0.39
Gunter	2006	colorectal	USA	Mixed	TaqMan	HCC	222	209	0.94
Savage	2004	esophageal	China	Asian	SNaPshot	PCC	116	382	0.31
El-El-Omar	2003	esophageal	USA	Mixed	TaqMan	PCC	161	210	0.42
Hsing	2008	gallbladder	China	Asian	TaqMan	PCC	237	728	0.56
Vishnoi	2007	gallbladder	India	Asian	PCR-RFLP	HCC	82	45	0.37
Kim	2012	gastric	Korea	Asian	MALDI-TOF	HCC	495	495	0.04
Zeng	2012	gastric	China	Asian	SNaPshot	HCC	151	153	0.46
Liu	2011	gastric	China	Asian	PCR-RFLP	HCC	234	243	0.77
Su	2010	gastric	China	Asian	PCR-RFLP	HCC	43	100	0.43
Kang	2009	gastric	Korea	Asian	PCR-RFLP	PCC	333	332	0.59
Ko	2009	gastric	Korea	Asian	TaqMan	PCC	83	326	0.03
Xiao	2009	gastric	China	Asian	PCR-RFLP	HCC	220	624	0.71
Crusius	2008	gastric	European	European	TaqMan	NCC	229	1094	0.02
Sugimoto	2007	gastric	Japan	Asian	AS-PCR	PCC	105	168	0.19
Kamangar	2006	gastric	Finland	European	TaqMan	PCC	98	152	0.66
Alpizar-Alpizar	2005	gastric	Costa Rica	Mixed	sequencing	PCC	45	45	0.18
Zambon	2005	gastric	Italy	European	TaqMan	HCC	129	644	0.69
Savage	2004	gastric	China	Asian	SNaPshot	PCC	84	382	0.31
El-El-Omar	2003	gastric	USA	Mixed	TaqMan	PCC	314	210	0.42
Wu	2003	gastric	China	Asian	sequencing	HCC	220	230	0.23
Bei	2011	hepatocellular	China	Asian	TaqMan	HCC	589	597	0.68
Liu	2010b	hepatocellular	China	Asian	TaqMan	HCC	170	187	0.29
Migita	2005	hepatocellular	Japan	Asian	PCR-SSP	HCC	48	193	0.38
Heneghan	2003	hepatocellular	China	Asian	PCR, probes hybridization	HCC	98	97	0.01
Brown	2006	kaposi sarcoma	Italy	European	TaqMan	PCC	132	168	0.11
Amirzargar	2005	leukaemia	Iran	European	PCR-SSP	PCC	30	40	0.04
Guzowski	2005	leukaemia	USA	Mixed	DHPLC	HCC	17	25	0.62
Colakogullari	2008	lung	Turkey	Asian	PCR-SSP	HCC	44	59	0.89
Hosgood	2008	lung	China	Asian	GoldenGate	PCC	122	108	1.00
Seifart	2005	lung	Germany	European	PCR-RFLP	PCC	183	423	0.24
Shih	2005	lung	China	Asian	PCR-RFLP	HCC	154	205	0.62
Andrie	2009	lymphoma	Greece	European	ARMS-PCR	HCC	85	85	0.59
Hellmig	2008	lymphoma	European	European	-	HCC	84	351	0.81
Purdue	2007a	lymphoma	Australia	Mixed	TaqMan	PCC	538	488	0.81
Kube	2007	lymphoma	Germany	European	TaqMan	PCC	100	100	0.50
Lan	2006	lymphoma	USA	Mixed	TaqMan	PCC	491	574	0.98
Persico	2006	lymphoma	Italy	European	PCR-RFLP	HCC	250	110	0.15
Lech-Maranda	2004	lymphoma	France	European	PCR-RFLP	HCC	199	112	0.53
Zhong	2011	melanoma	China	Asian	OpenArray	HCC	30	30	0.90
Gu	2008	melanoma	USA	Mixed	OpenArray	NCC	210	204	0.08
Alonso	2005	melanoma	Spain	European	TaqMan	HCC	98	100	0.20
Martinez-Escribano	2002	melanoma	Spain	European	PCR-SSP	HCC	42	48	0.57
Howell	2001	melanoma	UK	European	PCR-SSP	HCC	150	158	0.69
Lee	2010	multiple myeloma	USA	European	GoldenGate	PCC	112	499	0.69
Mazur	2005	multiple myeloma	Poland	European	PCR-SSP	HCC	54	50	0.21
Wei	2007	nasopharyngeal	China	Asian	PCR-RFLP	HCC	198	210	0.83
Pratesi	2006	nasopharyngeal	Italy	European	sequencing	PCC	89	130	0.27
Yao	2008	oral	China	Asian	PCR-RFLP	HCC	280	300	0.80

(*continued*)

Table 1. (Continued)

First author	Year	Cancer type	Study location	Ethnic group	Genotyping method	Study design	Case	Control	HWE
He	2008	ovarian	China	Asian	PCR-SSP	HCC	33	90	0.00
IoanaBraicu	2007	ovarian	Germany	European	sequencing	HCC	147	129	0.63
Bushley	2004	ovarian	USA	Mixed	5′-nuclease assay	PCC	181	219	0.00
Liu	2010a	prostate	China	Asian	PCR-RFLP	PCC	262	270	0.47
VanCleave	2010	prostate	USA	African	TaqMan	PCC	191	635	0.03
Kesarwani	2009	prostate	India	Asian	ARMS-PCR	HCC	159	259	0.57
Faupel-Badger	2008	prostate	Finland	European	TaqMan	PCC	507	384	0.58
Zabaleta	2008	prostate	USA	European	TaqMan	HCC	462	375	0.71
Zabaleta	2008	prostate	USA	African	TaqMan	HCC	64	119	0.54
Michaud	2006	prostate	USA	Mixed	TaqMan	PCC	1246	1762	0.07
Cozar	2007	renal	Spain	European	TaqMan	HCC	127	175	0.39
Basturk	2005	renal	Turkey	Asian	PCR-SSP	HCC	29	50	0.32
Purdue	2007b	testicular	USA	Mixed	TaqMan	PCC	504	605	0.16
Pogoda	2007	mixed	Russia	European	MALDI-TOF, minisequencing	PCC	120	600	0.78

ARMS-PCR, amplification refractory mutation specific polymerase chain reaction; AS-PCR, allele-specific polymerase chain reaction; DHPLC, denaturing high-performance liquid chromatography; HCC, hospital-based case-control; HWE, Hardy-Weinberg equilibrium; MALDI-TOF, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; NCC, nested case-control study; PCC, population-based case-control; PCR, polymerase chain reaction; PCR-SSP, polymerase chain reaction and sequence-specific primer typing; RFLP, restriction fragment length polymorphism.

de Oliveira et al., 2003; Eder et al., 2007; El-Omar et al., 2003; Faupel-Badger et al., 2008; Festa et al., 2005; Gonullu et al., 2007; Gunter et al., 2006; Guzowski et al., 2005; Hellmig et al., 2008; Howell et al., 2001; Hubner et al., 2007; Ioana Braicu et al., 2007; Kamangar et al., 2006; Kang et al., 2009; Kesarwani et al., 2009; Kong et al., 2010; Lan et al., 2006; Langsenlehner et al., 2005; Lech-Maranda et al., 2007; Lee et al., 2005; Liu et al., 2010a; Liu et al., 2011; Macarthur et al., 2005; Martinez-Escribano et al., 2002; Mazur et al., 2005; Michaud et al., 2006; Migita et al., 2005; Munro et al., 2003; Pharoah et al., 2007; Pogoda et al., 2007; Pratesi et al., 2006; Purdue et al., 2007; Roh et al., 2002; Savage et al., 2004; Seifart et al., 2005; Shih et al., 2005; Shin et al., 2003; Sicinschi et al., 2006; Singh et al., 2009; Su et al., 2010; Sugimoto et al., 2007; Tseng et al., 2006; VanCleave et al., 2010; Vogel et al., 2007; Vogel et al., 2008; Wang et al., 2009; Wei et al., 2007; Wu et al., 2003; Xiao et al., 2009; Yao et al., 2008; Zabaleta et al., 2008; Zambon et al., 2005; Zhang et al., 2004; Zoodsma et al., 2005).

