Int J Clin Exp Med 2017;10(7):9877-9890
www.ijcem.com /ISSN:1940-5901/IJCEM0049710

Review Article

Association between the NFκB1-94ins/del ATTG polymorphism and cancer risk: a meta-analysis and trial sequential analysis

Chuanjie Zhang[1*], Yuxiao Zheng[2*], Xiao Li[4*], Yang Wu[3], Haoxiang Xu[2], Zhiqiang Qin[2], Jie Wu[2], Cheng Zhang[2], Yincheng Liu[1], Hanyu Liu[1], Gong Cheng[2], Lixin Hua[2]

[1]First Clinical Medical College of Nanjing Medical University, Nanjing 210029, China; Departments of [2]Urology, [3]Pancreas Center, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China; [4]Department of Urology, The Affiliated Cancer Hospital of Jiangsu Province of Nanjing Medical University, Nanjing 210009, China. [*]Equal contributors.

Received November 7, 2016; Accepted June 5, 2017; Epub July 15, 2017; Published July 30, 2017

Abstract: Objective: This study aimed to perform a comprehensive meta-analysis and trial sequential analysis to clarify the association between the NFκB1 -94ins/del ATTG promoter polymorphism and cancer risk. Methods: A total of 42 studies including 16814 cases and 23367 controls were analyzed in this meta-analysis. We used pooled odds ratios (ORs) to evaluate the strength of the association, and 95% confidence intervals (CIs) to identify precision of the estimate. Results: We found that the NFκB1 promoter -94ins/del ATTG polymorphism was significantly associated with cancer risk in all five genetic models (Homozygote model, OR=1.33, 95% CI=1.12-1.59; Heterozygote model, OR=1.15, 95% CI=1.03-1.29; Dominant model, OR=1.21, 95% CI=1.07-1.38; Recessive model, OR=1.18, 95% CI=1.05-1.32; Allele model, OR=1.14, 95% CI=1.05-1.24). Subgroup analyses revealed a significant association between the polymorphism and cancer risk in Asian population and hospital-based studies. Stratified analysis was also performed in genotyping method, and significant associations were detected in all subgroups individually. We found the association was cancer-specific in cancer type subgroup analysis. The trial sequential analysis demonstrated statistical significance in favor of the NFκB1 promoter -94ins/del ATTG polymorphism increasing cancer risk, and the number of participants enrolled in this meta-analysis reached the low-bias heterogeneity adjusted information size. Conclusion: Our meta-analysis and TSA results suggested that the association between -94ins/del polymorphism in the promoter of NFκB1 and cancer risk is statistically significant and the association might be ethnic-specific.

Keywords: NFκB1, gene polymorphism, cancer, meta-analysis, trial sequential analysis

Introduction

Cancer is a terminal complex disease with high morbidity and mortality that results from the interactions between inherited and environmental factors [1]. In the past decades, many genes were found as influence factors of cancer [2]. Although the oncogenesis has been widely studied, the complex etiology of cancer is not yet fully clarified. Genetic susceptibility is a known possible explanation for the interindividual variation in cancer risk and contribute to the development of cancer [3].

Nuclear factor κB (NFκB) is a nuclear protein which was first identified by Sen and Baltimore in 1986 [4]. NFκB is known as a transcription factor that plays significant roles in various physiological process such as inflammation, cell survival, cell adhesion, differentiation, angiogenesis and apoptos [5-8]. There are five members of the NFκB family present in mammals: NFκB1 (p50), RelA (p65), c-Rel, RelB and NFκB2 (p52) [9]. The human NFκB1 gene that is located on chromosome 4q24 encodes protein p50 which can regulate inflammation and cancer development [10-13]. -94ins/del ATTG (rs28362491) is a common four nucleotides polymorphism in the promoter region of NFκB1 gene [13], which including three genotypes: wild homozygous (ins/ins), variant homozygous (del/del), and heterozygous (ins/del) [14]. The

association between the NFκB1 -94ins/del ATTG polymorphism and cancer susceptibility has been investigated by many studies which had inconsistent results [15-23]. In addition, some published meta-analysis focused on the association between the NFκB1 -94ins/del ATTG polymorphism and cancer risk also obtained conflicting results [24-26].

To explore the association between the NFκB1 -94ins/del ATTG promoter polymorphism and cancer in a better manner, we collected all available data to perform a comprehensive meta-analysis and performed a trial sequential analysis in the hope of providing more precise evidence.

Materials and methods

Search strategy

A systematic search on PubMed, EMBASE and Web of Science was performed to identify all published potentially appropriate studies (till May 20th, 2016). The key words were ("genetic polymorphism", "polymorphism", "SNP", "single nucleotide polymorphism", "gene mutation", or "genetic variant"), ("neoplasm", "cancer", "tumor", "carcinoma", or "carcinogenesis"), and ("NFκB1", "nuclear factor kappa B1", "NF kappa B1", or "nuclear factor κ B1". Additional publications were identified when we searched the reference list of original articles manually. A flow diagram of the study selection process is presented in **Figure 1**.

Inclusion criteria

(1) Studies were case-control studies. (2) Studies estimated the association between NFκB1 -94ins/del ATTG polymorphism and cancer risk. (3) The information from studies was performed in detail for calculation of odds ratio (OR) with 95% confidence interval (CI). (4) Data involved in different studies were not overlapping (if any, we selected the study with the largest samples).

Exclusion criteria

(1) Studies were not case-control studies. (2) Studies consisted no usable reported data. (3) Studies did not relate to cancer risk. (4) Studies had overlapped data.

Data extraction

Two investigators (Yuxiao Zheng and Xiao Li) independently extracted all useful information involved in eligible studies according to the inclusion criteria performed above. The review of result was carried out by a third investigator (Gong Cheng). The following information was recorded for each selected study: name of first author, year of publication, ethnicity, genotyping method, source of controls, frequencies of the genotypes in cases and controls, cancer type and Hardy-Weinberg equilibrium (HWE) of genotype distribution among controls. We considered studies which consisted more than one type of cancer as individual datasets only in subgroup analyses according to cancer type.

Statistical analysis

We used pooled odds ratio (OR) with corresponding 95% confidence interval (CI) to evaluate the strength of association between NFκB1 promoter -94ins/del ATTG polymorphism and cancer risk. Z test was performed to determine the statistical significance of the pooled OR, and a P value of < 0.05 was considered statistically significant. We used the Homozygote model (ins/ins vs. del/del), Heterozygote model (ins/del vs. del/del), Recessive model (ins/ins vs. del/del+ins/del), Dominant model (ins/ins+ins/del vs. del/del), and Allele (ins vs. del) model to examine NFκB1 -94ins/del ATTG genotypes. In addition to the overall comparison, we also performed subgroup analysis stratified by ethnicity, genotyping method, source of controls, cancer type.

The statistical heterogeneity between studies involved in this meta-analysis was evaluated using Q test which based on Cochran's chi-square and I^2 values. We calculated the summary OR by the random-effects model when P value of heterogeneity was < 0.05 and $I^2 > 50\%$ which indicated the presence of heterogeneity [27]; Otherwise, the fixed-effects model using the Mantel-Haenszel method was used [28]. We performed allele counting to regulate the allele frequencies of the NFκB1 promoter -94ins/del ATTG polymorphism from the individual study. HWE was evaluated using the goodness-of-fit test (chi-square or Fisher exact test) for the control groups in this investigation. The one-way sensitivity analyses (we cut out a single study in the meta-analysis each time to

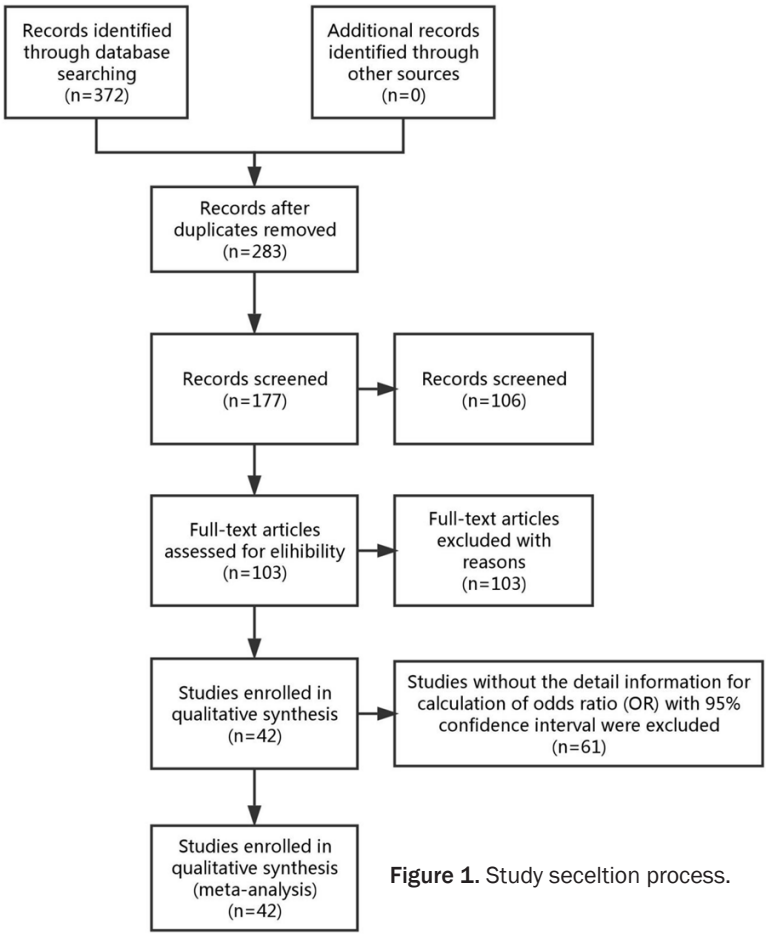

Figure 1. Study seceltion process.

reflect the influence of the individual data set to the pooled OR) were performed to evaluate the stability of the results. Egger's test and Begg's funnel plots were used to assessed the potential publication bias; *P* value < 0.05 and asymmetric plot suggest a potential publication bias. Statistical analyses were performed using STATA 12.0 software (Stata Corp, College Station, TX, USA).

