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Common Polymorphisms in the *NFKBIA* Gene and Cancer Susceptibility: A Meta-Analysis

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Background: *NFKBIA* encodes the inhibitors of nuclear factor-κB (NF-κB), which regulate the translation of the genes involved in the inflammatory and immune reactions. Polymorphisms (rs2233406, rs3138053, and rs696) of *NFKBIA* have been implicated in susceptibility to many cancer types.

Material/Methods: To evaluate the association between polymorphisms of *NFKBIA* and cancer susceptibility, a meta-analysis including a total of 7182 cancer cases and 10 057 controls from 28 case-control studies was performed. Data were extracted and pooled odds ratios (ORs) with 95% confidence intervals (CIs) were calculated.

Results: Combined data demonstrated that rs3138053 polymorphism of *NFKBIA* was associated with cancer susceptibility in an allelic model (C *vs.* T: OR=10.754, 95%CI=4.175–27.697, $P_{heterogeneity}$=0.000), while the polymorphism of rs696 appeared to play a protective role in tumorigenesis (CC+CT *vs.* TT: OR=0.879, 95%CI=0.787–0.982, $P_{heterogeneity}$=0.107). When stratification analysis was performed by cancer type, an increased association of rs3138053 was recognized in hepatocarcinoma (C *vs.* T: OR=42.180, 95%CI=27.970–63.612, $P_{heterogeneity}$=0.007), while a decreased association of rs696 was identified in Hodgkin lymphoma (C *vs.* T: OR=0.792, 95%CI=0.656–0.956, $P_{heterogeneity}$=0.116; CC *vs.* TT: OR=0.658, 95%CI=0.448–0.965, $P_{heterogeneity}$=0.076; CC *vs.* CT+TT: OR=0.734, 95%CI=0.562–0.958, $P_{heterogeneity}$=0.347). By ethnicity, rs696 appears to be a protective candidate among Caucasians (CT *vs.* TT: OR=0.809, 95%CI=0.676–0.969, $P_{heterogeneity}$=0.459).

Conclusions: Our data demonstrated that the rs3138053 polymorphism of *NFKBIA* gene is a candidate for susceptibility to overall cancers, while rs696 plays a protective role.

MeSH Keywords: Genetic Linkage • Medical Oncology • Meta-Analysis

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Background

Nuclear factor-κB (NF-κB) belongs to a family of transcription factors that play a crucial role in inflammatory and immune reactions [2]. The malfunctioning of NF-κB contributes to the inhibition of apoptosis, cell replication, and angiogenesis, all of which are occur in cancer cells [3]. Several pieces of evidence have demonstrated the connection between the defective function of IκB and cancer progression. Overexpression of NF-κB has been identified in several categories of cancer, including Hodgkin's lymphoma, multiple myeloma, colorectal cancer, and melanoma [1]. Additionally, it was discovered that the expression of IκB was decreased among prostate cancer patients [4]. These results indicate the significant role of IκBs in regulating the oncogenic potential of NF-κB and in cancer development. From these points of view, malfunctioning in the expression of IκB may remain a risk factor for cancer.

IκBα is encoded by *NFKBIA* genes located on chromosome 14q13. *NFKBIA* rs2233406, rs3138053, and rs696 polymorphisms are situated in the binding regions for CCAAT/enhancer binding protein and GATA binding protein 2, respectively. They may regulate IκBα expression, and influence NF-κB activation; these polymorphisms (rs2233406, rs3138053, and rs696) are directly related to apoptosis, inappropriate immune cell development, and delayed cell growth [5]. The effect of polymorphisms within the *NFKBIA* gene on cancer susceptibility has been investigated in a number of cancers [6–12]. It was reported that polymorphic variants in the 39-untranslated region of *NFKBIA* was associated with a susceptibility to multiple myeloma, Hodgkin's lymphoma, prostate cancer, breast cancer, colorectal cancer, gastric cancer, and melanoma [13–19].

However, the susceptibility modulation impacts of the polymorphisms were inconsistent in various studies because the sample sizes enrolled were limited and the ethnic backgrounds of subjects in various studies were different. Evidence of the relationship between genetic polymorphisms and cancer susceptibility can be provided by a quantitative synthesis to accumulate data from different studies. In this paper we present the results of a comprehensive meta-analysis performed on publicly available databases.

Material and Methods

Literature sources and search strategy

We conducted a systematic literature search in Google Scholar, PubMed, and Web of Science databases (up to 20 June 2015) to accumulate all available studies on the association between polymorphisms of *NFKBIA* (rs2233406, rs3138053, and rs696) and cancer susceptibility by using the following the search strategy: ("*NFKBIA*" OR "Nuclear factor kappa B inhibitor") AND ("polymorphism" OR "mutation" OR "variation") AND ("susceptibility" OR "risk" OR "effects") AND ("cancer" OR "tumour" OR "carcinoma"). Studies were also searched manually on the reference lists of reviews and retrieved studies for additional eligible studies.

