

RESEARCH COMMUNICATION

Updated Meta-Analysis of the NFκB1 -94ins/Delattg Promoter Polymorphism and Cancer Risk Based on 19 Case-Control Studies

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Abstract

Objective: Recently, a common insertion/deletion (-94insertion/deletion ATTG, rs28362491) polymorphism in the NFκB1 promoter region has been extensively investigated for association with cancer risk but the results have been inconsistent. In order to clarify the effect of the promoter polymorphism we performed an update meta-analysis of published case-control studies to better compare the results between studies. **Methods:** Relevant studies were identified via a thorough literature search on Medline and Embase database (up to August 10, 2011). The odds ratio (OR) and 95% confidence interval (95% CI) were used to investigate the strength of the association. **Results:** A total of 5,196 cases and 6,614 controls in 19 case-control studies from 16 publications were included in this meta-analysis. Overall, the variant genotypes were associated with a moderately decreased risk of all cancer types (OR =0.74, 95% CI =0.57-0.97 for DD versus II; OR =0.79, 95% CI =0.66-0.95 for DD versus II/ID). In the stratified analyses, significantly decreased risk was found among Asians (OR =0.52, 95% CI =0.42-0.65 for DD versus II; OR =0.74, 95% CI =0.66-0.83 for ID versus II; OR =0.64, 95% CI =0.53-0.78 for DD versus II/ID; OR =0.68, 95% CI =0.61-0.75 for DD/ID versus II). The validity of this association was further strengthened by the sensitivity analysis. No publication bias was observed in this study. **Conclusions:** Our results suggested that the -94deletion ATTG promoter polymorphism in NFκB1 gene might be associated with a decreased cancer risk, especially for Asian population.

Keywords: NFκB1 - genetic polymorphisms - carcinogenesis - meta-analysis

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Introduction

The perceived hypothetical role of inflammation has been bolstered by epidemiological observations linking infections and chronic inflammatory conditions to cancer (Balkwill and Mantovani, 2001). It is estimated that about 15% of human cancers are associated with chronic infections and inflammation (Coussens and Werb, 2002). Several recent studies have confirmed that inflammation may produce chronic damage leading to certain types of cancer (Shacter and Weitzman, 2002; Samsami Dehaghani et al., 2009; Zhang et al., 2010). Nuclear factor-kappa B (NF-κB), given its place as master regulator at the center of inflammation, is natural suspect in providing a mechanistic link between inflammation and carcinogenesis.

NF-κB, a family of dimeric transcription factors which control the expression of numerous genes affecting cell growth, differentiation and apoptosis (Baldwin, 1996; Pahl, 1999), appears to be a good candidate for studies on the pathogenesis of autoimmune and inflammatory

diseases (Baldwin, 2001). Customarily, inactive NF-κB is in the cytoplasm bound to IκBs, which are specific inhibitor proteins in cytoplasm. In presence of activating stimuli, IκBα is phosphorylated, leading to ubiquitination and degradation by the proteasome, thus NF-κB translocates into the nucleus regulating proinflammatory gene expression (Karin and Delhase, 2000). In mammals, there are five members in the NF-κB family: p105/p50, p52/p100, p65/RelA, RelB, and c-Rel. The major form of NF-κB is a heterodimer of the p50 and p65/RelA subunits, encoded by the NFKB1 and RelA genes, respectively (Chen et al., 1999). Human NFKB1 gene locates at chromosome 4q24 in human and encodes two p105 and p50 (Le Beau et al., 1992; Mathew et al., 1993).

The promoter, all coding exons, and their flanking introns of NFKB1 gene were first sequenced by Karban (2004). Of the six nucleotide variants detected, only -94insertion/deletion (-94 ins/del ATTG rs28362491) appeared to have a potential functional role and has been extensively investigated for association to cancer recently.

