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RESEARCH ARTICLE

NFKB1 -94 insertion/deletion polymorphism and cancer risk: a meta-analysis

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Abstract Previous studies on the associations of the NFKB1 -94 insertion/deletion polymorphism with cancer risk have produced conflicting results. The purpose of this meta-analysis is to define the effect of the NFKB1 -94 insertion/deletion polymorphism on cancer risk. A search of the literature by PubMed was performed to identify studies based on the predetermined inclusion criteria. Twenty-three studies consisting of 6,494 cases and 9,884 controls were identified and analyzed. Overall, significant association was observed between the polymorphism and cancer risk under all genetic models. Subgroup analysis according to ethnicity and cancer type also detected significant association. The NFKB1 -94 insertion/deletion polymorphism was associated with cancer risk in Asian population (dominant model: OR=1.52, 95 % CI=1.17–1.98; recessive model: OR=1.50, 95 % CI=1.26–1.79; II vs. DD: OR=1.90, 95 % CI=1.37–2.65; ID vs. DD: OR=1.32, 95 % CI=1.05–1.66; I vs. D: OR=1.37, 95 % CI=1.17–1.60), but not in Caucasian population. In addition, significant associations in OC, HCC, and OSCC were observed, but significant associations were not found in BC and LC. The current meta-analysis suggested that NFKB1 -94 insertion/deletion polymorphism may influence cancer risk in Asian population.

Keywords NFKB1 · Polymorphism cancer · Meta-analysis

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Introduction

Cancer is a complicated disease associated with individual genetic backgrounds and external factors such as lifestyle and inflammation [1, 2]. It has been reported that inflammation-associated molecules are associated with a majority of cancer types, and these molecules are activated by various elements related to environment and lifestyle [3].

Nuclear factor kappa B (NFKB) is an important transcription factor and is one of the key regulators of inflammatory mechanisms. NFKB comprises a number of related proteins that bind to a common sequence motif known as the kB site. Various homodimers and heterodimers of p65 and c-Rel or p50 protein subunits form the NFKB that acts on the canonical activation pathway dependent on inhibitor of kB kinase activation. The pathway is triggered by inflammatory cytokines via lipopolysaccharide receptors and the toll-like receptor signals induced by microbial, viral, and chemical exposure [4–7].

NFKB1 gene located on chromosome 4q23–24 and encoded p50 subunit. In the promoter region of NFKB1, there is a special -94 insertion/deletion (I/D) polymorphism (rs28362491) influencing the expression of NFKB1. A previous study found that the activity of I allele was twice as high as that of D allele [8]. In addition, several studies have demonstrated the -94 I/D polymorphism to be associated with increased cancer risk such as prostate cancer, hepatocellular

carcinoma, colorectal cancer, gastric cancer, and others [9–13]. The probable mechanism behind the observed association may be related to the expression and activity of NFKB1. However, in other studies, the -94 I/D polymorphism was not observed to be associated with cancer risk [14, 15]. Therefore, we carried out a meta-analysis to clarify the association between this polymorphism and cancer risk.

Materials and methods

Literature search

To identify all articles that examined the association of NFKB1 -94 I/D polymorphism with cancer risk, PubMed database searches were performed using the following keywords: 'NFKB1,' 'polymorphism,' and 'cancer' (up to November 29, 2013). Reference lists in retrieved articles were also screened. Eligible studies should meet the following criteria: (a) case–control studies, (b) detailed genotype data for estimating odds ratio (OR) and 95 % confidence interval (CI), (c) *P* value on Hardy-Weinberg equilibrium (HWE) of controls must be more than 0.05, and (d) studies published in English. If multiple studies had overlapping or duplicate data, only those with complete data were included.

Data extraction

Two investigators (Xu and Cai) independently evaluated and extracted data. Any controversy on the baseline information was resolved by discussion. For each study, the following information was extracted: first author, year of publication, ethnicity, cancer type, genotyping method, HWE, the numbers of genotyped cases and controls, and genotype distributions of cases and controls, respectively.