A meta-analysis database was established based on the extracted information from each eligible article. Among the 73 selected studies, there were two studies of African subjects, 31 studies of Asian subjects, 27 studies of European subjects, and 13 studies of mixed-ethnicity subjects.

With regard to cancer types, there were two studies of bladder cancer, four studies of breast cancer, three studies of cervical cancer, three studies of colorectal cancer, two studies of esophageal cancer, two studies of gallbladder cancer, 15 studies of gastric cancer, four studies of hepatocellular carcinoma, one study of Kaposi sarcoma, two studies of leukemia, four studies of lung cancer, seven studies of lymphoma, five studies of melanoma, two studies of multiple myeloma, two studies of nasopharyngeal carcinoma, one study of oral cancer, three studies of ovarian cancer, seven studies of prostate cancer, two studies of renal cell cancer, one study of testicular cancer, and one study of mixed cancer.

Of the 73 included studies, 42 studies were hospital-based, 29 studies were population-based, and two studies were nested case-control studies. Multiple genotyping methods were employed in the studies, such as PCR-RFLP, TaqMan PCR, PCR-SSP, and DNA sequencing. Of these, 25 studies recruited more than 500 subjects, and 48 studies recruited less than 500 subjects. The distributions of genotypes in the controls of 11 studies were not consistent with HWE. Detailed and summary characteristics of the eligible studies are shown in Table 1 and Supplementary Table S1 (supplementary data are available online at www.liebertpub.com/omi).

Quantitative synthesis

Frequency of the IL-10 −819C/T polymorphism in control populations. We only used data from the studies with control groups that were in HWE for the estimation of the frequency distributions for the alleles and genotypes of the *IL-10* −819C/T polymorphism in different ethnic groups with at least three studies. There were significant differences in terms of the T allele frequency between the Asian and European populations (6034 Asians and 6902 Europeans) (Supplementary Fig. S1). The frequency of the T allele was 60.06% (95%CI: 53.6, 66.49) among Asian controls, which was significantly higher than that in European controls (25.35%, 95%CI: 24.02, 26.68).

Overall data analyses

The association between the *IL-10* −819C/T polymorphism and cancer risk was investigated in 73 separate studies with a total of 15942 cases and 22336 controls. As shown in Table 2, no association was found in any genetic models in the overall population (T allele *vs.* C allele: OR = 0.96, 95%CI: 0.92, 1.00; TT *vs.* CC: OR = 0.92, 95%CI: 0.83, 1.01; CT *vs.* CC: OR = 0.98, 95%CI: 0.92, 1.04; TT *vs.* CT: OR = 0.94, 95%CI: 0.87, 1.01; TT/CT *vs.* CC: OR = 0.96, 95%CI: 0.91, 1.02; TT *vs.* CT/CC: OR = 0.93, 95%CI: 0.86, 1.00; TT/CC *vs.* CT: OR = 0.98, 95%CI: 0.94, 1.03). Between-study heterogeneity was moderate in the T allele versus C allele [$P_{\text{heterogeneity}} = 0.00$, $I^2 = 35.2\%$

Table 2. Odds Ratios and Corresponding 95% Confidence Intervals of Each Genotype of the *IL*-10 −819C/T Polymorphism in Overall and Subgroup Analyzed by a Random Effects Model