Trial sequential analysis

Trial sequential analysis (TSA) was used to assess the increased type I error caused by few enrolled data and repeated significance testing when updating with new published studies [29-34]. We cumulated sample size of studies included in this meta-analysis and then performed trial sequential analysis to estimated the information-size of meta-analysis. The latter, called trial sequential monitoring boundaries, reduce type I errors [29, 31, 33, 35]. We treated the addition of each individual study in a cumulative meta-analysis as an intern meta-analysis to elucidate whether additional trials are needed. If the TSA result showed no cross connection between Z-curve and the boundary and the required information size was not large enough, that means we should enroll more trials and collect more evidence to reach a conclusion [36-38]. In conclusion, TSA was used to reduce the risk of type I error to evaluate whether we should enroll more samples from more eligible studies in further trials.

Results

Characteristics of eligible studies

A total of 42 studies including 16814 cases and 23367 controls were analyzed in this meta-analysis. **Figure 1** described the process for study identification and selection, and the characteristics of all involved studies were presented in **Table 1**. Newcastle-Ottawa Scale was performed to estimate the strength of the evidence of included studies and the result was shown in Supplementary Table 1. We treated the study by Bu [23] as two independent studies in subgroup analysis of cancer type because two different cancer types were involved in this article. Finally, 3 bladder cancer, 2 breast cancer, 5 colorectal cancer, 3 gastric cancer, 2 hepatocellular carcinoma, 2 lung cancer, 2 nasopharyngeal carcinoma, 2 non-small cell lung cancer, 2 oral squamous cell carcinoma, 3 ovarian cancer, 4 prostate cancer, 1 cervical carcinoma, 1 cervical squamous cell carcinoma, 1 cutaneous melanoma, 1 epithelial ovarian cancer, 1 esophageal squambus cell carcinoma, 1 gastroenteropancreatic neuroendocrine tumors, 1 liver cancer, 1 melanoma, 1 multiple myeloma, 1 osteosarcoma, 1 papillary thyoid carcinoma and 1 renal cell carcinoma studies were enrolled in this meta-analysis. Among those eligible studies, 29 [16-18, 20, 22-23,

Table 1. Main characteristics of studies involved in this meta-analysis

Author	Year	Ethnicity	Genotyping method	SOC	Cases			Controls			Cancer Type	HWE
					del/del	ins/del	ins/ins	del/del	ins/del	ins/ins		
Lin [39]	2006	Asian	PCR-RFLP	HB	50	103	59	58	100	43	Oral Squamous Cell Carcinoma	Y
Bu-1 [23]	2007	Caucasian	PCR-RFLP	HB	34	84	67	67	255	116	Melanoma	N
Bu-2 [23]	2007	Caucasian	PCR-RFLP	HB	81	323	63	67	256	116	Colorectal Cancer	N
Lewander [15]	2007	Asian	PCR-RFLP	HB	42	101	50	79	266	113	Colorectal Cancer	N
Riemann [62]	2007	Caucasian	Others	HB	30	124	88	48	141	118	Bladder Cancer	Y
Lo [40]	2008	Asian	PCR-RFLP	HB	31	89	62	34	62	20	Gastric Cancer	Y
Barnik [41]	2009	Caucasian	PCR-RFLP	HB	2	30	18	12	58	30	Gastroenteropancreatic Neuroendocrine Tumors	N
Tang [63]	2009	Asian	PCR-RFLP	HB	26	92	89	46	108	74	Bladder Cancer	Y
Zhang [43]	2009	Asian	PCR-RFLP	HB	14	57	46	31	68	44	Prostate Cancer	Y
Zhou [42]	2009	Asian	PCR-RFLP	HB	22	67	74	42	90	71	Nasopharyngeal Carcinoma	Y
Andersen [22]	2010	Caucasian	Taqman	PB	62	195	121	102	347	307	Colorectal Cancer	Y
Zhou [44]	2010	Asian	PCR-RFLP	HB	20	105	108	64	166	135	Cervical Squamous Cell Carcinoma	Y
Fan [18]	2011	Asian	PCR-RFLP	HB	17	84	78	44	103	76	Ovarian Cancer	Y
Lin [20]	2012	Asian	Taqman	HB	100	246	116	168	271	81	Oral Squamous Cell Carcinoma	Y
Vangsted [45]	2012	Caucasian	Taqman	PB	55	163	110	253	778	665	Multiple Myeloma	Y
Arisawa [49]	2013	Asian	PCR-RFLP	HB	68	239	172	103	435	342	Gastric Cancer	N
Cai [17]	2013	Asian	Taqman	HB	153	473	401	153	562	379	Renal Cell Carcinoma	N
Cheng [16]	2013	Asian	PCR-RFLP	HB	29	64	42	168	271	81	Hepatocellular Carcinoma	Y
Ebrahim [64]	2013	Asian	Others	HB	18	122	96	35	106	62	Breast Cancer	Y
Huang [50]	2013	Asian	Taqman	PB	225	459	372	210	491	355	Lung Cancer	Y
Huo [47]	2013	Asian	PCR-RFLP	HB	22	82	83	47	103	71	Epithelial Ovarian Cancer	Y
Kopp [65]	2013	Caucasian	Taqman	PB	54	152	128	64	161	109	Prostate Cancer	Y
Li [19]	2013	Asian	PCR-RFLP	HB	151	269	189	93	324	223	Bladder Cancer	Y
Suzairi [46]	2013	Asian	PCR-RFLP	HB	75	127	35	83	138	16	Colorectal Cancer	N
Umar [48]	2013	Asian	PCR-RFLP	HB	27	132	131	22	129	160	Esophageal Squambus Cell Carcinoma	Y
Gao [53]	2014	Asian	Taqman	HB	40	102	68	79	160	171	Liver Cancer	N
Hua [51]	2014	Asian	Others	HB	127	182	92	83	230	120	Gastric Cancer	Y
Liu [67]	2014	Asian	Taqman	PB	152	438	316	224	512	336	Nasopharyngeal Carcinoma	Y
Oltulu [54]	2014	Caucasian	PCR-RFLP	HB	16	44	35	6	47	46	Non-small Cell Lung Cancer	Y
Wang [66]	2014	Asian	PCR-RFLP	HB	171	210	93	123	216	162	Breast Cancer	N
Wang [68]	2014	Asian	PCR-RFLP	HB	106	186	60	171	209	79	Papillary Thyoid Carcinoma	Y
Zhang [52]	2014	Asian	PCR-RFLP	HB	419	312	205	1064	790	542	Hepatocellular Carcinoma	N
Chen [70]	2015	Asian	Taqman	HB	95	195	120	122	235	85	Ovarian Cancer	Y
Cui [59]	2015	Asian	PCR-RFLP	HB	99	246	198	186	355	212	Prostate Cancer	Y
Han [60]	2015	Asian	PCR-RFLP	HB	534	339	63	567	331	38	Prostate Cancer	Y
Kopp [56]	2015	Caucasian	PCR-RFLP	PB	146	449	320	253	787	679	Colorectal Cancer	N
Li [58]	2015	Asian	PCR-RFLP	HB	46	114	60	66	106	50	Osteosarcoma	Y
Pallavi [55]	2015	Asian	PCR-RFLP	HB	42	133	110	113	104	73	Cervical Carcinoma	N
Wang [69]	2015	Asian	PCR-RFLP	HB	89	219	113	131	205	89	Non-small Cell Lung Cancer	Y
Zhang [57]	2015	Asian	PCR-RFLP	HB	32	252	434	76	290	352	Lung Cancer	Y
Escobar [71]	2016	Mixed	PCR-RFLP	HB	19	37	61	31	41	44	Cutaneous Melanoma	N
Lu [61]	2016	Asian	PCR-RFLP	HB	221	351	115	253	339	95	Ovarian Cancer	Y

HB: hospital-based study; PB: population-based study; SOC: source of controls; HWE: Hardy Weinberg equilibrium.

39-61] of them were obeyed HWE while 13 studies [15, 19, 23, 62-71] were not.