Statistical analysis

HWE was tested by the chi-square test, and $P<0.05$ was considered as departure from HWE. Heterogeneity among studies was tested using the *Q* statistics. Based on the heterogeneity test, the overall OR was calculated using fixed or random effects model with 95 % CI to measure the strength of the genetic association. The pooled OR were performed for dominant model (II + ID vs. DD), recessive model (II vs. ID + DD), and other genetic models (II vs. DD, ID vs. DD, and I vs. D), respectively. Subgroup analyses were also performed to test the effects of ethnicity and cancer type. Sensitivity analysis was conducted by removing each study and analyzing the others to ensure no single study was totally responsible for overall results. Begg's funnel plot and the Egger's linear regression test were performed to evaluate publication bias of literatures and $P<0.05$ was considered significant. All analyses were done with STATA 12.0 software (Stata Corporation, College Station, TX).

Results

Study characteristics

Figure 1 showed the detailed process of identifying eligible studies. A total of 20 articles, including 23 studies, met the inclusion criteria and were included in this meta-analysis. The main characteristics of the studies are listed in Table 1. Among these studies, including 6,494 cancer cases and 9,884 non-cancer controls, there were 14 studies of Asian population and 9 of Caucasian population. There were 3 bladder cancer (BC) studies, 2 prostate cancer (PC) studies, 2 ovarian cancer (OC) studies, 2 lung cancer (LC) studies, 2 hepatocellular carcinoma (HCC) studies, 2 oral squamous cell carcinoma (OSCC) studies, 2 colorectal cancer (CRC) studies, and 8 others.

Quantitative synthesis

The meta-analysis was assessed by a random effects model because the heterogeneity among studies was significant