			T vs. C		*TT vs. CC*		*CT vs. CC*		*TT vs. CT*		*TT/CT vs. CC*		*TT vs. CT/CC*		*TT/CC vs. CT*	
Group	*N*[a]	*Cases/Controls*	*OR (95%CI)*	P	*OR (95%CI)*	P	*OR (95%CI)*	P	*OR (95%CI)*	P	*OR (95%CI)*	P	*OR (95%CI)*	P	*OR (95%CI)*	P
Overall	73	15942/22336	0.96 (0.92, 1.00)	0.09	0.92 (0.83, 1.01)	0.10	0.98 (0.92, 1.04)	0.53	0.94 (0.87, 1.01)	0.13	0.96 (0.91, 1.02)	0.30	0.93 (0.86, 1.00)	0.07	0.98 (0.94, 1.03)	0.64
Ethnicity																
Asian	31	5442/7911	0.93 (0.87, 0.99)	0.03	0.86 (0.76, 0.98)	0.03	0.98 (0.86, 1.12)	0.81	0.91 (0.82, 1.00)	0.05	0.94 (0.83, 1.06)	0.32	0.90 (0.82, 0.98)	0.02	0.93 (0.85, 1.02)	0.14
European	27	5437/8036	1.00 (0.91, 1.09)	0.99	0.97 (0.78, 1.21)	0.85	1.01 (0.91, 1.11)	0.78	0.98 (0.81, 1.20)	0.90	1.00 (0.90, 1.11)	0.89	0.98 (0.79, 1.20)	0.86	0.98 (0.89, 1.07)	0.73
Cancer type																
breast	4	1278/1512	0.90 (0.79, 1.01)	0.08	0.83 (0.63, 1.09)	0.19	0.90 (0.76, 1.07)	0.26	0.89 (0.69, 1.14)	0.37	0.88 (0.75, 1.04)	0.14	0.86 (0.68, 1.08)	0.20	1.04 (0.89, 1.22)	0.57
cervical	3	948/947	1.20 (1.03, 1.40)	0.01	1.12 (0.76, 1.65)	0.54	1.39 (1.13, 1.72)	0.00	0.89 (0.59, 1.36)	0.61	1.35 (1.11, 1.65)	0.00	1.05 (0.77, 1.42)	0.74	0.78 (0.55, 1.12)	0.18
colorectal	3	477/544	1.20 (0.80, 1.78)	0.36	1.38 (0.33, 5.69)	0.64	1.18 (0.84, 1.68)	0.32	1.18 (0.30, 4.51)	0.80	1.22 (0.83, 1.80)	0.29	1.30 (0.33, 5.12)	0.70	0.86 (0.62, 1.21)	0.41
gastric	15	2783/5198	0.91 (0.82, 1.00)	0.06	0.96 (0.77, 1.19)	0.71	0.95 (0.82, 1.09)	0.47	0.88 (0.75, 1.04)	0.15	0.94 (0.82, 1.07)	0.35	0.88 (0.74, 1.04)	0.13	0.93 (0.82, 1.05)	0.28
Asian	10	1968/3053	0.88 (0.79, 0.99)	0.03	0.90 (0.73, 1.10)	0.31	1.07 (0.87, 1.31)	0.48	0.81 (0.71, 0.93)	0.00	0.97 (0.80, 1.18)	0.83	0.82 (0.71, 0.95)	0.00	0.84 (0.74, 0.94)	0.00
European	3	456/1890	0.92 (0.71, 1.19)	0.54	0.99 (0.46 2.11)	0.98	0.83 (0.66, 1.04)	0.11	1.19 (0.58, 2.44)	0.62	0.86 (0.69, 1.06)	0.16	1.06 (0.50, 2.25)	0.86	1.20 (0.96, 1.49)	0.10
hepatocellular	4	905/1074	0.99 (0.86, 1.13)	0.89	0.92 (0.67, 1.28)	0.64	1.05 (0.84, 1.30)	0.65	0.91 (0.67, 1.24)	0.58	1.02 (0.83, 1.25)	0.85	0.93 (0.71, 1.22)	0.64	0.95 (0.77, 1.16)	0.64
lung	4	503/795	0.87 (0.66, 1.15)	0.33	0.57 (0.32, 1.03)	0.06	0.82 (0.43, 1.55)	0.55	0.89 (0.65, 1.22)	0.47	0.77 (0.41, 1.44)	0.42	0.79 (0.59, 1.07)	0.13	0.93 (0.74, 1.17)	0.57
Asian	3	320/372	0.77 (0.58, 1.01)	0.06	0.47 (0.23, 0.94)	0.03	0.67 (0.31, 1.46)	0.32	0.93 (0.66, 1.31)	0.69	0.63 (0.30, 1.32)	0.22	0.79 (0.57, 1.09)	0.16	1.06 (0.78, 1.45)	0.67
lymphoma	7	1747/1820	0.95 (0.84, 1.07)	0.45	0.90 (0.64, 1.27)	0.57	0.96 (0.83, 1.11)	0.59	0.92 (0.68, 1.26)	0.63	0.95 (0.83, 1.09)	0.49	0.91 (0.66, 1.26)	0.59	1.02 (0.89, 1.18)	0.69
European	5	718/758	0.95 (0.77, 1.18)	0.69	0.98 (0.53, 1.81)	0.95	0.92 (0.73, 1.16)	0.50	1.03 (0.61, 1.74)	0.90	0.92 (0.74, 1.16)	0.51	1.01 (0.57, 1.79)	0.96	1.07 (0.85, 1.34)	0.54
melanoma	5	530/540	0.93 (0.76, 1.13)	0.50	0.88 (0.51, 1.54)	0.67	0.93 (0.72, 1.20)	0.60	0.94 (0.52, 1.71)	0.85	0.92 (0.72, 1.18)	0.53	0.9 (0.52, 1.55)	0.71	1.05 (0.82, 1.35)	0.67
European	3	290/306	0.83 (0.64, 1.09)	0.18	0.62 (0.30, 1.26)	0.18	0.90 (0.64, 1.29)	0.59	0.66 (0.31, 1.40)	0.28	0.85 (0.61, 1.18)	0.34	0.63 (0.31, 1.27)	0.20	1.01 (0.67, 1.53)	0.93
ovarian	3	361/438	1.21 (0.95, 1.54)	0.11	1.19 (0.53, 2.68)	0.65	1.60 (1.09, 2.35)	0.01	0.66 (0.25, 1.77)	0.41	1.47 (1.02, 2.10)	0.03	0.91 (0.44, 1.91)	0.81	0.69 (0.40, 1.17)	0.17
prostate	7	2891/3804	0.94 (0.82, 1.06)	0.34	0.89 (0.70, 1.14)	0.38	0.91 (0.78, 1.07)	0.26	0.97 (0.82, 1.15)	0.77	0.91 (0.76, 1.08)	0.28	0.93 (0.78, 1.10)	0.42	1.05 (0.94, 1.17)	0.37
Study design																
HCC	42	7476/9273	0.92 (0.87, 0.98)	0.00	0.86 (0.75, 0.98)	0.03	0.95 (0.86, 1.04)	0.28	0.91 (0.82, 1.02)	0.11	0.92 (0.85, 1.00)	0.08	0.89 (0.81, 0.99)	0.03	0.98 (0.90, 1.05)	0.61
PCC	29	8027/11765	1.01 (0.94, 1.09)	0.71	1.00 (0.87, 1.15)	0.96	1.01 (0.93, 1.10)	0.70	0.98 (0.88, 1.08)	0.69	1.02 (0.93, 1.12)	0.65	0.98 (0.88, 1.10)	0.81	0.98 (0.91, 1.06)	0.73
Sample size																
< 500	48	5471/7263	0.92 (0.86, 0.98)	0.02	0.83 (0.71, 0.96)	0.01	0.95 (0.86, 1.05)	0.33	0.9 (0.79, 1.01)	0.08	0.92 (0.84, 1.02)	0.12	0.87 (0.78, 0.98)	0.02	0.97 (0.89, 1.05)	0.48
≥ 500	25	10471/15073	0.99 (0.93, 1.05)	0.88	0.99 (0.88, 1.12)	0.96	0.99 (0.92, 1.07)	0.97	0.97 (0.89, 1.06)	0.62	0.99 (0.92, 1.07)	0.95	0.98 (0.89, 1.08)	0.75	1.00 (0.93, 1.06)	0.99
Genotyping method																
PCR-RFLP	16	3147/3724	0.92 (0.82, 1.02)	0.13	0.77 (0.61, 0.97)	0.03	0.92 (0.75, 1.12)	0.44	0.92 (0.81, 1.03)	0.18	0.88 (0.72, 1.08)	0.24	0.88 (0.79, 0.99)	0.04	0.95 (0.86, 1.06)	0.41
TaqMan	25	8172/11557	0.99 (0.93, 1.05)	0.80	0.96 (0.84, 1.11)	0.64	0.97 (0.91, 1.04)	0.49	1.01 (0.88, 1.16)	0.82	0.97 (0.91, 1.04)	0.51	1.00 (0.87, 1.15)	0.99	1.02 (0.95, 1.10)	0.45
other	32	4623/7055	0.95 (0.88, 1.03)	0.25	0.99 (0.85, 1.15)	0.90	0.99 (0.90, 1.09)	0.93	0.90 (0.79, 1.02)	0.11	0.98 (0.89, 1.07)	0.71	0.91 (0.80, 1.03)	0.16	0.95 (0.86, 1.04)	0.31

[a]Number of studies. CI, confidence interval; HWE, Hardy-Weinberg equilibrium; OR, odds ratio.