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It consists of three genotypes: wild homozygous II (ins/ins), variant homozygous DD (del/del) and heterozygous ID (ins/del). The presence of a 4-bp deletion resulted in the loss of binding to nuclear proteins, leading to reduced promoter activity (Karban et al., 2004). Since its discovery in 2004, a number of case-control studies were conducted to investigate the association between this polymorphisms and cancer risk, including ovarian cancer (Fan et al., 2011), bladder cancer (Riemann et al., 2007; Tang et al., 2010), colorectal cancer (Riemann et al., 2006; Lewander et al., 2007; Andersen et al., 2010; Song et al., 2011) and et al. But the results remain inconsistent. Thus, the association between NFκB1 -94ins/delATTG promoter polymorphism and cancer risk requires further investigation.

Zou et al. (2011) performed a meta-analysis which included 2,743 cases and 2,195 controls to assess the association between NFκB1 -94ins/delATTG promoter polymorphism and risk of cancer. After their publication, several important studies with large cases and controls were published, which may bias the results that have been reported. Here, to better compare the effect of the different gene types within the role of the NFκB1 in cancer, we conducted an update meta-analysis of 19 case-control studies with 5196 cancer cases and 6614 controls from 16 publications to evaluate the association between NFκB1 -94ins/delATTG promoter polymorphism and cancer risk.

Materials and Methods

Search strategy and criteria

An electronic search was completed on PUBMED and EMBASE to identify published articles of studies examining the polymorphism of NFκB1 for the cancer risk, including the following search terms: “NFκB1,” “polymorphism,” and “cancer” (the last search update was August 10, 2011). The search was limited to English-language articles. Moreover, references of all the included articles were also hand searched.

If more than one article was published using the same case series or by the same investigators, only the study with the largest sample size or providing more detail information was selected. Studies included in our meta-analysis have to meet the following criteria: (a) use a case-control design, (b) contain available genotype frequency, and (c) evaluation of the NFκB1 -94ins/delATTG promoter polymorphism and cancer risk.

Data extraction

Two investigators independently and carefully extracted the data and reached a consensus on all the items, and the result was reviewed by one of the reviewer. For each study, the following data were considered: the first author's name, year of publication, country of origin, ethnicity, types of cancer, numbers of cases and controls, genotype frequencies for cases and controls and Hardy-Weinberg equilibrium (HWE) of controls. Different ethnic descents were categorized as Asian and European.

Statistical analyses

The strength of association between NFκB1 -94ins/delATTG promoter polymorphism and cancer risk was

assessed by odds ratios (Ors) with 95% confidence intervals (CIs). The Z test was used to determine the statistical significance of the summary OR. First, we estimated the cancer risks with the ID and II genotypes, compared with the wild-type II homozygote, and then we evaluated the risks associated with DD versus II/ID and ID/DD versus II, assuming the dominant and recessive effects of the variant D allele, respectively. Stratified analyses were also carried out by ethnicity. Heterogeneity assumption was evaluated with a chi-square-based Q-test. If the P value is greater than 0.05 of the Q-test, which indicates a lack of heterogeneity among studies, the summary OR estimate of each study was calculated by a fixed effects model (the Mantel-Haenszel method) (Mantel and Haenszel, 1959). Otherwise, the random-effects model (the DerSimonian and Laird method) was performed. Funnel plots and Egger's linear regression test were used to provide diagnosis of the potential publication bias. All statistical analysis were done with the Stata software (version 11.0; StataCorp LP, College Station, TX), using two-sided P values.