Meta-analysis results

Overall, the statistically significant association between the NFκB1 promoter -94ins/del ATTG polymorphism and cancer risk across the five genetic models in the overall population were evaluated by the pooled ORs (Homozygote model, OR=1.33, 95% CI=1.12-1.59; Heterozygote model, OR=1.15, 95% CI=1.03-1.29; Dominant model, OR=1.21, 95% CI=1.07-1.38; Recessive model, OR=1.18, 95% CI=1.05-1.32;

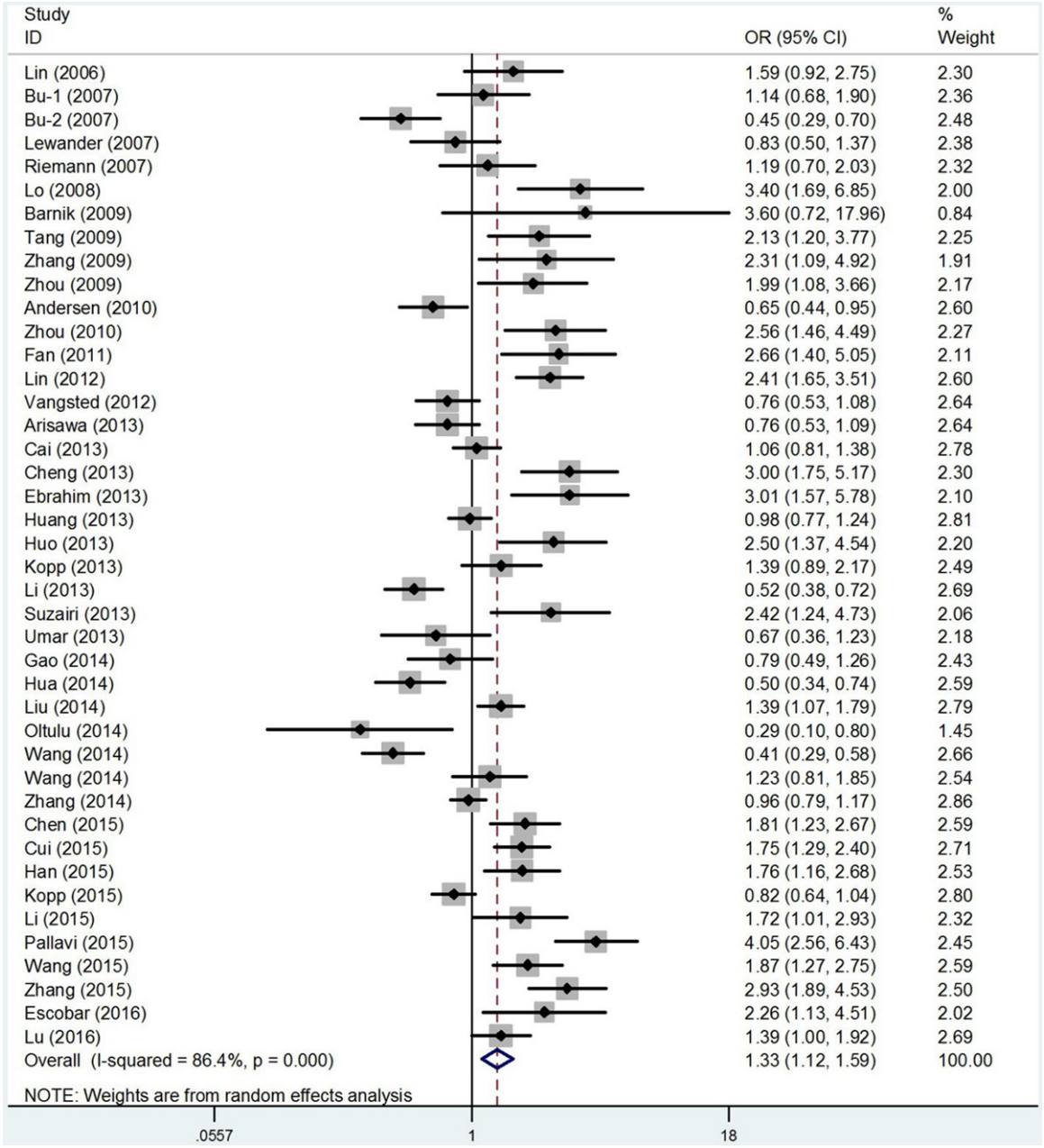

Figure 2. Forest plot of cancer risk associated with NFκB1 promoter -94insdel ATTG polymorphism (for Homozygote model) among all studies.

and Allele model, OR=1.14, 95% CI=1.05-1.24). Ethnic subgroup analyses showed cancer risk significant increases in all five models among Asians but not among Caucasians. The results of SOC subgroup analysis reveled that the association between the NFκB1 promoter -94ins/del ATTG polymorphism and hospital-based study is statistically significant. Stratified analysis was also performed in genotyping method, and significant associations were detected in all subgroups individually. The results of cancer type subgroup analysis demonstrated significant association existed between the NFκB1 -94ins allele and oral squamous cell carcinoma, bladder cancer, gastroenteropancreatic neuroendocrine tumors, prostate cancer, nasopharyngeal carcinoma, cervical squamous cell carcinoma, ovarian cancer, hepatocellular carcinoma, lung cancer, epithelial ovarian cancer, osteosarcoma, cevical carcinoma

Table 2. Meta-analysis of the NFκB1 -94ins/del ATTG promoter polymorphism and cancer risk