Table 3. Heterogeneity Test for Studies of Each Genotype in Overall and Subgroups with Cochran's Q Test and the Quantity I^2

		T vs. C			*TT vs. CC*			*CT vs. CC*			*TT vs. CT*			*TT/CT vs. CC*			*TT vs. CT/CC*			*TT/CC vs. CT*		
		Q-statistic			*Q-statistic*			*Q-statistic*			*Q-statistic*			*Q-statistic*			*Q-statistic*			*Q-statistic*		
Group	*N*[a]	*Q*	P	I^2 (%) (95%CI)	*Q*	P	I^2 (%) (95%CI)	*Q*	P	I^2 (%) (95%CI)	*Q*	P	I^2 (%) (95%CI)	*Q*	P	I^2 (%) (95%CI)	*Q*	P	I^2 (%) (95%CI)	*Q*	P	I^2 (%) (95%CI)
Overall	73	111.05	0.00	35 (13, 51)	93.29	0.05	22 (0, 43)	88.07	0.10	18 (0, 39)	83.67	0.16	13 (0, 36)	96.47	0.03	25 (0, 45)	90.76	0.07	20 (0, 41)	86.91	0.11	17 (0, 39)
Ethnicity																						
Asian	31	40.93	0.09	26 (0, 53)	34.29	0.27	12 (0, 43)	40.77	0.09	26 (0, 53)	38.54	0.14	22 (0, 50)	39.03	0.13	23 (0, 51)	37.27	0.17	19 (0, 48)	42.46	0.07	29 (0, 55)
European	27	52.56	0.00	50 (23, 68)	41.96	0.03	38 (1, 61)	36.06	0.09	27 (0, 55)	33.67	0.14	22 (0, 52)	43.64	0.02	40 (6, 62)	39.32	0.05	33 (0, 59)	32.74	0.17	20 (0, 51)
Cancer type																						
breast	4	0.37	0.95	0 (0, 85)	1.10	0.78	0 (0, 85)	0.31	0.96	0 (0, 85)	1.58	0.66	0 (0, 85)	0.06	1.00	0 (0, 85)	1.34	0.72	0 (0, 85)	1.40	0.71	0 (0, 85)
cervical	3	0.22	0.90	0 (0, 90)	0.23	0.89	0 (0, 90)	1.45	0.48	0 (0, 90)	3.32	0.19	39 (0, 81)	0.50	0.78	0 (0, 90)	1.54	0.46	0 (0, 90)	5.33	0.07	62 (0, 89)
colorectal	3	7.13	0.03	72 (5, 92)	8.88	0.01	77 (27, 93)	3.40	0.18	41 (0, 82)	7.75	0.02	74 (14, 92)	4.55	0.10	56 (0, 87)	8.59	0.01	76 (24, 93)	3.35	0.19	40 (0, 82)
gastric	15	22.00	0.08	36 (0, 66)	19.46	0.15	28 (0, 61)	10.52	0.72	0 (0, 54)	24.12	0.04	42 (0, 68)	12.21	0.59	0 (0, 54)	25.98	0.03	46 (2, 70)	20.54	0.11	31 (0, 63)
Asian	10	12.52	0.18	28 (0, 66)	8.86	0.45	0 (0, 62)	5.22	0.81	0 (0, 62)	10.19	0.33	11 (0, 53)	6.96	0.64	0 (0, 62)	12.03	0.21	25 (0, 64)	8.47	0.48	0 (0, 62)
European	3	4.05	0.13	50 (0, 86)	6.07	0.04	67 (0, 90)	0.09	0.95	0 (0, 90)	5.02	0.08	60 (0, 89)	1.19	0.55	0 (0, 90)	6.23	0.04	67 (0, 91)	0.17	0.92	0 (0. 90)
hepatocellular	4	2.14	0.55	0 (0, 85)	1.10	0.78	0 (0, 85)	0.88	0.83	0 (0, 85)	3.97	0.27	24 (0, 88)	0.55	0.91	0 (0, 85)	3.53	0.32	15 (0, 87)	3.28	0.35	8 (0, 86)
lung	4	6.67	0.08	55 (0, 85)	5.14	0.16	41 (0, 80)	11.25	0.01	73 (25, 91)	2.13	0.55	0 (0, 85)	12.02	0.01	75 (31, 91)	1.82	0.61	0 (0, 85)	3.00	0.39	0 (0, 85)
Asian	3	2.73	0.25	26 (0, 92)	3.13	0.20	36 (0, 80)	5.84	0.05	65 (0. 90)	1.70	0.42	0 (0, 90)	5.75	0.05	65 (0, 90)	1.82	0.40	0 (0, 90)	1.25	0.53	0 (0, 90)
lymphoma	7	6.57	0.36	8 (0, 73)	7.15	0.31	16 (0, 60)	3.33	0.77	0 (0, 71)	5.19	0.52	0 (0, 71)	4.63	0.59	0 (0, 71)	6.62	0.36	9 (0, 74)	2.86	0.83	0 (0, 71)
European	5	5.65	0.22	29 (0, 73)	6.91	0.14	42 (0, 79)	1.95	0.74	0 (0, 79)	4.91	0.29	18 (0, 83)	3.37	0.49	0 (0, 79)	6.39	0.17	37 (0, 77)	1.52	0.82	0 (0, 79)
melanoma	5	1.70	0.79	0 (0, 79)	3.18	0.53	0 (0, 79)	2.33	0.68	0 (0, 79)	4.30	0.37	7 (0, 81)	1.70	0.79	0 (0, 79)	3.71	0.45	0 (0, 79)	3.00	0.56	0 (0, 79)
European	3	0.19	0.91	0 (0, 90)	0.72	0.69	0(0, 90)	2.07	0.35	3 (0, 90)	2.06	0.35	2 (0, 90)	1.08	0.58	0 (0, 90)	1.18	0.55	0 (0, 90)	2.78	0.24	28 (0, 93)
ovarian	3	0.95	0.62	0 (0, 90)	3.30	0.19	39 (0, 81)	1.78	0.41	0 (0, 90)	5.57	0.06	64 (0, 90)	0.47	0.79	0 (0, 90)	3.74	0.15	46 (0, 84)	5.06	0.08	60 (0, 89)
prostate	7	13.10	0.04	54 (0, 80)	9.41	0.15	36 (0, 73)	9.22	0.16	05 (0, 72)	4.10	0.66	0 (0, 71)	12.23	0.06	50 (0, 79)	6.52	0.37	8 (0, 73)	6.31	0.39	5 (0, 72)
Study design																						
HCC	42	47.88	0.21	14 (0, 42)	53.33	0.09	23 (0, 48)	50.10	0.15	18 (0, 45)	53.25	0.09	23 (0, 48)	47.33	0.23	13 (0, 41)	51.10	0.13	19 (0, 46)	51.30	0.13	20 (0, 46)
PCC	29	57.02	0.00	50 (25, 68)	36.17	0.13	22 (0, 51)	35.94	0.14	22 (0, 51)	28.29	0.44	1 (0, 42)	45.58	0.01	38 (4, 61)	35.83	0.14	21 (0, 51)	34.59	0.18	19 (0, 49)
Sample size																						
< 500	48	60.86	0.08	22 (0, 46)	54.98	0.20	14 (0, 41)	53.51	0.24	12 (0, 39)	57.44	0.14	18 (0, 43)	54.78	0.20	14 (0, 40)	56.72	0.16	17 (0, 43)	55.83	0.18	15 (0, 42)
≥ 500	25	46.80	0.00	48 (18, 68)	33.88	0.09	29 (0, 57)	34.08	0.08	29 (0, 57)	24.77	0.42	3 (0, 46)	40.52	0.02	40 (4, 63)	30.88	0.16	22 (0, 53)	30.66	0.16	21 (0, 52)
Genotyping method																						
PCR-RFLP	16	28.40	0.02	47 (6, 70)	25.76	0.04	41 (0, 68)	32.19	0.01	53 (18, 74)	11.72	0.70	0 (0, 52)	36.27	0.00	58 (28, 76)	13.80	0.54	0 (0, 52)	15.43	0.42	2 (0, 54)
TaqMan	25	37.41	0.04	35 (0, 60)	29.96	0.19	19 (0, 51)	25.38	0.39	5 (0, 37)	32.46	0.12	26 (0, 55)	27.92	0.26	14 (0, 47)	35.35	0.06	32 (0, 58)	29.94	0.19	19 (0, 51)
other	32	43.33	0.07	28 (0, 54)	32.49	0.39	4 (0, 34)	30.32	0.50	0 (0, 40)	36.20	0.24	14 (0, 45)	31.76	0.43	2 (0, 41)	38.46	0.17	19 (0, 48)	38.71	0.16	19 (0, 48)