Results

Characteristics of the studies

A total of 16 publications, including 19 case-control studies on NFκB1 -94ins/delATTG promoter polymorphism and cancer risk, were identified. The selected study characteristics were summarized in Table 1. Among the 19 eligible studies, there were 5196 cases with different cancer types, including ovarian cancer (Fan et al., 2011), bladder cancer (Riemann et al., 2007; Tang et al., 2010), colorectal cancer (Andersen et al., 2010; Lewander et al., 2007; Riemann et al., 2006; Song et al., 2011), prostate cancer (Zhang et al., 2009), cervical cancer (Zhou et al., 2010), neuroendocrine tumor (Burnik and Yalcin, 2009), gastric cancer (Lo et al., 2009), nasopharyngeal cancer (Zhou et al., 2009), melanoma (Bu et al., 2007), leukemia (Riemann et al., 2007), renal cell cancer (Riemann et al., 2007), oral cancer (Lin et al., 2006), hepatocarcinogenesis (He et al., 2009), and Head and neck squamous cell carcinoma (HNSCC) (He et al., 2009). Of the 19 studies, 15 studies used frequency-matched controls to the cases by the age, sex, or ethnicity. A classic PCR-restriction fragment length polymorphism (PCR-RFLP) assay was performed in 11 of the 19 studies. Besides, there were 10 Asian studies and 9 Caucasian studies; 4 studies were related to colorectal cancer. The distribution of genotypes in the controls of all the eligible studies was in agreement with Hardy-Weinberg equilibrium except for 4 case-control studies by Bu et al. (2007), Lewander et al. (2007), and Burnik et al. (2009) as shown in Table 1.

Quantitative synthesis

All studies: Overall, as shown in Table 2, there was evidence of an association between the higher cancer risk and the wild-type genotypes in different genetic models when all eligible studies were pooled into the meta-analysis. Individuals with variant homozygote DD had a decreased risk of cancer compared with wild-type

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

ID	First au	Year	Country	Race	Cancer	Case	Control	HWE
1	Fan	2011	China	Asian	Ovarian cancer	179	223	0.396
2	Tang	2010	China	Asian	Bladder cancer	207	228	0.565
3	Andersen	2010	Denmark	Caucasian	Colorectal cancer	378	756	0.801
4	Zhang	2009	China	Asian	Prostate cancer	117	143	0.624
5	Zhou	2010	China	Asian	Cervical cancer	233	365	0.297
6	Burnik	2009	Turkey	Caucasian	Neuroendocrine tumor	50	100	0.048
7	Lo	2008	China taiwan	Asian	Gastric cancer	182	116	0.361
8	Zhou	2009	China	Asian	Nasopharyngeal cancer	163	203	0.177
9	Lewander	2007	Sweden	Caucasian	Colorectal cancer	477	439	0.0001
10	Lewander	2007	China	Asian	Colorectal cancer	193	458	0.0003
11	Bu	2007	Sweden	Caucasian	Melanoma	185	438	0.0002
12	Riemann	2006	German	Caucasian	Colorectal cancer	139	307	0.586
13	Riemann	2006	German	Caucasian	Leukemia	72	307	0.586
14	Riemann	2006	German	Caucasian	Renal Cell cancer	140	307	0.586
15	Lin	2006	China taiwan	Asian	Oral cancer	212	201	0.993
16	He	2009	China	Asian	Hepatocarcinogenesis	662	404	0.070
17	Riemann	2007	Germany	Caucasian	Bladder cancer	242	307	0.586
18	GF	2008	Germany	Caucasian	HNSCC	364	307	0.586
19	Song	2011	China	Asian	Colorectal cancer	1001	1005	0.102

HWE, Hardy-Weinberg Equilibrium of Genotype of Control

Table 2. Meta-analysis of the NFKB1 -94ins/delATTG Promoter Polymorphism and Cancer Risk Association