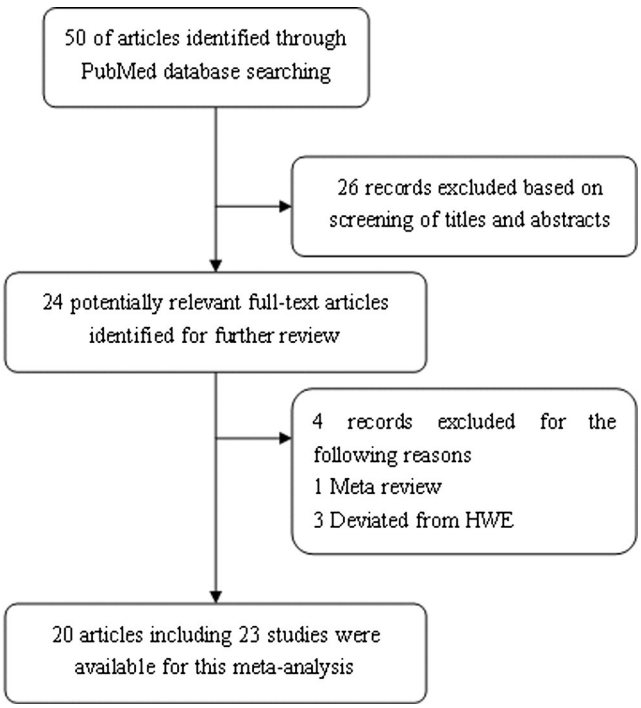

Fig. 1 The detailed process of identifying eligible studies

Table 1 Characteristics of eligible studies

First author [ref]	Year	Ethnicity	Cancer type	Genotyping method	HWE[a]	Cases	Controls	Cases			Controls		
								DD	ID	II	DD	ID	II
Li, P.[16]	2013	Asian	BC	TaqMan	0.16	609	640	151	269	189	93	324	223
Kopp, T. I.[17]	2013	Caucasian	PC	TaqMan	0.72	334	334	54	152	128	64	161	109
Huo, Z. H.[18]	2013	Asian	OC	MassARRAY	0.33	187	221	22	82	83	47	103	71
Huang, D.[19]	2013	Asian	LC	TaqMan	0.08	1056	1056	225	459	372	210	491	355
Huang, D.[19]	2013	Asian	LC	TaqMan	0.09	503	623	104	230	169	145	289	189
Cheng,C. W.[10]	2013	Asian	HCC	TaqMan	0.09	135	520	29	64	42	168	271	81
Vangsted, A. J.[20]	2012	Caucasian	MM	PCR	0.31	328	1696	55	163	110	253	778	665
Lin, C. W.[21]	2012	Asian	OSCC	TaqMan	0.09	462	520	100	246	116	168	271	81
Fan, Y.[22]	2011	Asian	OC	PCR	0.33	179	223	17	84	78	44	103	76
Zhou, B.[23]	2010	Asian	CSCC	PCR-PAGE	0.30	233	365	20	105	108	64	166	135
Tang, T.[24]	2010	Asian	BC	PCR-PAGE	0.49	207	228	26	92	89	46	108	74
Andersen, V.[25]	2010	Caucasian	CRC	TaqMan	0.78	378	756	62	195	121	102	347	307
Zhou, B.[26]	2009	Asian	NPC	PCR-PAGE	0.17	163	203	22	67	74	42	90	71
Zhang, P.[9]	2009	Asian	PC	PCR-PAGE	0.59	117	143	14	57	46	31	68	44
Lo, S. S.[12]	2009	Asian	GC	PCR	0.39	182	116	31	89	62	34	62	20
He, Y.[27]	2009	Asian	HCC	PCR-RFLP	0.06	202	404	35	84	83	124	183	97
Burnik, F. S.[28]	2009	Caucasian	GEP-NET	PCR-RFLP	0.06	50	100	2	30	18	12	58	30
Lehnerdt, G. F.[15]	2008	Caucasian	HNSCC	PCR	0.53	364	307	53	179	132	48	141	118
Riemann, K.[29]	2007	Caucasian	BC	PCR	0.53	242	307	30	124	88	48	141	118
Riemann, K.[14]	2006	Caucasian	CRC	PCR	0.53	139	307	27	58	54	48	141	118
Riemann, K.[14]	2006	Caucasian	B-cell CLL	PCR	0.53	72	307	13	41	18	48	141	118
Riemann, K.[14]	2006	Caucasian	RCC	PCR	0.53	140	307	17	76	47	48	141	118
Lin, S. C.[13]	2006	Asian	OSCC	PCR-PAGE	0.92	212	201	50	103	59	58	100	43

BC bladder cancer, *PC* prostate cancer, *OC* ovarian cancer, *LC* lung cancer, *HCC* hepatocellular carcinoma, *MM* multiple myeloma, *OSCC* oral squamous cell carcinoma, *CSCC* cervical squamous cell carcinoma, *CRC* colorectal cancer, *NPC* nasopharyngeal carcinoma, *GC* gastric cancer, *GEP-NET* gastroenteropancreatic neuroendocrine tumor, *HNSCC* squamous cell carcinomas of the head and neck region, *B cell CLL* B cell chronic lymphocytic leukemia, *RCC* renal cell carcinoma

under all genetic models ($P<0.01$). The evaluations of the association of NFKB1 -94 I/D polymorphism with cancer risk are shown in Table 2.

When all the eligible studies were pooled into the meta-analysis, results showed that the polymorphism was significantly associated with cancer risk under all genetic models (Fig. 2; dominant model: OR=1.32, 95 % CI=1.09–1.58; recessive model: OR=1.23, 95 % CI=1.05–1.43; II vs. DD: OR=1.47, 95 % CI=1.15–1.87; ID vs. DD: OR=1.22, 95 % CI=1.04–1.43; I vs. D: OR=1.19, 95 % CI=1.06–1.34). In the stratified analysis by cancer type, significant associations were not found in BC and LC, but significant associations in OC, HCC, and OSCC were observed. Subgroup analysis based on ethnicity was performed; the NFKB1-94 I/D polymorphism was found to contribute to cancer risk in Asian population (dominant model: OR=1.52, 95 % CI=1.17–1.98; recessive model: OR=1.50, 95 % CI=1.26–1.79; II vs. DD: OR=1.90, 95 % CI=1.37–2.65; ID vs. DD: OR=1.32, 95 % CI=1.05–1.66; I vs. D: OR=1.37, 95 % CI=1.17–1.60), but not in Caucasian population (Table 2).

Sensitivity analysis

The sensitivity analysis was performed to assess the influence of an individual study on the overall OR. Results showed that no individual study affected the pooled OR markedly, since omission of any single study made no substantial difference. The results verified the stability of this meta-analysis.

Publication bias

The Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. No evidence of publication bias was observed under the recessive model (Fig. 3; $P=0.054$). However, there was publication bias under other genetic models (ID vs. DD: $P=0.004$; II vs. DD: $P=0.016$; I vs. D: $P=0.026$).