[a]Number of studies. CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

(95%CI: 13, 51)] and TT/CT versus CC models [$P_{heterogeneity} = 0.03$, $I^2 = 25.4\%$ (95%CI: 0, 45)] (Table 3). Although the p values for the Q statistic were less than 0.10 in the TT versus CC model and TT versus CT/CC model, the I^2 was less than 25%, implying low heterogeneity. The results did not differ significantly in the sensitivity analyses, excluding 11 studies that did not fulfill HWE (Supplementary Tables S2 and S3).

Subgroup analyses by ethnicity

After stratification for ethnicity, we observed that in the Asian population, based on 31 studies with 5442 patients and 7911 controls, the T allele, the homozygote variant (TT), and the recessive genetic model were significantly associated with decreased risk of cancers [T allele *vs.* C allele: OR = 0.93, 95%CI: 0.87, 0.99, $P_{heterogeneity} = 0.09$, $I^2 = 26.7\%$ (95%CI: 0, 53); TT *vs.* CC: OR = 0.86, 95%CI: 0.76, 0.98, $P_{heterogeneity} = 0.27$, $I^2 = 12.5\%$ (95%CI: 0, 43); TT *vs.* CT/CC: OR = 0.90, 95%CI: 0.82, 0.98, $P_{heterogeneity} = 0.13$, $I^2 = 23.1\%$ (95%CI: 0, 51)] (Tables 2 and 3, and Fig. 2). Sensitivity analyses were performed by excluding seven studies for which the data for the controls were not observed to be in HWE (Supplementary Tables S2 and S3). Significant effects were found in the allele comparison, homozygous comparison, and dominant model comparison with non-significant heterogeneity. However, the effect in the recessive model comparison did not reach statistical significance [OR = 0.90, 95%CI: 0.81, 1.01, $P_{heterogeneity} = 0.10$, $I^2 = 27.7\%$ (95%CI: 0, 37)].

In the European population, including 27 studies with 5437 cases and 8036 controls, no significant association between the *IL-10* −819C/T polymorphism and the susceptibility to cancer was found for any of the variant genotypes (Table 2 and Table 3). Sensitivity analyses were performed after excluding two studies conducted by Amirzargar et al. (2005) and Crusius et al. (2008) because their controls were not in HWE. The results were similar and showed no genetic effects (Supplementary Tables S2 and S3).

Subgroup analyses by cancer types

By further stratifying the analysis by cancer types, we found that individuals with the T allele in different genetic models had a significantly lower risk of gastric cancer but higher risks of cervical and ovarian cancer (Table 2).

There was a significant association between the *IL-10* −819C/T polymorphism and a reduced risk for gastric cancer in the Asian population in the T allele versus C allele model [OR = 0.88, 95%CI: 0.79, 0.99, $P_{heterogeneity} = 0.18$, $I^2 = 28\%$ (95%CI: 0, 66)], the TT versus CT model [OR = 0.81, 95%CI: 0.71, 0.93, $P_{heterogeneity} = 0.81$, $I^2 = 0\%$ (95%CI: 0, 62)], the TT versus CT/CC model [OR = 0.82, 95%CI: 0.71, 0.95, $P_{heterogeneity} = 0.64$, $I^2 = 0\%$

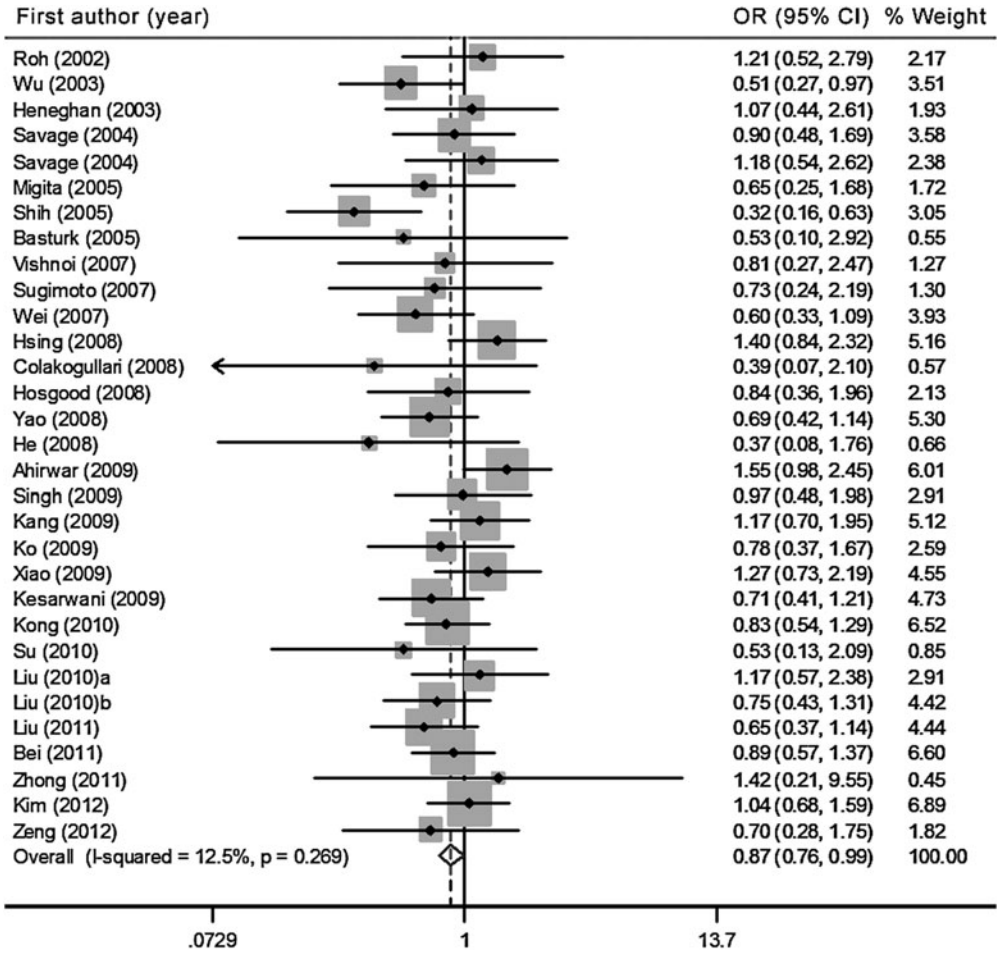

FIG. 2. Forest plot of the cancer risk in Asian populations associated with the *IL-10* −819C/T polymorphism (TT versus CC model).