Variables	N*	Cases/ Controls	ins/ins versus del/del		ins/del versus del/del		ins/ins+ins/del versus del/del		ins/ins versus ins/del+del/del		ins allele versus del allele	
			OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)	OR (95% CI)	I^2 (%)
Total	42	16814/23367	1.33 (1.12-1.59)	86.4	1.15 (1.03-1.29)	73.8	1.21 (1.07-1.38)	82.3	1.18 (1.05-1.32)	81.9	1.14 (1.05-1.24)	86.7
Ethnicities												
Asian	32	13703/17363	1.48 (1.22-1.81)	87.2	1.20 (1.15-1.37)	78.1	1.29 (1.11-1.50)	84.9	1.27 (1.13-1.42)	78.7	1.20 (1.09-1.32)	87.1
Caucasion	9	2994/5888	0.83 (0.63-1.09)	67.8	0.97 (0.82-1.15)	29	0.92 (0.77-1.09)	35.4	0.86 (0.69-1.08)	78.6	0.92 (1.81-1.04)	65.8
Mixed	1	117/116	2.26 (1.13-4.51)	/	1.47 (0.71-3.04)	/	1.88 (0.99-3.57)	/	1.78 (1.06-3)	/	1.69 (1.16-2.47)	/
Genotyping Method												
PCR-RFLP	30	10824/15044	1.43 (1.14-1.81)	87.5	1.20 (1.04-1.38)	74.9	1.28 (1.09-1.51)	83.6	1.24 (1.07-1.43)	82.9	1.19 (1.07-1.33)	87.7
Taqman	9	5111/7380	1.15 (0.89-1.48)	80.7	1.06 (0.92-1.22)	46.4	1.09 (0.92-1.28)	65.4	1.09 (0.89-1.33)	83.1	1.06 (0.93-1.21)	82.5
Others	3	879/943	1.18 (0.43-3.25)	91.3	1.14 (0.46-2.84)	90.6	1.16 (0.45-2.99)	92.1	1.02 (0.69-1.51)	73.5	1.02 (0.66-1.59)	90.3
SOC												
HB	36	12897/16734	1.43 (1.16-1.76)	87	1.19 (1.04-1.36)	76.5	1.27 (1.09-1.48)	83.8	1.24 (1.09-1.41)	81.4	1.18 (1.07-1.30)	87
PB	6	3971/6633	0.96 (0.75-1.21)	72.3	1.01 (0.90-1.14)	6.9	0.99 (0.84-1.16)	51	0.94 (0.79-1.13)	76.3	0.97 (0.85-1.10)	77.4
Cancer Type												
Oral Squamous Cell Carcinoma	2	674/721	2.06 (1.39-3.05)	33	1.42 (1.10-1.83)	0	1.59 (1.24-2.03)	3.9	1.67 (1.29-2.17)	0	1.42 (1.22-1.67)	6.9
Melanoma	1	185/438	1.14 (0.68-1.90)	/	0.65 (0.40-1.05)	/	0.80 (0.51-2.03)	/	1.56 (1.09-2.26)	/	1.15 (0.90-1.47)	/
Colorectal Cancer	5	2190/3609	0.82 (0.55-1.21)	77.8	0.95 (0.82-1.11)	0	0.89 (0.77-1.03)	0	0.85 (0.59-1.22)	85.6	0.89 (0.77-1.03)	68.6
Bladder Cancer	3	1058/1175	1.07 (0.45-2.53)	90.1	1.00 (0.46-2.18)	88.8	1.04 (0.46-2.33)	90.7	1.04 (0.73-1.48)	72.7	1.03 (0.70-1.51)	89
Gastric Cancer	3	1062/1429	1.03 (0.43-2.46)	90.9	0.84 (0.48-1.46)	82.1	0.90 (0.47-1.76)	88.8	1.11 (0.67-1.84)	84.4	1.02 (0.67-1.55)	91.2
Gastroenteropancreatic Neuroendocrine Tumors	1	50/100	3.60 (0.72-17.96)	/	3.10 (0.65-14.78)	/	3.27 (0.70-15.23)	/	1.31 (0.64-2.69)	/	1.35 (0.82-2.23)	/
Prostate Cancer	4	1930/2166	1.70 (1.38-2.10)	0	1.17 (1.01-1.35)	0	1.30 (1.09-1.55)	24	1.45 (1.23-1.70)	0	1.26 (1.15-1.39)	0
Nasopharyngeal Carcinoma	2	1069/1275	1.49 (1.12-1.97)	12.8	1.28 (1.02-1.61)	0	1.36 (1.10-1.68)	0	1.26 (0.99-1.59)	26.9	1.25 (1.03-1.51)	40.8
Cervical Squamous Cell Carcinoma	1	233/365	2.56 (1.46-4.49)	/	2.02 (1.16-3.54)	/	2.26 (1.33-3.85)	2.26	1.47 (1.05-2.06)	/	1.49 (1.17-1.91)	/
Ovarian Cancer	3	1276/1352	1.73 (1.26-2.39)	41.7	1.25 (0.95-1.64)	44.5	1.38 (1.05-1.82)	49.8	1.47 (1.20-1.79)	8.9	1.29 (1.12-1.48)	30.9
Mutipule Myeloma	1	328/1696	0.76 (0.53-1.06)	/	0.96 (0.69-1.35)	/	0.87 (0.63-1.20)	/	0.78 (0.61-1.00)	/	0.85 (0.72-1.01)	/
Renal Cell Carcinoma	1	1027/1094	1.06 (0.81-1.36)	/	0.84 (0.65-1.09)	/	0.93 (0.73-1.18)	/	1.21 (1.01-1.40)	/	1.08 (0.95-1.22)	/
Hepatocellular Carcinoma	2	1071/2916	1.65 (0.54-5.04)	93.3	1.08 (0.83-1.39)	30	1.26 (0.72-2.19)	82	1.50 (0.60-3.75)	93.4	1.27 (0.74-2.19)	92.8
Breast Cancer	2	710/704	1.09 (0.16-7.67)	96.4	1.21 (0.39-3.78)	90.8	1.18 (0.28-5.00)	94.7	0.89 (0.30-2.64)	94.9	0.96 (0.39-2.34)	96.6
Lung Cancer	2	1774/1774	1.67 (0.57-4.88)	94.7	1.31 (0.56-3.05)	91.2	1.50 (0.55-4.07)	94.3	1.30 (0.89-1.91)	87.1	1.25 (0.81-1.95)	94.5
Epithelial Ovarian Cancer	1	187/221	2.50 (1.37-4.54)	/	1.70 (0.95-3.05)	/	2.03 (1.17-3.51)	/	1.69 (1.13-2.52)	/	1.58 (1.19-2.10)	/
Esophageal Squambus Cell Carcinoma	1	290/311	0.67 (0.36-1.23)	/	0.83 (0.45-1.54)	/	0.74 (0.41-1.33)	/	0.78 (0.56-1.07)	/	0.82 (0.64-1.05)	/
Liver Cancer	1	210/410	0.79 (0.49-1.26)	/	1.26 (0.80-1.98)	/	1.01 (0.66-1.55)	/	0.67 (0.47-0.95)	/	0.83 (0.65-1.05)	/
Non-small Cell Lung Cancer	2	516/524	0.78 (0.12-4.90)	91	0.81 (0.19-3.48)	86.6	0.78 (0.15-3.92)	89.8	1.01 (0.50-2.03)	78.6	0.96 (0.45-2.02)	90.5
Papillary Thyoid Carcinoma	1	352/459	1.23 (0.81-1.85)	/	1.44 (1.05-1.96)	/	1.38 (1.02-1.85)	/	0.99 (0.68-1.43)	/	1.15 (0.95-1.41)	/
Osteosarcoma	1	220/222	1.72 (1.01-2.93)	/	1.54 (0.97-2.44)	/	1.60 (1.04-2.47)	/	1.29 (0.84-1.99)	/	1.31 (1.01-1.71)	/
Cevical Carcinoma	1	285/290	4.05 (2.56-6.43)	/	3.44 (2.22-5.33)	/	3.69 (2.47-5.53)	/	1.87 (1.31-2.67)	/	2.15 (1.70-2.72)	/
Cutaneous Melanoma	1	117/116	2.26 (1.13-4.51)	/	1.47 (0.71-3.04)	/	1.88 (0.99-3.57)	/	1.18 (1.05-1.32)	/	1.69 (1.16-2.47)	/

*: Number of comparisons/No data; HB: hospital-based study; PB: population-based study; SOC: source of controls; HWE: Hardy Weinberg equilibrium.

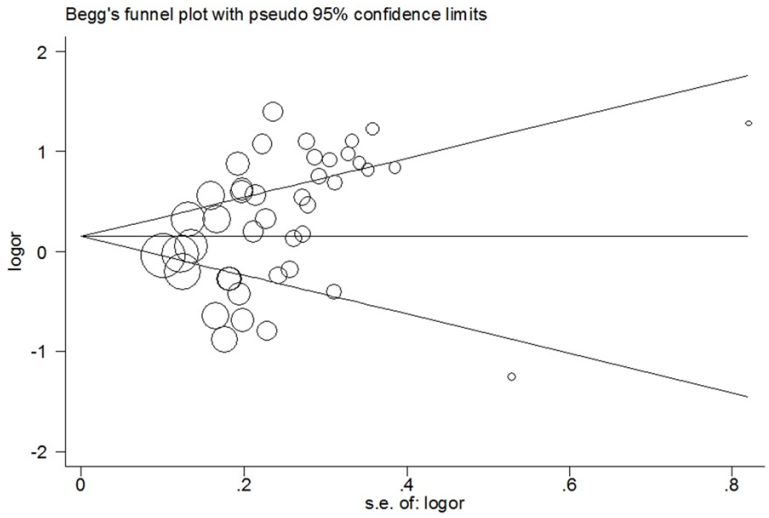

Figure 3. Funnel plot for publication bias test (for Homozygote model). Each circle represents an individual study for the indicated association.

and cutaneous melanoma, while the association were not revealed in colorectal cancer, multiple myeloma and esophageal squamous cell carcinoma in all 5 models. **Figure 2** reveals the association between -94ins/del polymorphism in the promoter of NFκB1 and cancer risk is statistically significant (data was extracted from Homozygote model). All the results of overall meta-analysis and subgroup analysis were showed in **Table 2**.

Evaluation of publication bias

We performed Begg's funnel plot and Egger's test to evaluate publication bias, and no evidence of publication bias was found for all analyses. The funnel plot analysis was showed in **Figure 3**.

Trial sequential analysis

The result of TSA with a type I error of 5% on NFκB1 promoter -94ins/del ATTG polymorphism and cancer risk was provided in **Figure 4**. 42 studies which marked with black squares were enrolled in TSA, and the result demonstrated that the cumulative Z-curve (blue line with black squares) crosses the monitoring boundary (red lines with black diamonds). Additionally, the cumulative Z-curve also crossed the line represents the low-bias heterogeneity adjusted information size (39651 patients) which was estimated by assuming a 10% relative risk reduction (RRR). The TSA result demonstrated statistical significance in favor of the NFκB1 promoter -94ins/del ATTG polymorphism can increase cancer risk and the number of participants enrolled in this meta-analysis reached the low-bias heterogeneity adjusted information size.

Discussion

Studies involving NFκB has grown tremendously in the past decades since it was discovered in 1986 by Sen and Baltimore [4]. NFκB is one of approximately 2000 estimated transcription factors in human [72, 73], and is the key transcription factor involved in the inflammatory pathway. Thus, NFκB is constitutively active in most cancers [74].

NFκB1/p50 is one of the five family members (the rest are RelA/p65, c-Rel, RelB and NFkB2/P52) of NFκB transcription factors family [75], which is among the major signaling pathways participated in the cellular response to environmental stress [13]. NFκB1 plays a significant role in inhibiting cell apoptosis by regulating the level of survival genes including bcl-2 homologue A1 [76], PAI-2 [77], and IAP gene family [78]. In addition, previous studies have suggested that NFκB1 signaling pathway is involved in the process of cellular proliferation by increasing IL-5 [79], promoting MAPK phosphorylation [13] and modulating cyclin D1 expression [80]. In recent years, a -94ins/del ATTG polymorphism in the promoter region of NFκB1 was reported in association with the risk of numerous cancers. Accumulated evidence illustrated that the insertion allele that can inhibit apoptosis and promote cellular proliferation by upregulating the expression of NFκB1 [14, 19, 62], which was implicated in the mechanism mentioned above.