Inclusion and exclusion criteria

The articles enrolled in the present meta-analysis were consistent with these criteria: (a) the relationship between the polymorphisms in *NFKBIA* and cancer susceptibility was identified in the studies; (b) the study method was case-control; and (c) we could extract the ORs with 95%CIs of all the cases and controls. Studies were excluded when they were: (a) studies without sufficient raw data to evaluate odds ratios with 95% confidence intervals; (b) case-only studies; (c) duplicated publications; and (d) studies based on animals or families.

Data extraction

The data were extracted independently by 3 investigators (M. Zhang, J. J. Huang, and X. X. Tan). Data with discrepancies were discussed by all authors. The following data were collected: name of first author, publication year, country of origin, ethnicity, cancer type, total numbers of cases and controls, source of controls, and genotype or allele distribution in cases and controls. Ethnic backgrounds were categorized as Asian and Caucasian.

Statistical analysis

We assessed the relationship between the *NFKBIA* polymorphisms and cancer susceptibility by employing the ORs and 95% CIs in the studies and calculated the pooled ORs on the allele contrast (t *vs.* T), dominant (Tt+tt *vs.* TT), and recessive (tt *vs.* Tt+TT) models. Comparisons were also performed in heterozygote (Tt *vs.* TT) and homozygote (tt *vs.* TT) (TT, homozygotes for the common allele; Tt, heterozygotes; tt, homozygotes for the rare allele). The *P* values of HWE were calculated by χ^2 test for the genotype distribution in controls. The meta-analyses were conducted by using STATA 12.0 software (Stata Corporation, College Station, Texas). A chi-square based Q-statistic test was performed to evaluate the heterogeneity of studies in the case-control studies [20]. If the Q test ($P>0.1$) indicated homogeneity within studies, the fixed-effects model was used [21]; otherwise, the random-effects model was used [22]. We also evaluated heterogeneity across studies by calculation of the inconsistency index ($I^2<25\%$: no heterogeneity; $I^2=25–50\%$: moderate heterogeneity; $I^2>50\%$: significant heterogeneity). Stratification analyses were performed by source of control, cancer type, and ethnicity. We removed a single study each time to evaluate the stability of

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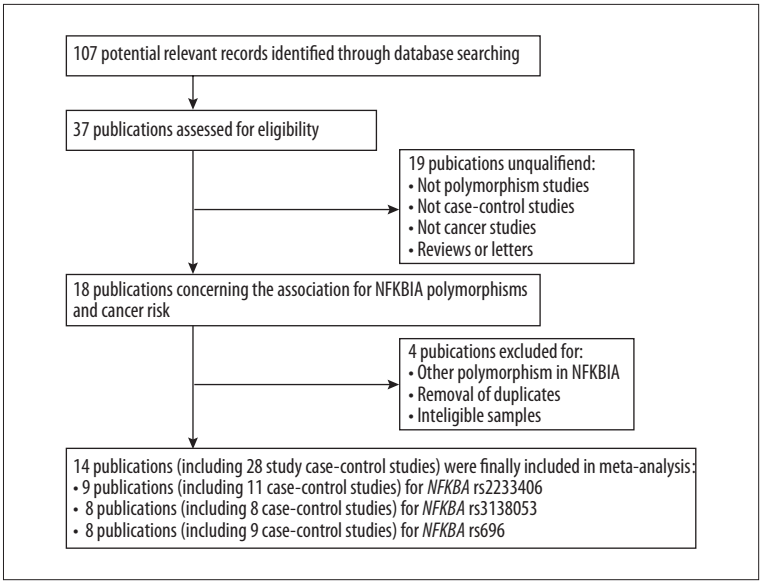

Figure 1. Flow chart presenting the study selection procedure.

the results. Begg's funnel plot and Egger's test were used to assess publication bias.

Results

The identification and characteristics of eligible studies

As demonstrated in Figure 1, after a systematic literature search in the databases on the relevance between *NFKBIA* polymorphisms and cancer susceptibility, a total of 107 potential records were initially identified. After checking the abstracts, 70 irrelevant studies were excluded, some studies were with insufficient data and others were duplicated studies. When the full texts were examined, we excluded 19 articles with no polymorphism studies, non-case-control studies, studies not on cancer, and reviews. Another 4 publications were excluded because they were on other polymorphisms in *NFKBIA*, were duplicates, or lacked eligible samples. Finally, 14 articles containing 28 independent case-control studies with a total of 7182 cases and 10 057 controls were enrolled in this meta-analysis [23–36]. Table 1 presents the characteristics of all eligible studies; 9 were population-based and the others were hospital-based. All studies were case-controlled, including 9 liver cancer studies, 5 colorectal cancer studies, 3 breast cancer studies, 3 prostate cancer studies, 2 oral cancer studies, 2 oesophageal cancer studies, 1 ovarian cancer study, and 1 multiple myeloma study. The ethnicities in these case-control studies were categorized as Asian (23 studies) and Caucasian (5 studies).