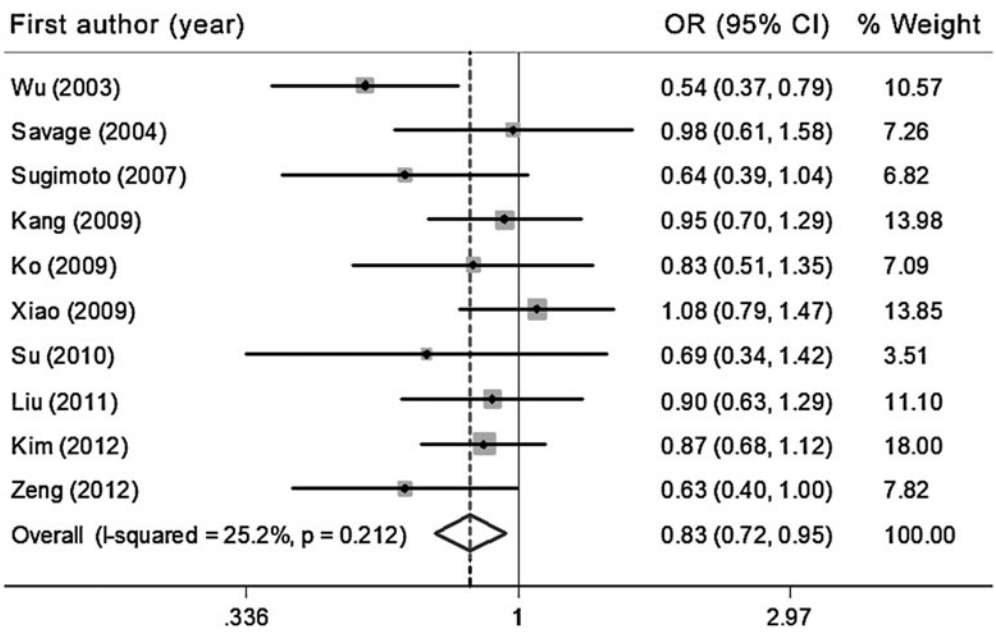

FIG. 3. Forest plot of the gastric cancer risk in Asian populations associated with the *IL-10* −819C/T polymorphism (TT versus CT/CC model).

(95%CI: 0, 62)], and the TT/CC versus CT model [OR = 0.86, 95%CI: 0.74, 0.94, $P_{\text{heterogeneity}} = 0.48$, $I^2 = 0\%$ (95%CI: 0, 62)] (Fig. 3, Tables 2 and 3). The sensitivity analyses indicated that the association between the T allele and the decreased risk of gastric cancer in Asians was not significant after the exclusion of two studies with controls that were not in HWE (T allele *vs.* C allele: OR = 0.87, 95%CI: 0.75, 1.00) (Supplementary Tables S2 and S3).

In the three cervical cancer studies (Roh et al., 2002; Singh et al., 2009; Zoodsma et al., 2005) with 948 cases and 947 controls from one European population and two Asian populations, there was a significant association of the *IL-10* −819C/T polymorphism with an increased risk for cervical cancer in the allele comparison model [T allele *vs.* C allele: OR = 1.20, 95%CI: 1.03, 1.40, $P_{\text{heterogeneity}} = 0.90$, $I^2 = 0\%$ (95%CI: 0, 90)], the heterozygote comparison model [CT *vs.* CC: OR = 1.39, 95%CI: 1.13, 1.72, $P_{\text{heterogeneity}} = 0.48$, $I^2 = 0\%$ (95%CI: 0, 90)], and the dominant model [TT/CT *vs.* CC: OR = 1.35, 95%CI: 1.11, 1.65, $P_{\text{heterogeneity}} = 0.78$, $I^2 = 0\%$ (95%CI: 0, 90)] (Fig. 4, Tables 2 and 3). Sensitivity analysis was performed after excluding one study because the controls were not in HWE, but this exclusion did not alter the pattern of results (Supplementary Tables S2 and S3).

Three studies (Bushley et al., 2004; He et al., 2008; Ioana Braicu et al., 2007) for ovarian cancer were retrieved comprising three different sample populations (one European, one Asian, and one mixed population) including 361 cases and 438 controls. A significantly increased risk was associated with the variant genotypes (CT and TT/CT), compared with the wild homozygote CC genotype [CT *vs.* CC: OR = 1.61, 95%CI: 1.09, 2.35, $P_{\text{heterogeneity}} = 0.41$, $I^2 = 0\%$ (95%CI: 0, 90); TT/CT *vs.* CC: OR = 1.47, 95%CI: 1.02, 2.10, $P_{\text{heterogeneity}} = 0.79$, $I^2 = 0\%$ (95%CI: 0, 90)] (Fig. 4, Tables 2 and 3). Because of the limited data after two studies were excluded that significantly deviated from HWE, we did not perform a sensitivity analysis.

However, the *IL-10* −819C/T polymorphism was not significantly associated with breast cancer, colorectal cancer, lung cancer, hepatocellular carcinoma, prostate cancer, lymphoma, or melanoma (Tables 2 and 3). Additionally, no significant changes in other ORs were observed in any other genetic models of other cancer types in the sensitivity analyses (Supplementary Tables S2 and S3).

Subgroup analyses by study design

In the subgroup analyses by study design, pooled analysis of hospital-based case-control (HCC) studies showed that the T allele of *IL-10* −819C/T polymorphism was associated with reduced cancer risk in the allele comparison model [T allele *vs.*

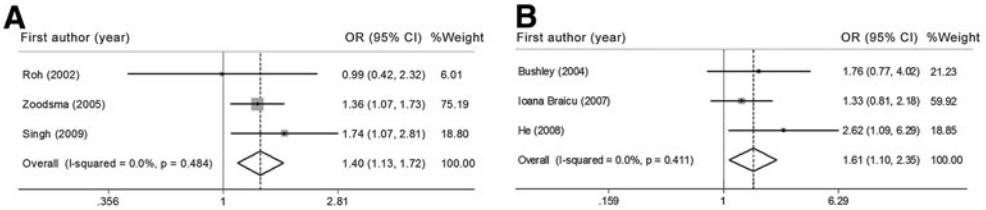

FIG. 4. Forest plot of the risk of cervical cancer **(A)** and ovarian cancer **(B)** associated with the *IL-10* −819C/T polymorphism (CT versus CC model).

C allele: OR = 0.92, 95%CI: 0.87, 0.98, $P_{heterogeneity} = 0.21$, $I^2 = 14\%$ (95%CI: 0, 42)], the homozygote comparison model [TT *vs.* CC: OR = 0.86, 95%CI: 0.75, 0.98, $P_{heterogeneity} = 0.09$, $I^2 = 23\%$ (95%CI: 0, 48)], and the recessive model [TT *vs.* CT/CC: OR = 1.35, 95%CI: 1.11, 1.65, $P_{heterogeneity} = 0.13$, $I^2 = 19\%$ (95%CI: 0, 46)] (Tables 2 and 3). Sensitivity analysis was performed after excluding two studies and the association was observed in the T allele versus C allele, TT versus CC, CT versus CC, and TT/CT versus CC models with no significant heterogeneity, but the association disappeared in the TT versus CT/CC model (Supplementary Tables S2 and S3). None of these ORs in population-based case-control (PCC) studies were statistically significant.