Several meta-analyses had studied on the association between the NFκB1 promoter -94ins/del ATTG polymorphism and cancer risk in the past decade. However, the results of these meta-analyses are not completely consistent. For example, results of meta-analyses from Yang et al [81] and Duan et al [82] showed

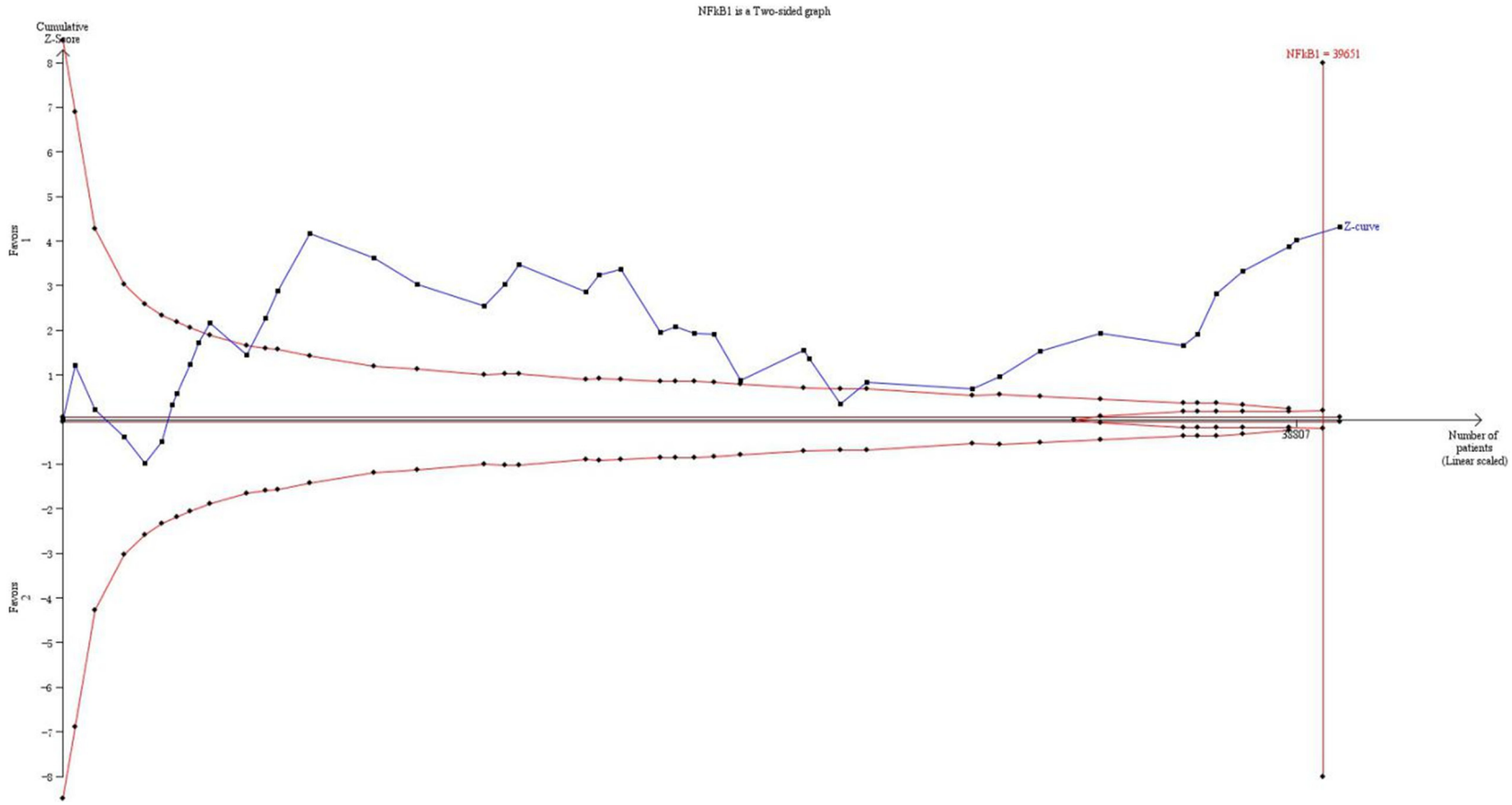

Figure 4. Trial sequential analysis with a type I error of 5% on NFκB1 promoter 94insdel ATTG polymorphism and cancer risk.

NFκB1 -94ins/del ATTG promoter polymorphism can increase the overall cancer risk. However, this result was contradictory with the meta-analysis performed by Zou et al [26]. Those contradictory results might be caused by the bias due to limited samples enrolled in meta-analyses.

After the reported study, numerous high-quality, large-sample case-control studies further evaluated the relationship between the NFκB1 promoter -94ins/del ATTG polymorphism and cancer risk. In this meta-analysis we enrolled 42 case-control studies with 16814 cases and 23367 controls. Our results indicated that the NFκB1 -94ins allele was a risk factor of cancer.

The result in ethnicity subgroup analyses indicated that the NFκB1 -94ins allele was a risk factor on cancer in Asian and Mixed population but had no effect on cancer in Caucasian population. This discrepancy may caused by the different function of the -94ins/del polymorphism in different populations, which may result from interactions with non-genetic risk factors including diet, environment and lifestyle [83-86]. Our results indicated genotyping method will not affect the result that the NFκB1 -94ins allele was a risk factor on cancer. In SOC subgroup analysis, the result suggested that the -94ins allele was a risk factor on cancer in hospital-based studies in all five models, but not in population-based studies in dominant, recessive and allele model. This result suggested that more high-quality population-based studies with large samples should be enrolled in meta-analysis to reduce the bias. We provided the cancer type subgroup analysis and the result suggested that except colorectal cancer, multiple myeloma and esophageal squamous cell carcinoma (the NFκB -94ins allele has no association to cancer risk in all five models), NFκB -94ins allele was a risk factor on the rest types of cancer involved in our meta-analysis. This result suggested that the NFκB1 gene might function as a prominent factor in these cancers.

The TSA result showed statistical significance in favor of NFκB -94ins/del ATTG polymorphism increasing cancer risk. In addition, the number of samples has reached the low-bias heterogeneity adjusted information size (39651), which suggested the evidence of our meta-analysis is sufficient and the result is reliable and robust.

Limitations also inevitably existed in our meta-analysis like any other meta-analysis. First, we only enrolled the articles which studied on the association between the NFκB1 -94ins/del polymorphism and cancer risk from genetic perspective. Considering the complex of mechanism of tumor occurrence, more studies focus on the interaction between gene and environment should be enrolled. Second, limited studies of some type of cancer were involved in the meta-analysis, which could increase the bias in subgroup analysis. On the other hand, many several strengths were shown in our metaanalysis. First, the number of articles, samples enrolled in meta-analysis was much larger than previous meta-analysis [81, 82, 86, 87]. Second, a more comprehensive subgroup analysis by cancer type was performed and the result suggested that the -94ins/del polymorphism may play a different role in different cancer types. Third, the sufficient evidence and robust result were proved by trial sequential analysis.

In conclusion,our meta-analysis and TSA result suggested that the association between NFκB -94ins/del polymorphism and cancer risk is statistically significant and the association might be ethnic-specific. The result of our study will provide clues and evidence for further therapeutic approaches target on interruption of the NFκB signaling pathway.

Disclosure of conflict of interest

None.

Address correspondence to: Gong Cheng and Lixin Hua, Department of Urology, The First Affiliated Hospital of Nanjing Medical University, Nanjing 210029, China. Tel: +86 13813992799; E-mail: cheng_gongurology@163.com (GC); Tel: +86 189-13975911; E-mail: lixinhua@njmu.edu.cn (LXH)

References

[1] Roukos DH. Novel clinico-genome network modeling for revolutionizing genotype-phenotype-based personalized cancer care. Expert Rev Mol Diagn 2010; 10: 33-48.
[2] Pharoah PD, Dunning AM, Ponder BA and Easton DF. Association studies for finding cancer-susceptibility genetic variants. Nat Rev Cancer 2004; 4: 850-860.
[3] Foulkes WD. Inherited susceptibility to common cancers. N Engl J Med 2008; 359: 2143-2153.