Polymorphism	Study	Sample Size			Test of Association			Test of Heterogeneity			
		Case	Control	N ^a	OR (95% CI)	Z	P value	Model ^b	χ ²	P value	I ² (%)
DD versus II Ethnicity	Overall	2613	3325	19	0.74(0.57-0.97)	2.19	0.029	R	89.40	<0.001	79.9
	Asian	1463	1615	10	0.52(0.42-0.65)	5.68	<0.001	R	17.45	0.042	48.4
	Caucasian	937	1647	9	1.19(0.88-1.61)	1.11	0.265	R	20.9	0.007	61.7
	Cancer type	Colorectal cancer	1012	1433	5	1.27(0.24-2.19)	0.86	0.389	R	35.05	<0.001
	Other cancers	1601	1892	14	0.60(0.47-0.76)	4.24	<0.001	R	29.51	0.006	56.0
ID versus II Ethnicity	Overall	4361	5418	19	0.92(0.77-1.10)	0.89	0.371	R	74.47	<0.001	75.8
	Asian	2643	2638	10	0.74(0.66-0.83)	5.29	<0.001	F	5.18	0.818	0.0
	Caucasian	1718	2780	9	1.21(0.91-1.60)	1.32	0.186	R	34.24	<0.001	76.6
	Cancer type	Colorectal cancer	1828	2483	5	1.15(0.76-1.74)	0.67	0.505	R	34.71	<0.001
	Other cancers	2533	2935	14	0.84(0.70-1.00)	1.92	0.055	R	31.50	0.003	58.7
DD versus II/ID Ethnicity	Overall	5197	6614	19	0.79(0.66-0.95)	2.54	0.011	R	50.42	<0.001	64.3
	Asian	3150	3346	10	0.64(0.53-0.78)	4.37	<0.001	R	18.03	0.035	50.1
	Caucasian	2047	3268	9	1.09(0.93-1.27)	1.03	0.301	F	9.43	0.307	15.2
	Cancer type	Colorectal cancer	2189	2965	5	1.12(0.83-1.52)	0.74	0.460	R	14.68	0.005
	Other cancers	3008	3649	14	0.68(0.57-0.81)	4.29	<0.001	R	20.84	0.076	37.6
ID/DD versus II Ethnicity	Overall	5197	6614	19	0.87(0.72-1.06)	1.40	0.160	R	94.25	<0.001	80.9
	Asian	3150	3346	10	0.68(0.61-0.75)	7.21	<0.001	F	8.84	0.452	0.0
	Caucasian	2047	3268	9	1.20(0.92-1.56)	1.33	0.183	R	34.02	<0.001	76.5
	Cancer type	Colorectal cancer	2189	2965	5	0.85(0.55-1.30)	0.76	0.449	R	41.86	<0.001
	Other cancers	3008	3649	14	0.77(0.64-0.93)	2.78	0.005	R	36.80	<0.001	64.7

^aNumber of comparisons; ^bRandom-effects model was used when P value for heterogeneity test < 0.10; otherwise, fix-effects model was used

homozygote II carriers (DD versus II, random-effects, OR =0.74, 95%CI =0.57-0.97, P heterogeneity < 0.001, P = 0.029, I² = 79.9), also in the dominant genetic model (DD versus II/ID, random-effects, OR =0.79, 95%CI =0.66-0.95, P heterogeneity < 0.001, P = 0.011, I² = 64.3), and the forest plots of the distribution of the ORs are shown in Figures 1(a) and (b). However, no association was observed in the heterozygote comparison (ID versus

II, random-effects, OR =0.92, 95%CI =0.77-1.10, P heterogeneity = 0.29, P = 0.20, I² = 42.0), and recessive genetic model (ID/DD versus II, random-effects, OR =0.87, 95%CI =0.72-1.06, P heterogeneity < 0.001, P = 0.160, I² = 80.9).

Subgroup analyses: Subgroup analyses were performed by ethnicity and cancer type. For ethnicity, the analysis