Subgroup analyses by sample size

In the stratified analyses by sample size with a cutoff of 500 subjects ("sample size <500" and "sample size ≥500"), a lower risk of cancer was observed in the studies with less than 500 subjects ("sample size < 500" subgroup) [T allele *vs.* C allele: OR = 0.92, 95%CI: 0.86, 0.98, $P_{heterogeneity} = 0.08$, $I^2 = 22\%$ (95%CI: 0, 46); TT *vs.* CC: OR = 0.83, 95%CI: 0.71, 0.96, $P_{heterogeneity} = 0.20$, $I^2 = 14\%$ (95%CI: 0, 41); TT *vs.* CT/CC: OR = 0.92, 95%CI: 0.86, 0.98, $P_{heterogeneity} = 0.08$, $I^2 = 22\%$ (95%CI: 0, 46)] (Tables 2 and 3). No significant changes in ORs were observed in these three genetic models in the sensitivity analyses. Additionally, a significantly reduced risk was associated with the variant genotypes (CT and TT/CT), compared with the wild homozygote CC genotype [CT *vs.* CC: OR = 0.90, 95%CI: 0.82, 0.99, $P_{heterogeneity} = 0.61$, $I^2 = 0\%$ (95%CI: 0, 35); TT/CT *vs.* CC: OR = 0.89, 95%CI: 0.81, 0.97, $P_{heterogeneity} = 0.41$, $I^2 = 3\%$ (95%CI: 0,29)] (Supplementary Tables S2 and S3). None of these ORs in the "sample size ≥500" subgroup were statistically significant.

Subgroup analyses by genotyping method

In subgroup analyses by genotyping methods, no statistically significant results were found in either the PCR-RFLP subgroup, the TaqMan subgroup, or the other method subgroup (Tables 2 and 3). The results did not differ significantly in the sensitivity analyses excluding the studies that did not fulfill HWE (Supplementary Tables S2 and S3).

Cumulative meta-analyses

Cumulative meta-analysis of the *IL-10* −819C/T polymorphism was also conducted via assortment of studies in chronologic order. Supplementary Figure S2 show the results from the cumulative meta-analyses for the association of the TT/CT genotypes compared with the CC genotype and the overall cancer risk in chronological order. The effect of the *IL-10* −819C/T polymorphism tended to be not significant over time. The 95% confidence intervals became increasingly narrower with increasing data, indicating that the precision of the estimates was progressively enhanced by the continual addition of more studies.

Publication bias

The results of the Begg's funnel plots did not reveal any evidence of obvious asymmetry (Fig. 5). The results of Egger's test also did not suggest any evidence of publication bias in the overall analysis (T allele *vs.* C allele: $p = 0.70$; TT *vs.* CC: $p = 0.77$; CT *vs.* CC: $p = 0.95$; TT *vs.* CT: $p = 0.82$; TT/CT *vs.* CC: $p = 0.69$; TT *vs.* CT/CC: $p = 0.81$; TT/CC *vs.* CT: $p = 0.46$).

Assessment of cumulative evidence

We also assessed the cumulative evidence for the association between the *IL-10* −819C/T polymorphism and cancer

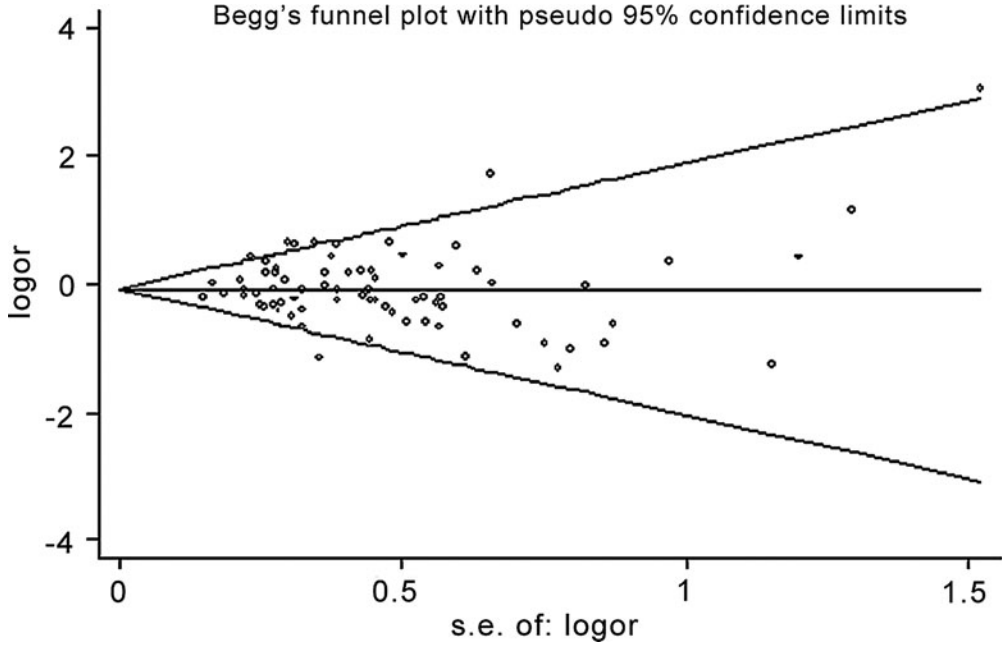

FIG. 5. Begg's funnel plot (TT versus CC model) for the identification of publication bias in the overall analysis. No significant funnel asymmetry was observed that could indicate publication bias. The *horizontal line* in the funnel plot indicates the random effects summary estimate, while the *sloping lines* indicate the expected 95% CI for a given standard error, assuming no heterogeneity between studies. Logor, natural logarithm of the OR; s.e. of: logor, standard error of the logor.

risk using three criteria (amount of evidence, replication, and protection from bias) of the Venice interim guidelines. For the amount of evidence, the Asian population subgroup, gastric cancer in the Asian subgroup, the cervical cancer subgroup, the HCC subgroup, and the "sample size <500" subgroup contained the largest number of subjects with minor alleles, while the ovarian cancer subgroup contained a moderate number of subjects. Furthermore, to assess replication of the associations, I^2 values ranging from 12% to 26% were used in the Asian population subgroup, values ranging from 0%–28% in gastric cancer in the Asian subgroup, ranging from 14%–23% in the HCC subgroup, and ranging from 14%–22% in "sample size <500" subgroup. The I^2 values were 0% in the cervical cancer and ovarian cancer subgroups. There was no obvious bias from phenotype misclassification or population stratification. However, the information on quality control procedures for genotyping was insufficient. Overall, the credibility of these associations was considered 'moderate'.

Previous meta-analyses

There were six previous meta-analyses for the *IL-10* −819C/T polymorphism and cancer risk (Supplementary Table S4). The previous meta-analyses on prostate cancer (Shao et al., 2011; Zou et al., 2011) and hepatocellular carcinoma (Wei et al., 2011) reported no statistically significant results, similar to the findings of the current meta-analysis. Three meta-analyses found that overall ORs for gastric cancer for not statistically significant (Chen et al., 2010; Persson et al., 2011; Xue et al., 2012). The *IL-10* −819 TT genotype is associated with the reduced gastric cancer risk among Asians, with two meta-analyses showing statistically significant results (Chen et al., 2010; Xue et al., 2012). The OR in the TT versus CT/CC model reported by Xue et al. was 0.82, which was statistically significant and similar to the results of the current meta-analysis (Xue et al., 2012).