Pooled analysis

The primary results of the present meta-analysis and the heterogeneity test are summarized in Table 2. In addition, we also rated the methodological quality of the included studies according to the Newcastle-Ottawa Scale (Table 3). By pooling ORs and 95% CIs, we discovered that rs2233406 polymorphism of *NFKBIA* was not associated with susceptibility to cancers (Table 2A). However, we identified a significant increased susceptibility in the rs3138053 polymorphism of *NFKBIA* (C *vs.* T: OR=10.754, 95%CI=4.175–27.697, $P_{heterogeneity}$=0.000; Figure 2A, Table 2B). Another impressive finding was that the polymorphism of rs696 appeared to play a protective role in tumorigenesis, as suggested by the pooled ORs (CC+CT *vs.* TT: OR=0.879, 95%CI=0.787–0.982, $P_{heterogeneity}$=0.107; Figure 2B, Table 2C).

Subgroup analysis

In the subgroup meta-analysis by cancer type, the rs3138053 polymorphism of *NFKBIA* was revealed to be an important factor in HCC cancer susceptibility, and the pooled results were statistically significant (C *vs.* T: OR=42.180, 95%CI=27.970-63.612, $P_{heterogeneity}$=0.007; Table 2B). Some significantly decreased susceptibility of the rs696 polymorphism of *NFKBIA* was observed in Hodgkin lymphoma (C *vs.* T: OR=0.792, 95%CI=0.656–0.956, $P_{heterogeneity}$=0.116; CC *vs.* TT: OR=0.658, 95%CI=0.448–0.965, $P_{heterogeneity}$=0.076; CC *vs.* CT+TT: OR=0.734, 95%CI=0.562–0.958, $P_{heterogeneity}$=0.347; Table 2C). The source analysis indicated positive association of the rs3138053 polymorphism in the hospital-based group (C *vs.* T: OR=10.381, 95%CI=3.513–30.677, $P_{heterogeneity}$=0.000; CC+TC *vs.* TT: OR=1.405, 95%CI=1.146–1.721, $P_{heterogeneity}$=0.114; CC *vs.* TC+TT: OR=2.460, 95%CI=1.686–3.590, $P_{heterogeneity}$=0.867; Table 2B) and the population-based group (C *vs.* T: OR=11.377, 95%CI=1.472–87.963, $P_{heterogeneity}$=0.000; Table 2B). Caucasians seems to benefit more from the polymorphism of rs696 (CT *vs.* TT: OR=0.809, 95%CI=0.676–0.969, $P_{heterogeneity}$=0.459; Table 2C) than Asians (CT *vs.* TT: OR=0.921, 95%CI=0.691–1.227, $P_{heterogeneity}$=0.015; Table 2C).

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Table 1. Characteristics of the enrolled studies.

SNP	First author	Year	Ethnicity	Genotyping method	Source of control	Cancer type	Control					Case		
							AA	AB	BB	*P* (HWE)	Y or N	AA	AB	BB
rs2233406	Lu et al.	2015	Asian	PCR-RFLP	HB	OC	478	190	19	0.982	Y	486	181	20
	Zhang et al.	2014	Asian	PCR	HB	HCC	1292	321	28	0.123	Y	204	41	6
	Cheng et al.	2013	Asian	PCR	HB	HCC	438	78	4	0.797	Y	106	27	2
	Lin et al.	2012	Asian	TaqMan	HB	ORC	438	78	4	0.797	Y	351	101	10
	Tan et al.	2013	Asian	PCR	HB	CRC	163	69	5	0.459	Y	169	60	8
	Wang et al.	2014	Asian	PCR-RFLP	HB	BC	297	162	42	**0.004**	N	212	102	32
	Wang et al.	2014	Asian	PCR-RFLP	HB	BC	297	162	42	**0.004**	N	46	25	0
	Wang et al.	2014	Asian	PCR-RFLP	HB	BC	297	162	42	**0.004**	N	30	20	7
	He et al.	2009	Asian	PCR	HB	HCC	685	181	20	0.056	Y	149	52	1
	Han et al.	2015	Asian	PCR-RFLP	HB	PC	586	321	29	0.058	Y	508	356	72
	Umar et al.	2013	Asian	PCR	PB	ESCC	149	141	21	0.106	Y	145	122	23
rs3138053	Lin et al.	2012	Asian	TaqMan	HB	ORC	438	78	4	0.797	Y	351	101	10
	Tan et al.	2013	Asian	PCR	HB	CRC	163	69	5	0.459	Y	169	60	8
	Gao et al.	2014	Asian	PCR	PB	HCC	336	48	40	**0.000**	N	173	21	19
	Spink et al.	2006	Caucasian	PCR	PB	MM	94	91	11	0.066	Y	64	77	16
	He et al.	2009	Asian	PCR	HB	HCC	780	106	0	0.058	Y	164	38	0
	Han et al.	2015	Asian	PCR-RFLP	HB	PC	586	321	29	0.058	Y	508	356	72
	Zhang et al.	2014	Asian	PCR	PB	HCC	1289	308	27	0.087	Y	214	38	1
	Cheng et al.	2013	Asian	PCR	HB	HCC	438	78	4	0.797	Y	106	27	2
rs696	Umar et al.	2013	Asian	PCR	PB	ESCC	59	165	87	0.219	Y	71	140	79
	Gao et al.	2006	Asian	PCR-RFLP	HB	CRC	81	259	237	0.450	Y	26	109	64
	Gao et al.	2006	Caucasian	PCR-RFLP	HB	CRC	74	221	143	0.466	Y	29	72	54
	Zhang et al.	2014	Asian	PCR	HB	HCC	248	794	561	0.231	Y	55	109	84
	Gao et al.	2014	Asian	HapMap	PB	HCC	149	196	76	0.412	Y	65	115	33
	Osborne et al.	2005	Caucasian	PCR	PB	HL	8	22	20	0.64	Y	4	26	21
	Chang et al.	2009	Caucasian	Taqman	PB	HL	53	158	153	0.245	Y	92	215	156
	Han et al.	2015	Asian	PCR-RFLP	HB	PC	165	458	313	0.909	Y	173	442	321
	Song et al.	2011	Caucasian	PCR-RFLP	PB	CRC	212	531	262	0.06	Y	233	460	308