Table 2 Meta-analysis of the associations between NFKB1 -94 insertion/deletion polymorphism and cancer risk in all genetic models

Variables	No.	Dominant model		Recessive model		II versus DD		ID versus DD		I versus D	
		OR (95 % CI)	P_{het}	OR (95 % CI)	P_{het}	OR (95 % CI)	P_{het}	OR (95 % CI)	P_{het}	OR (95 % CI)	P_{het}
Total	23	1.32 (1.09–1.58)	<0.01	1.23 (1.05–1.43)	<0.01	1.47 (1.15–1.87)	<0.01	1.22 (1.04–1.43)	<0.01	1.19 (1.06–1.34)	<0.01
Cancer type											
BC	3	1.04 (0.46–2.33)	<0.01	1.04 (0.73–1.48)	0.03	1.07 (0.45–2.53)	<0.01	1.00 (0.46–2.18)	<0.01	1.03 (0.70–1.51)	<0.01
PC	2	1.46 (0.91–2.34)	0.21	1.33 (1.01–1.74)	0.68	1.63 (1.03–2.59)	0.25	1.32 (0.83–2.10)	0.24	1.26 (1.05–1.52)	0.35
OC	2	2.17 (1.44–3.25)	0.73	1.59 (1.19–2.11)	0.68	2.57 (1.66–3.98)	0.89	1.88 (1.23–2.88)	0.62	1.55 (1.27–1.90)	0.85
LC	2	1.01 (0.80–1.28)	0.19	1.10 (0.95–1.28)	0.62	1.08 (0.85–1.36)	0.24	0.96 (0.76–1.21)	0.22	1.05 (0.94–1.17)	0.28
HCC	2	1.93 (1.42–2.63)	0.54	2.30 (1.74–3.04)	0.72	3.02 (2.11–4.32)	0.98	1.50 (1.08–2.08)	0.61	1.78 (1.49–2.14)	0.64
OSCC	2	1.59 (1.24–2.03)	0.31	1.67 (1.29–2.17)	0.38	2.06 (1.39–3.05)	0.22	1.42 (1.10–1.83)	0.39	1.42 (1.22–1.67)	0.30
CRC	2	0.79 (0.59–1.05)	0.92	0.81 (0.56–1.18)	0.12	0.70 (0.51–0.95)	0.52	0.86 (0.64–1.17)	0.49	0.82 (0.71–0.96)	0.33
Other cancer	8	1.37 (1.01–1.85)	0.02	1.09 (0.81–1.46)	<0.01	1.42 (0.91–2.23)	<0.01	1.29 (1.05–1.59)	0.34	1.14 (0.92–1.41)	<0.01
Ethnicity											
Asian	14	1.52 (1.17–1.98)	<0.01	1.50 (1.26–1.79)	<0.01	1.90 (1.37–2.65)	<0.01	1.32 (1.05–1.66)	<0.01	1.37 (1.17–1.60)	<0.01
Caucasian	9	1.00 (0.84–1.18)	0.32	0.87 (0.74–1.03)	0.07	0.93 (0.74–1.17)	0.09	1.06 (0.91–1.25)	0.54	0.94 (0.84–1.05)	0.07