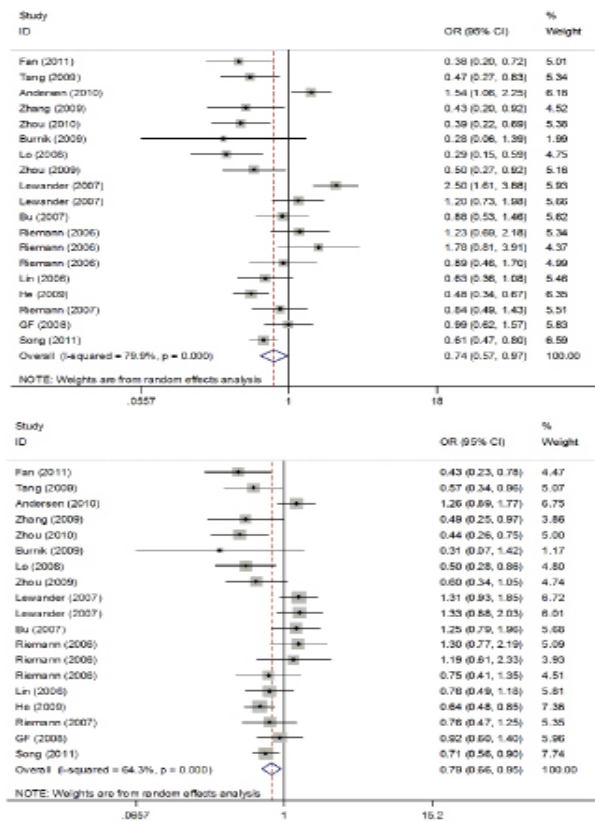


Figure 1. Forest Plot Showed the Association Between -94 Insertion/Deletion ATTG Polymorphism and Risk of Malignancy. (Above) DD versus II; (Below) DD versus II/ID. Random effect model was used

was stratified into two subgroups: Asian and Caucasian. Significant decreased risks were also found among Asians (OR =0.52, 95%CI =0.42-0.65 for DD versus II; OR =0.74, 95%CI =0.66-0.83 for ID versus II; OR =0.64, 95%CI =0.53-0.78 for DD versus II/ID; OR =0.68, 95%CI =0.61-0.75 for ID/DD versus II) but not among Caucasians. For cancer type, the analysis was also stratified into two subgroups: colorectal cancer and other cancers. Significant associations were found among other cancers but not among colorectal cancer (OR =0.60, 95%CI =0.47-0.76 for DD versus II; OR =0.68, 95%CI =0.57-0.81 for DD versus II/ID; OR =0.77, 95%CI =0.64-0.93 for ID /DD versus II).

Test for heterogeneity

There was significant heterogeneity for homozygote comparison (DD versus II, P heterogeneity <0.001), heterozygote comparison (ID versus II, P heterogeneity < 0.001), dominant genetic model (DD versus II/ID, P heterogeneity <0.001) and recessive genetic model (ID/DD versus II, P heterogeneity <0.001). Then, we assessed the source of heterogeneity for dominant genetic model by cancer type and ethnicity. As a result, cancer type (P < 0.001, df =1) and ethnicity (P < 0.001, df = 1) was found to contribute to substantial heterogeneity

Sensitivity analyses

Significant heterogeneity between studies was observed in overall comparisons. We examined the influence of each study on the pooled ORs by repeating

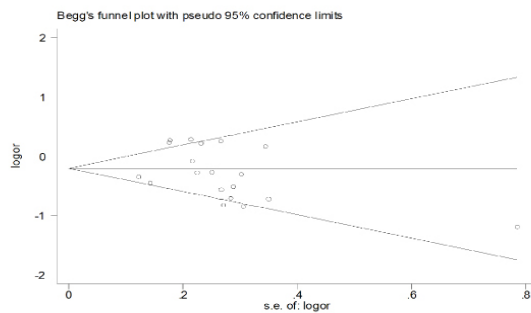


Figure 2. Begg's Funnel Plot for Publication Bias Test, DD Versus II/ID; each point represents a separate study for the indicated association. Log [OR]: natural logarithm of OR. Horizontal line: mean effect size.

the meta-analysis omitting each study one at a time. This procedure did not change the pooled ORs supporting the robustness of our findings.

Publication bias

We used Begg's funnel plot and Egger's test to assess the publication bias of studies. No evidence of publication bias was observed (DD versus II, t = 0.44, p = 0.664; ID versus II, t = 0.07, p = 0.947; DD versus II/ID, t = 0.89, p = 0.384; ID/DD versus II, t = 0.06, p = 0.953). For instance, the shape of the Begg's funnel plots seemed symmetrical in the DD versus II dominant genetic model (Figure 2).