PCR – polymerase chain reaction; PCR-RFLP – polymerase chain reaction-restriction fragment length polymorphism; Y – $P_{(HWE)}$ >0.05; N – $P_{(HWE)}$ ≤0.05; HCC – hepatocellular carcinoma; OC – ovarian cancer; BC – breast cancer; CRC – colorectal cancer; HL – Hodgkin lymphoma; PC – prostate cancer; ESCC – esophageal squamous cell carcinoma; MM – multiple myeloma; ORC – oral cancer; HB – hospital-based; PB – population-based;

In addition, polymorphisms that conformed to HWE in the control group showed positive association in rs2233406 (CC *vs.* CT+TT: OR=1.535, 95%CI=1.027–2.296, $P_{heterogeneity}$=0.099; Figure 2C and Table 2A) and rs3138053 (CC *vs.* TT: OR=2.133, 95%CI=1.317–3.455, $P_{heterogeneity}$=0.217; CC *vs.* TC+TT: OR=2.063, 95%CI=1.350–3.154, $P_{heterogeneity}$=0.296; Table 2B).

Sensitivity analysis and publication bias risk

The sensitivity analyses were conducted by excluding each single case-control study in turn, and no separate study shows an influence on the pooled OR. Begg's funnel plot and Egger's test were performed to assess the risk of publication bias and no visual publication bias was shown (rs3138053: C *vs.* T: *P*=0.181 for egger's test; rs696: CC+CT *vs.* TT: *P*=0.552 for

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Table 2A. Results of meta-analysis for rs2233406 polymorphism in *NFKBA* and cancer susceptibility.

Variables (rs2233406)	Case/ control	C *vs.* T			CC *vs.* TT			CT *vs.* TT		
		OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)
Total	3674/7241	1.098 (0.944–1.277)	0.000	47.1	1.387 (0.942–2.042)	0.017	28.9	1.077 (0.931–1.246)	0.030	24.8
Source of control										
HB	3384/6930	1.112 (0.942–1.312)	0.000	49.4	1.417 (0.914–2.198)	0.014	32.1	1.099 (0.941–1.284)	0.031	25.9
Cancer type										
HCC	588/3047	1.082 (0.851–1.375)	0.236	9.5	1.038 (0.348–3.103)	0.187	16.3	1.131 (0.789–1.622)	0.082	35.8
BC	474/1503	0.841 (0.581–1.215)	0.132	31.2	0.390 (0.026–5.968)	0.048	55.2	1.222 (0.673–2.221)	0.693	0.0
HWE										
Y	3200/5738	1.148 (0.967–1.362)	0.002	48.9	1.535 (0.982–2.400)	0.046	26.1	1.103 (0.924–1.318)	0.014	36.2
N	474/1503	0.952 (0.691–1.310)	0.096	32.9	0.994 (0.398–2.484)	0.084	35.5	0.954 (0.750–1.214)	0.624	0.0
	Case/ control	CC+CT *vs.* TT			CC *vs.* CT+TT					
		OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)			
Total	3674/7241	1.097 (0.937–1.283)	0.005	36.2	1.390 (0.977–1.978)	0.043	21.8			
Source of control										
HB	3384/6930	1.117 (0.944–1.323)	0.005	37.9	1.409 (0.940–2.111)	0.032	25.7			
Cancer type										
HCC	588/3047	1.115 (0.821–1.515)	0.146	23.0	1.014 (0.324–3.175)	0.165	19.9			
BC	474/1503	0.889 (0.695–1.138)	0.616	0.0	0.396 (0.024–6.446)	0.043	57.0			
HWE										
Y	3200/5738	1.137 (0.944–1.369)	0.004	43.7	**1.535 (1.027–2.296)***	0.099	17.6			
N	474/1503	0.949 (0.758–1.188)	0.398	0.0	1.009 (0.425–2.396)	0.094	33.3			

Egger's test, Figure 3A; rs2233406: CC *vs.* CT+TT: *P*=0.175 for Egger's test, Figure 3B).