[4] Sen R and Baltimore D. Inducibility of kappa immunoglobulin enhancer-binding protein Nf-kappa B by a posttranslational mechanism. Cell 1986; 47: 921-928.
[5] Lin SC, Lu SY, Lee SY, Lin CY, Chen CH and Chang KW. Areca (betel) nut extract activates mitogen-activated protein kinases and NF-kappaB in oral keratinocytes. Int J Cancer 2005; 116: 526-535.
[6] Canniff JP, Harvey W and Harris M. Oral submucous fibrosis: its pathogenesis and management. Br Dent J 1986; 160: 429-434.
[7] Vermeulen L, De Wilde G, Notebaert S, Vanden Berghe W and Haegeman G. Regulation of the transcriptional activity of the nuclear factor-kappaB p65 subunit. Biochem Pharmacol 2002; 64: 963-970.
[8] Beinke S and Ley SC. Functions of NF-kappaB1 and NF-kappaB2 in immune cell biology. Biochem J 2004; 382: 393-409.
[9] Barnes PJ. Nuclear factor-kappa B. Int J Biochem Cell Biol 1997; 29: 867-870.
[10] Mathew S, Murty VV, Dalla-Favera R and Chaganti RS. Chromosomal localization of genes encoding the transcription factors, c-rel, NF-kappa Bp50, NF-kappa Bp65, and lyt-10 by fluorescence in situ hybridization. Oncogene 1993; 8: 191-193.
[11] Sun XF and Zhang H. NFκB and NFκBI polymorphisms in relation to susceptibility of tumour and other diseases. Histol Histopathol 2007; 22: 1387-1398.
[12] Chen F, Castranova V, Shi X and Demers LM. New insights into the role of nuclear factor-kappaB, a ubiquitous transcription factor in the initiation of diseases. Clin Chem 1999; 45: 7-17.
[13] Yu Y, Wan Y and Huang C. The biological functions of NF-kappaB1 (p50) and its potential as an anti-cancer target. Curr Cancer Drug Targets 2009; 9: 566-571.
[14] Karban AS, Okazaki T, Panhuysen CI, Gallegos T, Potter JJ, Bailey-Wilson JE, Silverberg MS, Duerr RH, Cho JH, Gregersen PK, Wu Y, Achkar JP, Dassopoulos T, Mezey E, Bayless TM, Nouvet FJ and Brant SR. Functional annotation of a novel NFκB1 promoter polymorphism that increases risk for ulcerative colitis. Hum Mol Genet 2004; 13: 35-45.
[15] Lewander A, Butchi AK, Gao J, He LJ, Lindblom A, Arbman G, Carstensen J, Zhang ZY, Sun XF; Swedish Low-Risk Colorectal Cancer Study Group. Polymorphism in the promoter region of the NFκB1 gene increases the risk of sporadic colorectal cancer in Swedish but not in Chinese populations. Scand J Gastroenterol 2007; 42: 1332-1338.
[16] Cheng CW, Su JL, Lin CW, Su CW, Shih CH, Yang SF and Chien MH. Effects of NFκB1 and NFκBIA gene polymorphisms on hepatocellular carcinoma susceptibility and clinicopathological features. PLoS One 2013; 8: e56130.
[17] Cai H, Sun L, Cui L, Cao Q, Qin C, Zhang G, Mao X, Wang M, Zhang Z, Shao P and Yin C. A functional insertion/deletion polymorphism (-94ins/del ATTG) in the promoter region of the NFκB1 gene is related to the risk of renal cell carcinoma. Urol Int 2013; 91: 206-212.
[18] Fan Y, Yu W, Ye P, Wang H, Wang Z, Meng Q, Duan Y, Liang X and An W. NFκB1 insertion/deletion promoter polymorphism increases the risk of advanced ovarian cancer in a Chinese population. DNA Cell Biol 2011; 30: 241-245.
[19] Li P, Gu J, Yang X, Cai H, Tao J, Yang X, Lu Q, Wang Z, Yin C and Gu M. Functional promoter -94ins/del ATTG polymorphism in NFκB1 gene is associated with bladder cancer risk in a Chinese population. PLoS One 2013; 8: e71604.
[20] Meyre D, Froguel P, Horber FF and Kral JG. Comment on: Valette et al. Melanocortin-4 receptor mutations and polymorphisms do not affect weight loss after bariatric surgery. PLOS ONE 2012; 7(11):E48221. PLoS One 2014; 9: e93324.
[21] Song S, Chen D, Lu J, Liao J, Luo Y, Yang Z, Fu X, Fan X, Wei Y, Yang L, Wang L and Wang J. NFkappaB1 and NFkappaBIA polymorphisms are associated with increased risk for sporadic colorectal cancer in a southern Chinese population. PLoS One 2011; 6: e21726.
[22] Andersen V, Christensen J, Overvad K, Tjonneland A and Vogel U. Polymorphisms in NFκB, PXR, LXR and risk of colorectal cancer in a prospective study of Danes. BMC Cancer 2010; 10: 484.
[23] Bu H, Rosdahl I, Sun XF and Zhang H. Importance of polymorphisms in NF-kappaB1 and NF-kappaBIalpha genes for melanoma risk, clinicopathological features and tumor progression in Swedish melanoma patients. J Cancer Res Clin Oncol 2007; 133: 859-866.
[24] Zou YF, Yuan FL, Feng XL, Tao JH, Ding N, Pan FM and Wang F. Association between NFκB1 -94ins/del ATTG promoter polymorphism and cancer risk: a meta-analysis. Cancer Invest 2011; 29: 78-85.
[25] Wang X, Lu P, Xu L, Xu Y, Shi Z, Xu J, Wang Y, Zhang J, Wang X, Cao L, Liu N, Yin Y and You Y. Updated meta-analysis of NFkappaB1 -94ins/Del ATTG promoter polymorphism and cancer risk based on 19 case-control studies. Asian Pac J Cancer Prev 2011; 12: 2479-2484.
[26] Zou YF, Wang F, Feng XL, Tao JH, Zhu JM, Pan FM and Su H. Association of NFκB1 -94ins/del ATTG promoter polymorphism with susceptibility to autoimmune and inflammatory diseases: a meta-analysis. Tissue Antigens 2011; 77: 9-17.

[27] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.
[28] Mantel N and Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.
[29] Wetterslev J, Thorlund K, Brok J and Gluud C. Trial sequential analysis may establish when firm evidence is reached in cumulative meta-analysis. J Clin Epidemiol 2008; 61: 64-75.
[30] Moher D, Liberati A, Tetzlaff J, Altman DG and Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8: 336-341.
[31] Thorlund K, Devereaux PJ, Wetterslev J, Guyatt G, Ioannidis JP, Thabane L, Gluud LL, Als-Nielsen B and Gluud C. Can trial sequential monitoring boundaries reduce spurious inferences from meta-analyses? Int J Epidemiol 2009; 38: 276-286.
[32] Brok J, Thorlund K, Gluud C and Wetterslev J. Trial sequential analysis reveals insufficient information size and potentially false positive results in many meta-analyses. J Clin Epidemiol 2008; 61: 763-769.
[33] Brok J, Thorlund K, Wetterslev J and Gluud C. Apparently conclusive meta-analyses may be inconclusive--Trial sequential analysis adjustment of random error risk due to repetitive testing of accumulating data in apparently conclusive neonatal meta-analyses. Int J Epidemiol 2009; 38: 287-298.
[34] Sormani MP. Modeling the distribution of new MRI cortical lesions in multiple sclerosis longitudinal studies by Sormani MP, Calabrese M, Signori A, Giorgio A, Gallo P, De Stefano N [PLoS One 2011;6(10):e26712. Epub 2011 October 20]. Mult Scler Relat Disord 2012; 1: 108.
[35] Afshari A, Brok J, Moller AM and Wetterslev J. Inhaled nitric oxide for acute respiratory distress syndrome and acute lung injury in adults and children: a systematic review with meta-analysis and trial sequential analysis. Anesth Analg 2011; 112: 1411-1421.
[36] Pogue J and Yusuf S. Overcoming the limitations of current meta-analysis of randomised controlled trials. Lancet 1998; 351: 47-52.
[37] Pogue JM and Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. Control Clin Trials 1997; 18: 580-593; discussion 661-586.
[38] Wetterslev J, Thorlund K, Brok J and Gluud C. Estimating required information size by quantifying diversity in random-effects model meta-analyses. BMC Med Res Methodol 2009; 9: 86.
[39] Lin SC, Liu CJ, Yeh WI, Lui MT, Chang KW and Chang CS. Functional polymorphism in NFκB1 promoter is related to the risks of oral squamous cell carcinoma occurring on older male areca (betel) chewers. Cancer Lett 2006; 243: 47-54.
[40] Lo SS, Chen JH, Wu CW and Lui WY. Functional polymorphism of NFκB1 promoter may correlate to the susceptibility of gastric cancer in aged patients. Surgery 2009; 145: 280-285.
[41] Burnik FS and Yalcin S. NFκB1 -94 insertion/deletion ATTG polymorphism in gastroenteropancreatic neuroendocrine tumors. Chemotherapy 2009; 55: 381-385.
[42] Zhou B, Rao L, Li Y, Gao L, Wang Y, Chen Y, Xue H, Song Y, Peng Y, Liao M and Zhang L. A functional insertion/deletion polymorphism in the promoter region of NFκB1 gene increases susceptibility for nasopharyngeal carcinoma. Cancer Lett 2009; 275: 72-76.
[43] Zhang P, Wei Q, Li X, Wang K, Zeng H, Bu H and Li H. A functional insertion/deletion polymorphism in the promoter region of the NFκB1 gene increases susceptibility for prostate cancer. Cancer Genet Cytogenet 2009; 191: 73-77.
[44] Zhou B, Qie M, Wang Y, Yan L, Zhang Z, Liang A, Wang T, Wang X, Song Y and Zhang L. Relationship between NFκB1 -94 insertion/deletion ATTG polymorphism and susceptibility of cervical squamous cell carcinoma risk. Ann Oncol 2010; 21: 506-511.
[45] Vangsted AJ, Nielsen KR, Klausen TW, Haukaas E, Tjonneland A and Vogel U. A functional polymorphism in the promoter region of the IL1B gene is associated with risk of multiple myeloma. Br J Haematol 2012; 158: 515-518.
[46] Mohd Suzairi MS, Tan SC, Ahmad Aizat AA, Mohd Aminudin M, Siti Nurfatimah MS, Andee ZD and Ankathil R. The functional -94 insertion/deletion ATTG polymorphism in the promoter region of NFκB1 gene increases the risk of sporadic colorectal cancer. Cancer Epidemiol 2013; 37: 634-638.
[47] Huo ZH, Zhong HJ, Zhu YS, Xing B and Tang H. Roles of functional NFκB1 and beta-TrCP insertion/deletion polymorphisms in mRNA expression and epithelial ovarian cancer susceptibility. Genet Mol Res 2013; 12: 3435-3443.
[48] Umar M, Upadhyay R, Kumar S, Ghoshal UC and Mittal B. Association of common polymorphisms in TNFA, NFκB1 and NFκBIA with risk and prognosis of esophageal squamous cell carcinoma. PLoS One 2013; 8: e81999.
[49] Arisawa T, Tahara T, Shiroeda H, Yamada K, Nomura T, Yamada H, Hayashi R, Matsunaga K, Otsuka T, Nakamura M, Shimasaki T, Toshikuni N, Kawada N and Shibata T. Functional promoter polymorphisms of NFκB1 influence sus-