P_{het} P value for heterogeneity

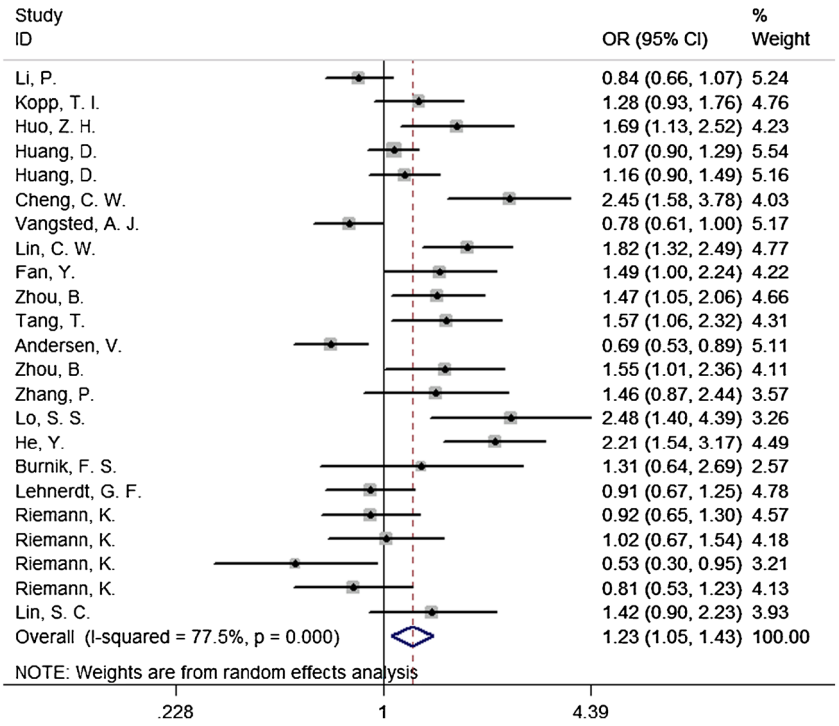

Fig. 2 Forest plot representing the pooled result of ORs for the association between NFKB1 -94 insertion/deletion polymorphism and cancer risk under recessive model

Discussion

The NFKB1 -94 I/D polymorphism was found to be not associated with cancer risk in previous meta-analysis including 2,743 cases and 2,195 controls [30]. However, when stratified by ethnicity, the significant association of NFKB1 -94 I/D polymorphism with cancer risk was observed in Asian and Caucasian populations.

In the present study, we collected more studies and a larger number of subjects to assess the association between the NFKB1 -94 I/D polymorphism and cancer risk. There are obvious discrepancies between the previous meta-analysis and ours. We detected a statistically significant association between the polymorphism and cancer risk. Moreover, in the stratified analysis based on ethnicity, significantly increased risks were observed in Asian population, but not in Caucasian population. However, the abovementioned results were not found in previous meta-analysis. These diverse results may be due to the differences in the studies included in the meta-analysis. Three case–control studies departure from HWE were included in previous meta-analysis based on 11 publications, but they were excluded in ours [31, 32]. In addition, recently published 12 studies were included in our analysis [16–23, 25, 27]. Therefore, our meta-analysis has stronger evidence to clarify the association between the NFKB1 -94 I/D polymorphism and cancer risk. We also conducted subgroup analysis of cancer type, which was not performed in the previous analysis. The result revealed that NFKB1 polymorphism was associated with the risk of OC, HCC, and OSCC.

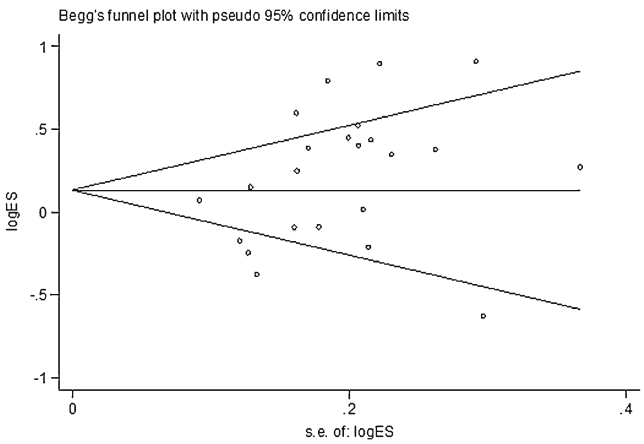

Fig. 3 Begg's Funnel plot in the meta-analysis of the association between NFKB1 -94 insertion/deletion polymorphism and cancer risk under recessive model

Heterogeneity for the NFKB1 -94 I/D polymorphism was observed in these studies. In order to explain the main reasons for the heterogeneity across studies, we performed the stratified analysis by ethnicity and cancer type. The results showed that heterogeneity for the total population may come from different ethnicities and different cancer types. In addition, the heterogeneity was also found in Asian population, which may result from differences in the number of cases and controls, study design, or genotyping method. Publication bias was not observed under recessive model. However, we found a potential publication bias under other genetic models. This reason may arise from a lack of publication of trials with opposite results.

Several limitations of this analysis should be considered. First, our results were based on unadjusted estimates, while a

more precise analysis could be conducted if individual data were available. Second, the studies searched on PubMed were full text in English. This may result in a language bias that is partially responsible for the observed publication bias. Third, the number of studies for subgroup analysis was small and restrains further our analysis for risk factors.

In conclusion, we found significant associations between the NFKB1 -94 I/D polymorphism and cancer risk in Asian population. However, further studies are needed to warrant and validate the association between NFKB1 -94 I/D polymorphism and the risk of cancer.

Conflicts of interest None

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