Discussion

The activation and translocation of NF-κB to the nucleus modulate the translation of the genes involved in inflammatory and immune activities, cell adhering, differentiating, growing, angiogenesis, and apoptosis through kinases, which leads to the phosphorylation, ubiquitination, and degradation of IκBs [37]. The p50 subunit, encoded by the NF-κB, has several common polymorphisms in the promoter region. The promoter sequence polymorphisms contribute to an increased expression of NF-κB messenger (m) RNA. NF-κB is important to cancer pathogenesis, preventing apoptosis and enhancing growth and survival by the upregulation of several genes [38]. Individual single-nucleotide polymorphisms (rs2233406, rs3138053, and rs696) in the *NFKBIA* gene may affect expression and function of the protein. Specifically, allelic differences in the *NFKBIA* promoter and 30UTR region may change IκBa expression and affect complex formation with NF-κB. In this way, cell growth and anti-apoptosis are regulated [39].

Li et al. [40] and Zou et al. [41] reported that genetic polymorphisms of the *NFKBIA* gene were associated with cancer

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Table 2B. Results of meta-analysis for rs3138053 polymorphism in *NFKBA* and cancer susceptibility.

Variables (rs3138053)	Case/ control	C *vs.* T			CC *vs.* TT			TC *vs.* TT		
		OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)
Total	2595/5343	**10.754 (4.175–27.697)***	0.000	97.8	1.683 (0.979–2.891)	0.023	34.8	1.178 (0.954–1.455)	0.012	39.9
Source of control										
HB	1972/3099	**10.381 (3.513–30.677)***	0.000	97.4	2.652 (1.810–3.886)	0.767	0.0	1.335 (1.075–1.657)	0.093	24.7
PB	623/2244	**11.377 (1.472–87.963)***	0.000	98.6	1.029 (0.415–2.551)	0.068	39.3	0.913 (0.662–1.259)	0.205	13.5
Ethnicity										
Asian	2438/5147	13.628 (4.922–37.731)	0.000	97.8	1.577 (0.817–3.043)	0.013	42.9	1.168 (0.920–1.483)	0.006	44.5
Cancer type										
HCC	590/3030	**42.180 (27.970–63.612)***	0.007	63.8	0.718 (0.070–7.340)	0.077	46.2	1.206 (0.706–2.062)	0.007	63.7
HWE										
Y	2382/4919	10.585 (3.663–30.581)	0.000	98.0	**2.133 (1.317–3.455)***	0.217	8.5	1.216 (0.975–1.518)	0.012	40.1
N	213/424	12.036 (8.430–17.184)	–	–	0.923 (0.519–1.641)	–	–	0.850 (0.493–1.465)	–	–

	Case/ control	CC+TC *vs.* TT			CC *vs.* TC+TT		
		OR (95% CI)	*P*[a]	I^2 (%)	OR (95% CI)	*P*[a]	I^2 (%)
Total	2595/5343	1.209 (0.964–1.517)	0.002	48.9	1.632 (1.001–2.660)	0.055	26.3
Source of control							
HB	1972/3099	**1.405 (1.146–1.721)***	0.114	21.4	**2.460 (1.686–3.590)***	0.867	39.0
PB	623/2244	0.928 (0.639–1.347)	0.074	37.9	1.632 (1.001–2.660)	0.105	26.3
Ethnicity							
Asian	2438/5147	1.192 (0.923_1.539)	0.001	54.9	1.553 (0.851–2.834)	0.031	35.2
Cancer type							
HCC	590/3030	1.192 (0.668–2.127)	0.003	69.1	0.716 (0.080–6.438)	0.094	41.3
HWE							
Y	2382/4919	1.260 (0.992–1.601)	0.003	49.3	**2.063 (1.350–3.154)***	0.296	3.3
N	213/424	0.883 (0.582–1.339)	–	–	0.940 (0.530–1.667)	–	–

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Table 2C. Results of meta-analysis for rs696 polymorphism in *NFKBA* and cancer susceptibility.