ceptibility to the diffuse type of gastric cancer. Oncol Rep 2013; 30: 3013-3019.
[50] Huang D, Yang L, Liu Y, Zhou Y, Guo Y, Pan M, Wang Y, Tan Y, Zhong H, Hu M, Lu W, Ji W, Wang J, Ran P, Zhong N, Zhou Y and Lu J. Functional polymorphisms in NFkappaB1/IkappaBalpha predict risks of chronic obstructive pulmonary disease and lung cancer in Chinese. Hum Genet 2013; 132: 451-460.
[51] Hua T, Qinsheng W, Xuxia W, Shuguang Z, Ming Q, Zhenxiong L and Jingjie W. Nuclear factor-kappa B1 is associated with gastric cancer in a Chinese population. Medicine (Baltimore) 2014; 93: e279.
[52] Zhang Q, Ji XW, Hou XM, Lu FM, Du Y, Yin JH, Sun XY, Deng Y, Zhao J, Han X, Yang GS, Zhang HW, Chen XM, Shen HB, Wang HY and Cao GW. Effect of functional nuclear factor-kappaB genetic polymorphisms on hepatitis B virus persistence and their interactions with viral mutations on the risk of hepatocellular carcinoma. Ann Oncol 2014; 25: 2413-2419.
[53] Gao J, Xu HL, Gao S, Zhang W, Tan YT, Rothman N, Purdue M, Gao YT, Zheng W, Shu XO and Xiang YB. Genetic polymorphism of NFκB1 and NFκBIA genes and liver cancer risk: a nested case-control study in Shanghai, China. BMJ Open 2014; 4: e004427.
[54] Oltulu YM, Coskunpinar E, Ozkan G, Aynaci E, Yildiz P, Isbir T and Yaylim I. Investigation of NF-kappaB1 and NF-kappaBIA gene polymorphism in non-small cell lung cancer. Biomed Res Int 2014; 2014: 530381.
[55] Pallavi S, Anoop K, Showket H, Alo N and Mausumi B. NFκB1/NFκBIa polymorphisms are associated with the progression of cervical carcinoma in HPV-infected postmenopausal women from rural area. Tumour Biol 2015; 36: 6265-6276.
[56] Kopp TI, Andersen V, Tjonneland A and Vogel U. Polymorphisms in NFκB1 and TLR4 and interaction with dietary and life style factors in relation to colorectal cancer in a Danish prospective case-cohort study. PLoS One 2015; 10: e0116394.
[57] Zhang JW, Chen QS, Zhai JX, Lv PJ and Sun XY. Polymorphisms in NF-kappaB pathway genes & their association with risk of lung cancer in the Chinese population. Pak J Med Sci 2015; 31: 1411-1416.
[58] Li X, Zhang C, Qiao W, Zhou X and Sun M. NFκB1 -94ins/del ATTG polymorphism increases osteosarcoma risk in a Chinese Han population. Int J Clin Exp Med 2015; 8: 1420-1423.
[59] Knobloch TJ, Uhrig LK, Pearl DK, Casto BC, Warner BM, Clinton SK, Sardo-Molmenti CL, Ferguson JM, Daly BT, Riedl K, Schwartz SJ, Vodovotz Y, Buchta AJ Sr, Schuller DE, Ozer E, Agrawal A and Weghorst CM. Suppression of proinflammatory and prosurvival biomarkers in oral cancer patients consuming a black raspberry phytochemical-rich troche. Cancer Prev Res (Phila) 2016; 9: 159-171.
[60] Han X, Zhang JJ, Yao N, Wang G, Mei J, Li B, Li C and Wang ZA. Polymorphisms in NFκB1 and NFκBIA genes modulate the risk of developing prostate cancer among Han Chinese. Med Sci Monit 2015; 21: 1707-1715.
[61] Lu ZH, Gu XJ, Shi KZ, Li X, Chen DD and Chen L. Association between genetic polymorphisms of inflammatory response genes and the risk of ovarian cancer. J Formos Med Assoc 2016; 115: 31-37.
[62] Riemann K, Becker L, Struwe H, Rubben H, Eisenhardt A and Siffert W. Insertion/deletion polymorphism in the promoter of NFκB1 as a potential molecular marker for the risk of recurrence in superficial bladder cancer. Int J Clin Pharmacol Ther 2007; 45: 423-430.
[63] Tang T, Cui S, Deng X, Gong Z, Jiang G, Wang P, Liao B, Fei Z, Xian S, Zeng D and Li J. Insertion/deletion polymorphism in the promoter region of NFκB1 gene increases susceptibility for superficial bladder cancer in Chinese. DNA Cell Biol 2010; 29: 9-12.
[64] Eskandari-Nasab E, Hashemi M, Ebrahimi M and Amininia S. The functional 4-bp insertion/deletion ATTG polymorphism in the promoter region of NF-KB1 reduces the risk of BC. Cancer Biomark 2016; 16: 109-115.
[65] Kopp TI, Friis S, Christensen J, Tjonneland A and Vogel U. Polymorphisms in genes related to inflammation, NSAID use, and the risk of prostate cancer among Danish men. Cancer Genet 2013; 206: 266-278.
[66] Wang Z, Liu QL, Sun W, Yang CJ, Tang L, Zhang X and Zhong XM. Genetic polymorphisms in inflammatory response genes and their associations with breast cancer risk. Croat Med J 2014; 55: 638-646.
[67] Liu Y, Qiu F, Yang L, Yang R, Yang X, Huang D, Fang W, Zhang L, Jiang Q, Zhang L, Zhou Y and Lu J. Polymorphisms of NFkappaB1 and IkappaBalpha and their synergistic effect on nasopharyngeal carcinoma susceptibility. Biomed Res Int 2015; 2015: 362542.
[68] Wang X, Peng H, Liang Y, Sun R, Wei T, Li Z, Gong Y, Gong R, Liu F, Zhang L and Zhu J. A functional insertion/deletion polymorphism in the promoter region of the NFκB1 gene increases the risk of papillary thyroid carcinoma. Genet Test Mol Biomarkers 2015; 19: 167-171.
[69] Wang Y, Chen L, Pan L, Xue J and Yu H. The association between NFκB1 -94ins/del ATTG polymorphism and non-small cell lung cancer risk in a Chinese Han population. Int J Clin Exp Med 2015; 8: 8153-8157.

[70] Chen LP, Cai PS and Liang HB. Association of the genetic polymorphisms of NFκB1 with susceptibility to ovarian cancer. Genet Mol Res 2015; 14: 8273-8282.

[71] Escobar GF, Arraes JA, Bakos L, Ashton-Prolla P, Giugliani R, Callegari-Jacques SM, Santos S and Bakos RM. Polymorphisms in CYP19A1 and NFκB1 genes are associated with cutaneous melanoma risk in southern Brazilian patients. Melanoma Res 2016; 26: 348-53.