Discussion

In our meta-analysis, based on 73 studies that included 15,942 cases and 22,336 controls, we found that the T allele and TT genotype of the *IL-10* −819C/T polymorphism demonstrated a moderately reduced risk of cancer among Asians. The carriers of the CT or TT genotypes had a higher risk of cervical and ovarian cancer, and carriers of the TT genotype had lower risk of gastric cancer in Asians. The depressed cancer risk of the TT genotype was also found in studies of hospital-based case-control studies and studies that recruited less than 500 subjects, but no statistically significant results were found in the analyses stratified by genotyping method.

It is well known that the excessive and constant production of pro-inflammatory mediators is a major contributor to tumor promotion and progression (Coussens and Werb, 2002). IL-10 is a multifunctional cytokine with both immunosuppressive and anti-angiogenic functions, suggesting that IL-10 may inhibit tumor development and progression. However, the precise mechanisms by which the *IL-10* −819C/T polymorphism may modulate cancer progression remains unknown. Polymorphisms in the promoter of the IL-10 gene have been reported to influence the production capacity of IL-10 (Turner et al., 1997) and to be associated with the risk of different cancer types, including gallbladder carcinoma (Vishnoi et al., 2007), bladder cancer (Ahirwar et al., 2009), colon cancer (Cacev et al., 2008), and hepatocellular carcinoma (Liu et al., 2010b).

Although many studies have investigated the association between the *IL-10* −819C/T polymorphism and cancer risk, the results have been inconsistent. Hence, it is necessary to use a quantitative approach for combining the results of these studies, and for estimating and explaining their diversity. Heterogeneity is a potential problem when interpreting the results of any meta-analysis. In this study, low or moderate heterogeneity in most comparisons for the *IL-10* −819C/T polymorphism was detected using Cochran's Q test and the quantity I^2. Because the data could be affected by the contributions of subgroup differences, we conducted analyses stratified by ethnicity, cancer type, study design, sample size, and genotyping method.

The incidence of the gene polymorphisms can vary substantially between different racial or ethnic populations with different genetic backgrounds, which can influence the association between polymorphisms and cancer susceptibility. In this meta-analysis, a highly significant difference in the prevalence of the −819T allele of the *IL-10* gene among Asian (60.06%) and European (25.35%) controls was found. Subgroup analyses by ethnicity showed that the association between the TT variant genotypes and a decreased risk of cancer was significant in the Asian but not in the European population. This finding suggests that there is genetic diversity among the different ethnicities. These ethnic differences in the allele frequencies may be a result of natural selection or balance to other related genetic variants.

Our study represents a systematic review of the literature on the *IL-10* −819C/T polymorphism and multifarious cancer risk. In the analysis stratified by cancer type, we provide the summary risk estimates for ten cancer types. While previously published meta-analyses have reported only on prostate cancer (Shao et al., 2011; Zou et al., 2011), hepatocellular carcinoma (Wei et al., 2011), and gastric cancer (Chen et al., 2010; Persson et al., 2011; Xue et al., 2012), we were able to provide a complete description of the role of the IL-10 −819C/T polymorphism in cancer risk. Our meta-analysis included two new studies (Bei et al., 2011; Liu et al., 2010b) on hepatocellular carcinoma that were not included in a 2011 meta-analysis (Wei et al., 2011) and four new studies (El-Omar et al., 2003; Kang et al., 2009; Kim et al., 2012; Zeng et al., 2012) on gastric cancer that were not included in a 2012 meta-analysis (Xue et al., 2012). However, one study for hepatocellular carcinoma included in the previous meta-analysis was excluded in our study because the genotype numbers for CT and CC genotypes were insufficient (Nieters et al., 2005). The study by Leon et al., which included 12 prostate cancer cases and 24 controls, was also excluded in this meta-analysis because the full text of this study was not assessed (Leon et al., 2010).

Our results suggest that the *IL-10* −819C/T polymorphism increased risk for cervical and ovarian cancers but was a protective factor for gastric cancer in Asians. The −819 TT genotype was more protective for gastric cancer in Asians, which is a finding consistent with two previous meta-analyses (Chen et al., 2010; Xue et al., 2012). However, we did not find any significant associations among studies of breast cancer, colorectal cancer, prostate cancer, hepatocellular carcinoma, lymphoma, or melanoma in any of the genetic models. This

result suggests that the influence of the genetic variation may be obscured by the presence of other unknown contributory factors involved in carcinogenesis.

Our subgroup analyses indicate that the difference in study design or the number of subjects affects the risk associations. Statistically significant associations between the carriers of the T allele and the reduced risk of cancers were identified in the HCC subgroup and the "sample size <500" subgroup but not in the PCC subgroup and the "sample size ≥500" subgroup. Therefore, more rigorous and uniform studies should be conducted to accurately explore the true association between the *IL-10* −819C/T polymorphism and cancer susceptibility.

Additionally, different genotyping technologies were reported in these association studies. In our meta-analysis, no statistically significant association with cancer risk was found among any of the PCR-RFLP, TaqMan, or other method subgroups because the sensitivity and specificity of those genotyping techniques are sufficient to minimize the genotyping errors.

There were several limitations of this study. First, because of the limits of raw data and publication, some relevant studies were excluded in this meta-analysis. Second, the sample sizes in some subgroup analyses were extremely small. Third, the sources of the controls were not consistent. Both population-based healthy individuals and hospitalized patients without cancer were included in the control group. Thus, the controls may not have always been truly representative of the underlying source populations, especially when the polymorphism was also expected to affect the risk of other diseases. Finally, this meta-analysis was based on unadjusted data, and a more precise analysis could be performed if individual data were available.

A previous study reported that a haplotype formed by the *IL-10* −1082 G/A, −819 C/T and −592 C/A polymorphisms is associated with the production of IL-10 (Eskdale et al., 1998). However, few studies have been conducted to evaluate the association between the haplotypes of *IL-10* and cancer risk in diverse populations. Pogoda et al. (2007) reported that of *IL-10* gene haplotypes determined by these polymorphisms, the ACC haplotype was more incident in cancer patients, while the ATA haplotype was more rare. A significantly higher frequency of the GCC haplotype was observed in early-stage patients in comparison to advanced prostate cancer patients, suggesting an association of GCC haplotype with prostate cancer grade in the Chinese population (Liu et al., 2010a). Our results support a role for *IL-10* −819C/T polymorphism in cancer risk, but the OR values are relatively low. These results imply that other mechanisms, such as linkage with other polymorphisms, might be responsible for the association with cancer risk. Further studies estimating the effect of the haplotype of *IL-10* polymorphisms interactions may eventually provide a better, more comprehensive understanding.

In conclusion, in spite of the limitations mentioned above, our meta-analysis supports the growing body of evidence that the −819TT genotype in the promoter region of the *IL-10* gene is emerging as a protective factor for cancer in Asian populations, especially for gastric cancer. However, the CT genotype and dominant model present risk factors for cervical and ovarian cancer. The importance of stratifying by ethnicity, cancer type, study design, and sample size needs to be standardized in future studies, together with consideration of the association between the *IL-10* −819C/T polymorphism and cancer risk. Furthermore, the linkage of the −819C/T polymorphism with other polymorphisms of *IL-10* may help explain the variability in findings.

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Author Disclosure statement

The authors declare that no potential conflicts of interest exist.

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