Variables (rs696)	Case/ control	C *vs.* T			CC *vs.* TT			CT *vs.* TT		
		OR (95% CI)	P^a	I^2 (%)	OR (95% CI)	P^a	I^2 (%)	OR (95% CI)	P^a	I^2 (%)
Total	3556/5705	0.952 (0.894–1.014)	0.121	13.8	0.891 (0.783–1.013)	0.194	79.5	0.884 (0.738–1.058)	0.044	24.6
Ethnicity										
Caucasian	1670/1857	0.971 (0.882–1.069)	0.034	0.0	0.930 (0.766–1.128)	0.055	36.5	**0.809 (0.676–0.969)***	0.459	0.0
Asian	1886/3848	0.939 (0.863–1.021)	0.431	42.6	0.861 (0.725–1.023)	0.527	0.0	0.921 (0.691–1.227)	0.015	45.8
Source of control										
PB	2018/2151	0.963 (0.882–1.051)	0.047	34.2	0.906 (0.759–1.081)	0.080	27.1	0.908 (0.687–1.200)	0.050	33.4
HB	1538/3554	0.941 (0.858–1.031)	0.397	0.0	0.875 (0.726–1.054)	0.439	0.0	0.868 (0.656–1.148)	0.093	28.3
Cancer type										
HL	514/414	**0.792 (0.656–0.956)***	0.116	34.8	**0.658 (0.448–0.965)***	0.076	46.6	1.126 (0.408–3.111)	0.118	34.8
CRC	1355/2020	1.003 (0.907–1.110)	0.269	5.7	1.014 (0.825–1.2480	0.702	0.0	0.901 (0.673–1.206)	0.184	16.7
	Case/ control	CC+CT *vs.* TT			CC *vs.* CT+TT					
		OR (95% CI)	P^a	I^2 (%)	OR (95% CI)	P^a	I^2 (%)			
Total	3556/5705	**0.879 (0.787–0.982)***	0.107	15.3	0.946 (0.811–1.103)	0.025	29.5			
Ethnicity										
Caucasian	1670/1857	0.851 (0.719–1.007)	0.304	3.1	1.002 (0.718–1.399)	0.010	53.7			
Asian	1886/3848	0.901 (0.778–1.044)	0.054	32.5	0.923 (0.798–1.068)	0.306	2.9			
Source of control										
PB	2018/2151	0.887 (0.765–1.028)	0.075	28.1	0.945 (0.718–1.243)	0.016	45.0			
HB	1538/3554	0.870 (0.736–1.028)	0.205	11.9	0.942 (0.781–1.136)	0.165	16.9			
Cancer type										
HL	514/414	0.758 (0.534–1.077)	0.080	45.3	**0.734 (0.562–0.958)***	0.347	0.0			
CRC	1355/2020	0.908 (0.760–1.086)	0.726	0.0	0.995 (0.680–1.456)	0.009	62.4			

I^2 – 0–25, means no heterogeneity; 25–50, means modest heterogeneity; >50, means high heterogeneity; HWE – Hardy-Weinberg equilibrium; Y – polymorphisms conformed to HWE in the control group; N – polymorphisms did not conform to HWE in the control group; P^a – *P* value of Q test for heterogeneity test; * means statistically significant ($P<0.05$); The source of control, HB – hospital-based; PB – population-based; HCC – hepatocellular carcinoma; HL – Hodgkin lymphoma; CRC – colorectal cancer; BC – breast cancer.

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Table 3. Methodological quality of the included studies according to the Newcastle-Ottawa Scale.

	Author	Ethnicity	Adequacy of Case Definition	Representa-tiveness of the Cases	Selection of Controls	Definition of Controls	Comparability Cases/ Controls	Ascertainment of exposure	Same method of ascertainment	Non-response rate
rs2233406	Lu et al.	Asian	*	*	NA	*	**	*	*	*
	Zhang et al.	Asian	*	*	NA	*	**	*	*	*
	Cheng et al.	Asian	*	*	NA	*	**	*	*	*
	Lin et al.	Asian	*	*	NA	*	**	*	*	*
	Tan et al.	Asian	*	*	NA	*	**	*	*	*
	Wang et al.	Asian	*	*	NA	*	**	*	*	*
	Wang et al.	Asian	*	*	NA	*	**	*	*	*
	Wang et al.	Asian	*	*	NA	*	**	*	*	*
	He et al.	Asian	*	*	NA	*	**	*	*	*
	Han et al.	Asian	*	*	NA	*	**	*	*	*
	Umar et al.	Asian	*	*	*	*	**	*	*	*
rs3138053	Lin et al.	Asian	*	*	NA	*	**	*	*	*
	Tan et al.	Asian	*	*	NA	*	**	*	*	*
	Gao et al.	Asian	*	*	*	*	**	*	*	*
	Spink et al.	Caucasian	*	*	*	NA	**	*	*	*
	He et al.	Asian	*	*	NA	*	**	*	*	*
	Han et al.	Asian	*	*	NA	*	**	*	*	*
	Zhang et al.	Asian	*	*	*	*	**	*	*	*
	Cheng et al.	Asian	*	*	NA	*	**	*	*	*
rs696	Umar et al.	Asian	*	*	*	*	**	*	*	*
	Gao et al.	Asian	*	*	NA	*	**	*	*	*
	Gao et al.	Caucasian	*	*	NA	*	**	*	*	*
	Zhang et al.	Asian	*	*	NA	*	**	*	*	*
	Gao et al.	Asian	*	*	*	*	**	*	*	*
	Osborne et al.	Caucasian	*	*	*	NA	**	*	*	*
	Chang et al.	Caucasian	*	*	*	NA	**	*	*	*
	Han et al.	Asian	*	*	NA	*	**	*	*	*
	Song et al.	Caucasian	*	*	*	*	**	*	*	*