[72] Lander ES, Linton LM, Birren B, Nusbaum C, Zody MC, Baldwin J, Devon K, Dewar K, Doyle M, FitzHugh W, Funke R, Gage D, Harris K, Heaford A, Howland J, Kann L, Lehoczky J, LeVine R, McEwan P, McKernan K, Meldrim J, Mesirov JP, Miranda C, Morris W, Naylor J, Raymond C, Rosetti M, Santos R, Sheridan A, Sougnez C, Stange-Thomann Y, Stojanovic N, Subramanian A, Wyman D, Rogers J, Sulston J, Ainscough R, Beck S, Bentley D, Burton J, Clee C, Carter N, Coulson A, Deadman R, Deloukas P, Dunham A, Dunham I, Durbin R, French L, Grafham D, Gregory S, Hubbard T, Humphray S, Hunt A, Jones M, Lloyd C, McMurray A, Matthews L, Mercer S, Milne S, Mullikin JC, Mungall A, Plumb R, Ross M, Shownkeen R, Sims S, Waterston RH, Wilson RK, Hillier LW, McPherson JD, Marra MA, Mardis ER, Fulton LA, Chinwalla AT, Pepin KH, Gish WR, Chissoe SL, Wendl MC, Delehaunty KD, Miner TL, Delehaunty A, Kramer JB, Cook LL, Fulton RS, Johnson DL, Minx PJ, Clifton SW, Hawkins T, Branscomb E, Predki P, Richardson P, Wenning S, Slezak T, Doggett N, Cheng JF, Olsen A, Lucas S, Elkin C, Uberbacher E, Frazier M, Gibbs RA, Muzny DM, Scherer SE, Bouck JB, Sodergren EJ, Worley KC, Rives CM, Gorrell JH, Metzker ML, Naylor SL, Kucherlapati RS, Nelson DL, Weinstock GM, Sakaki Y, Fujiyama A, Hattori M, Yada T, Toyoda A, Itoh T, Kawagoe C, Watanabe H, Totoki Y, Taylor T, Weissenbach J, Heilig R, Saurin W, Artiguenave F, Brottier P, Bruls T, Pelletier E, Robert C, Wincker P, Smith DR, Doucette-Stamm L, Rubenfield M, Weinstock K, Lee HM, Dubois J, Rosenthal A, Platzer M, Nyakatura G, Taudien S, Rump A, Yang H, Yu J, Wang J, Huang G, Gu J, Hood L, Rowen L, Madan A, Qin S, Davis RW, Federspiel NA, Abola AP, Proctor MJ, Myers RM, Schmutz J, Dickson M, Grimwood J, Cox DR, Olson MV, Kaul R, Raymond C, Shimizu N, Kawasaki K, Minoshima S, Evans GA, Athanasiou M, Schultz R, Roe BA, Chen F, Pan H, Ramser J, Lehrach H, Reinhardt R, McCombie WR, de la Bastide M, Dedhia N, Blocker H, Hornischer K, Nordsiek G, Agarwala R, Aravind L, Bailey JA, Bateman A, Batzoglou S, Birney E, Bork P, Brown DG, Burge CB, Cerutti L, Chen HC, Church D, Clamp M, Copley RR, Doerks T, Eddy SR, Eichler EE, Furey TS, Galagan J, Gilbert JG, Harmon C, Hayashizaki Y, Haussler D, Hermjakob H, Hokamp K, Jang W, Johnson LS, Jones TA, Kasif S, Kaspryzk A, Kennedy S, Kent WJ, Kitts P, Koonin EV, Korf I, Kulp D, Lancet D, Lowe TM, McLysaght A, Mikkelsen T, Moran JV, Mulder N, Pollara VJ, Ponting CP, Schuler G, Schultz J, Slater G, Smit AF, Stupka E, Szustakowki J, Thierry-Mieg D, Thierry-Mieg J, Wagner L, Wallis J, Wheeler R, Williams A, Wolf YI, Wolfe KH, Yang SP, Yeh RF, Collins F, Guyer MS, Peterson J, Felsenfeld A, Wetterstrand KA, Patrinos A, Morgan MJ, de Jong P, Catanese JJ, Osoegawa K, Shizuya H, Choi S, Chen YJ, Szustakowki J; International Human Genome Sequencing Consortium. Initial sequencing and analysis of the human genome. Nature 2001; 409: 860-921.

[73] GuhaThakurta D. Computational identification of transcriptional regulatory elements in DNA sequence. Nucleic Acids Res 2006; 34: 3585-3598.

[74] Chaturvedi MM, Sung B, Yadav VR, Kannappan R and Aggarwal BB. NF-kappaB addiction and its role in cancer: 'one size does not fit all'. Oncogene 2011; 30: 1615-1630.

[75] Vallabhapurapu S and Karin M. Regulation and function of NF-kappaB transcription factors in the immune system. Annu Rev Immunol 2009; 27: 693-733.

[76] Karsan A, Yee E, Kaushansky K and Harlan JM. Cloning of human Bcl-2 homologue: inflammatory cytokines induce human A1 in cultured endothelial cells. Blood 1996; 87: 3089-3096.

[77] Kumar S and Baglioni C. Protection from tumor necrosis factor-mediated cytolysis by overexpression of plasminogen activator inhibitor type-2. J Biol Chem 1991; 266: 20960-20964.

[78] LaCasse EC, Baird S, Korneluk RG and MacKenzie AE. The inhibitors of apoptosis (IAPs) and their emerging role in cancer. Oncogene 1998; 17: 3247-3259.

[79] Yang L, Cohn L, Zhang DH, Homer R, Ray A and Ray P. Essential role of nuclear factor kappaB in the induction of eosinophilia in allergic airway inflammation. J Exp Med 1998; 188: 1739-1750.

[80] Shukla S, Maclennan GT, Marengo SR, Resnick MI and Gupta S. Constitutive activation of P I3 K-Akt and NF-kappaB during prostate cancer progression in autochthonous transgenic mouse model. Prostate 2005; 64: 224-239.

[81] Yang X, Li P, Tao J, Qin C, Cao Q, Gu J, Deng X, Wang J, Liu X, Wang Z, Wu B, Gu M, Lu Q and Yin C. Association between NFκB1 -94ins/del ATTG promoter polymorphism and cancer susceptibility: an updated meta-analysis. Int J Genomics 2014; 2014: 612972.

[82] Duan W, Wang E, Zhang F, Wang T, You X and Qiao B. Association between the NFκB1

-94ins/del ATTG polymorphism and cancer risk: an updated meta-analysis. Cancer Invest 2014; 32: 311-320.

[83] Andersen V, Holst R, Kopp TI, Tjonneland A and Vogel U. Interactions between diet, lifestyle and IL10, IL1B, and PTGS2/COX-2 gene polymorphisms in relation to risk of colorectal cancer in a prospective Danish case-cohort study. PLoS One 2013; 8: e78366.

[84] Hutter CM, Mechanic LE, Chatterjee N, Kraft P, Gillanders EM; NCI Gene-Environment Think Tank. Gene-environment interactions in cancer epidemiology: a national cancer institute think tank report. Genet Epidemiol 2013; 37: 643-657.

[85] Liu J, Huang J, Zhang Y, Lan Q, Rothman N, Zheng T and Ma S. Identification of gene-environment interactions in cancer studies using penalization. Genomics 2013; 102: 189-194.

[86] Nickels S, Truong T, Hein R, Stevens K, Buck K, Behrens S, Eilber U, Schmidt M, Haberle L, Vrieling A, Gaudet M, Figueroa J, Schoof N, Spurdle AB, Rudolph A, Fasching PA, Hopper JL, Makalic E, Schmidt DF, Southey MC, Beckmann MW, Ekici AB, Fletcher O, Gibson L, Silva Idos S, Peto J, Humphreys MK, Wang J, Cordina-Duverger E, Menegaux F, Nordestgaard BG, Bojesen SE, Lanng C, Anton-Culver H, Ziogas A, Bernstein L, Clarke CA, Brenner H, Muller H, Arndt V, Stegmaier C, Brauch H, Bruning T, Harth V, Genica N, Mannermaa A, Kataja V, Kosma VM, Hartikainen JM, kConFab, Group AM, Lambrechts D, Smeets D, Neven P, Paridaens R, Flesch-Janys D, Obi N, Wang-Gohrke S, Couch FJ, Olson JE, Vachon CM, Giles GG, Severi G, Baglietto L, Offit K, John EM, Miron A, Andrulis IL, Knight JA, Glendon G, Mulligan AM, Chanock SJ, Lissowska J, Liu J, Cox A, Cramp H, Connley D, Balasubramanian S, Dunning AM, Shah M, Trentham-Dietz A, Newcomb P, Titus L, Egan K, Cahoon EK, Rajaraman P, Sigurdson AJ, Doody MM, Guenel P, Pharoah PD, Schmidt MK, Hall P, Easton DF, Garcia-Closas M, Milne RL and Chang-Claude J. Evidence of gene-environment interactions between common breast cancer susceptibility loci and established environmental risk factors. PLoS Genet 2013; 9: e1003284.

[87] Nian X, Zhang W, Li L, Sun Y, Sun E and Han R. Meta-analysis of studies on the association between the NF-kappaB1-94ins/del ATTG promoter polymorphism and cancer. Tumour Biol 2014; 35: 11921-11931.

Supplementary Table 1. Newcastle-Ottawa Scale was performed to estimate the strength of the evidence of included studies

Author	Year	NOS score	Author	Year	NOS score
Lin [39]	2006	6	Kopp [65]	2013	8
Bu-1 [23]	2007	8	Li [19]	2013	7
Bu-2 [23]	2007	8	Suzairi [46]	2013	7
Lewander [15]	2007	7	Umar [48]	2013	7
Riemann [62]	2007	7	Gao [53]	2014	7
Lo [40]	2008	6	Hua [51]	2014	7
Barnik [41]	2009	6	Liu [67]	2014	6
Tang [63]	2009	7	Oltulu [54]	2014	8
Zhang [43]	2009	7	Wang [66]	2014	7
Zhou [42]	2009	7	Wang [68]	2014	8
Andersen [22]	2010	8	Zhang [52]	2014	7
Zhou [44]	2010	7	Chen [70]	2015	8
Fan [18]	2011	7	Cui [59]	2015	8
Lin [20]	2012	7	Han [60]	2015	7
Vangsted [45]	2012	8	Kopp [56]	2015	8
Arisawa [49]	2013	8	Li [58]	2015	7
Cai [17]	2013	7	Pallavi [55]	2015	7
Cheng [16]	2013	7	Wang [69]	2015	8
Ebrahim [64]	2013	8	Zhang [57]	2015	7
Huang [50]	2013	7	Escobar [71]	2016	7
Huo [47]	2013	7	Lu [61]	2016	8

NOS: Newcastle-Ottawa Scale.