This table identifies 'high' quality choices with a 'star'. A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. *, Yes; NA – not applicable. (*http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm*).

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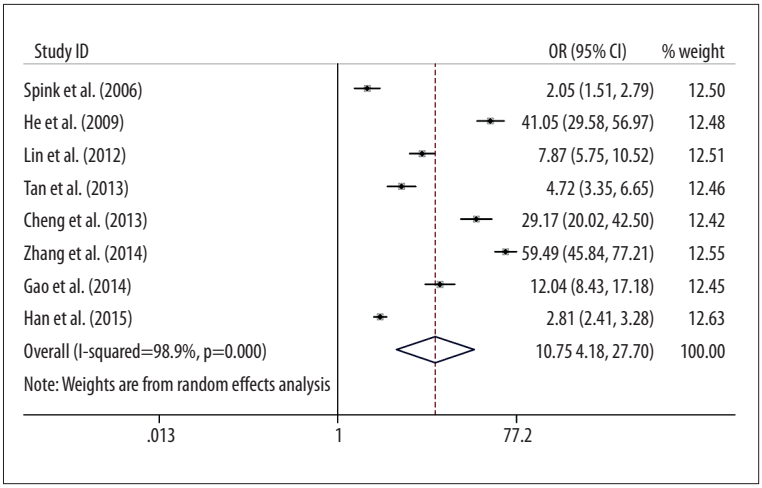

Figure 2A. Meta-analysis of the association between *NFKBIA* rs3138053 polymorphism and overall cancer susceptibility (C *vs.* T).

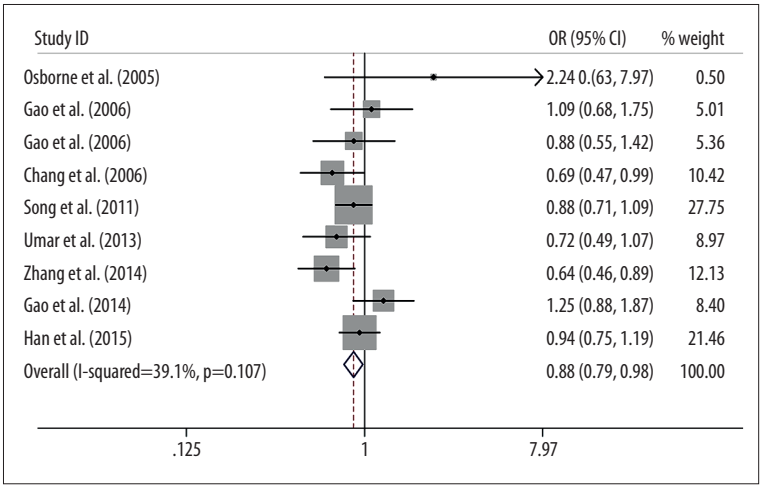

Figure 2B. Meta-analysis of the association between *NFKBIA* rs696 polymorphism and overall cancer susceptibility (CC+CT *vs.* TT).

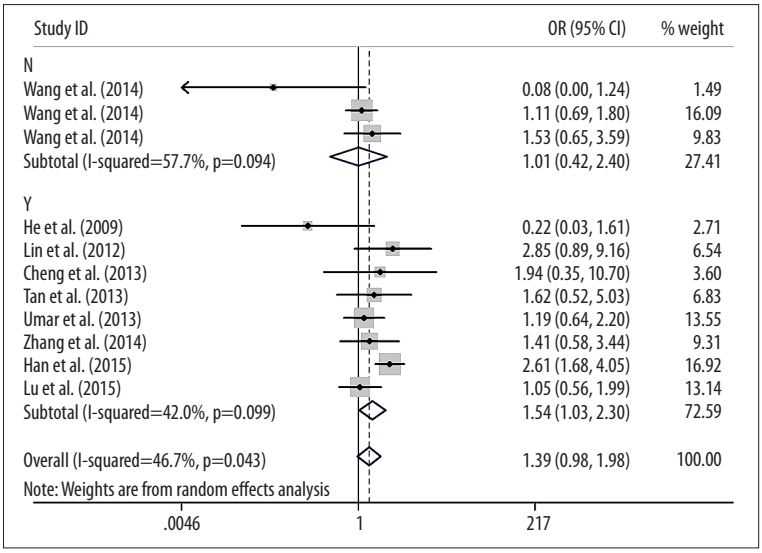

Figure 2C. Subgroup analysis of the association between *NFKBIA* polymorphisms and overall cancer risk by HWE (Hardy-Weinberg equilibrium).

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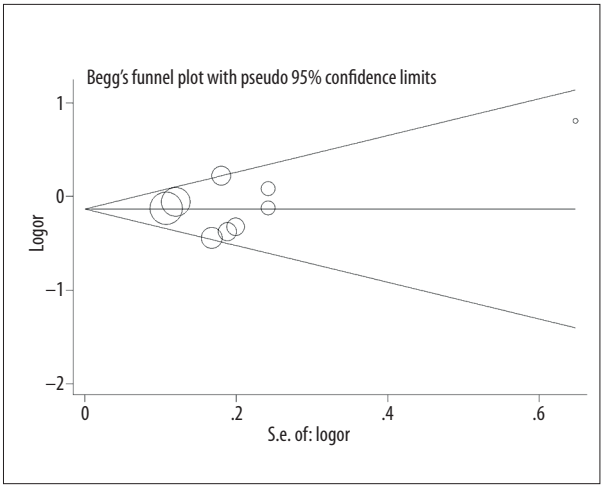

Figure 3A. Publication bias examinations by Begg's funnel plots and Egger's test (rs696: CC+CT *vs.* TT). Asymmetrical plots or P<0.10 suggest potential bias. Each point represents a separate study for the indicated association, and the horizontal line depicts mean effect size. Logor natural logarithm of OR; s.e. standard error.

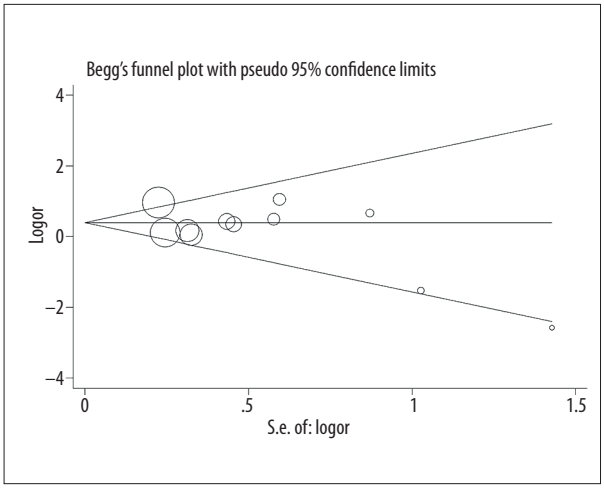

Figure 3B. Publication bias examinations by Begg's funnel plots and Egger's test (rs2233406: CC *vs.* CT+TT). Asymmetrical plots or P<0.10 suggest potential bias. Each point represents a separate study for the indicated association, and the horizontal line depicts mean effect size. Logor natural logarithm of OR; s.e. standard error.

susceptibility and severity in sporadic colorectal cancer and oral cancer. Klein et al. [42] proved that the polymorphism of *NFKBIA* was linked to Crohn's disease. Other studies also drew similar conclusions in breast [9], prostate [13], and stomach [14] cancers. However, results from studies in various geographic areas were not consistent. To the best of our knowledge, this is the first meta-analysis to assess the relationship between these 3 polymorphisms (rs2233406, rs3138053, and rs696) of *NFKBIA* gene and overall cancer susceptibility. Our analysis validated that individuals with the variant allele (rs3138053) appear to have increased susceptibility to cancer. Interestingly, we found a contrary effect of variant allele (rs696), which seems to be associated with decreased susceptibility to cancer. In the subgroup analysis by cancer type, significantly decreased susceptibility of Hodgkin lymphoma with rs696 polymorphism was observed, whereas no significant association was found among studies of colorectal cancer.

The heterogeneity test in the present study showed that there was no evident heterogeneity in terms of the 3 polymorphisms for all cancer types between the studies. Additionally, various cancer categories did not contribute to the overall heterogeneity in association with the polymorphisms, suggesting that our present combined analyses were unbiased, regardless of cancer types. Despite the obvious advantages of our meta-analysis containing large sample sizes, some limitations of this study should be mentioned. The complex factors such as age, sex, and region may bring some bias. Studies reported in other languages may bias the present results because the negative findings are usually difficult to be included. Therefore, further study is needed to evaluate the independent and combined effect of these polymorphisms.

Conclusions

In conclusion, this meta-analysis indicated that the rs3138053 polymorphism of *NFKBIA* gene is a candidate for susceptibility to overall cancers, especially in HCC cancer, while the rs696 plays a protective role against cancers, especially in Hodgkin lymphoma patients and in Caucasians. Moreover, because of the limitations described above, well-designed studies considering gene-gene and gene-environment effects should be conducted to confirm these relationships.

Conflict of interest statement

None.

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