Discussion

The NFκB1 -94ins/delATTG promoter polymorphism was well characterized in association studies. In the previous work, Zou et al. (2011) confirmed that when all groups were pooled, no association was found between NFκB1-94ins/delATTG promoter polymorphism and cancer risk. They also claimed that in the subgroup analysis, the association was found both in Asians and Caucasians. However, in the present study, we found that the variant genotype of the -94ins/delATTG promoter polymorphism was associated with significant decrease in overall cancer risk. In addition, our meta-analysis detected a significant genetic association of NFκB1 -94ins/delATTG promoter polymorphism with cancer risk in Asians but not in Caucasians. Furthermore, the association may be cancer specific for it was not found among colorectal cancers.

Our results showed that the variant genotypes were associated with a significantly decreased cancer risk in several genetic models. In the subgroup analyses by cancer site, significant associations were found among other cancers but not among colorectal cancers, indicating that this polymorphism might play a different role in different cancer sites. Several reasons may lead to the cancer site difference. First, for each of the other cancer, the number of the studies was limited. There was only one case-control study for most of our reviewed cancers. Second, even for colorectal cancer, only five studies with limited sample size were presented. Third, two colorectal cancer studies were not in Hardy-Weinberg equilibrium (Lewander et al., 2007), which may bias the conclusion. Thus, larger studies are still wanted. In the subgroup analyses by ethnicity,

we found an evidence for the association between the NFKB1 -94ins/delATTG promoter polymorphism and cancer risk among Asians but not among Caucasians. Cancer is a multifactor disease caused by different incidence in different populations, and the different results between Asians and Caucasians suggested a possible role of ethnic differences in genetic backgrounds and the environment they lived in (Hirschhorn et al., 2002), which has been generally accepted and has been proven by migration studies showing an adaptation after few generations (Geddes et al., 1991; Iscovich and Howe, 1998; Maskarinec and Noh, 2004).

Identifying the source of heterogeneity is one of the most important goals of the meta-analysis. Although we performed a careful search for publications, used strict criteria for study inclusion, data extraction and data analysis, significant between-study heterogeneity still existed. As previous meta-analysis studies concluded, ethnicity, different sources of control, different types of cancer and sample size might be the potential contributors to the heterogeneity. After subgroup analysis, we found that in our study, ethnicity and cancer type may have contributed to the observed heterogeneity. These data suggested that certain effects of genetic polymorphisms are cancer and ethno specific.

Some limitations of our meta-analysis should be considered. Firstly, meta-analysis is a type of retrospective study and is limited by the qualities of primary studies, misclassifications on genotypes and disease status may influence the results, because cases in several studies were not confirmed by pathology or other gold standard method. Secondly, the search was limited to English-language articles and other-language articles which may bias the results were not included. Thirdly, some of the reviewed studies had a small sample size and did not have adequate power to detect the possible risk for NFKB1-94ins/delATTG promoter polymorphism, and the observed significant ORs in some studies of small sample size may be false association. Fourthly, significant between-study heterogeneity was detected in some comparisons and may be distorting the meta-analysis. Lastly, four case-control studies (Bu et al., 2007; Lewander et al., 2007; Burnik and Yalcin, 2009) were not in Hardy-Weinberg equilibrium in the present meta-analysis, which may affect the validity of conclusion.

In conclusion, despite these limitations, our study performed a systematic literature review to evaluate the relationships between NFKB1 -94ins/delATTG promoter polymorphism and the risk of cancer in different sites. Individuals with wild-type genotypes of this polymorphism are associated with higher cancer risk, particularly among Asians, which suggested that this elevated cancer risk may be ethno-specific. We also showed that the association may in fact be cancer specific. Larger numbers of standardized unbiased homogenous cancer patients and well-matched controls are required in the future to examine associations between NFKB1 -94ins/delATTG promoter polymorphism and cancer risk and to draw more comprehensive conclusions for cancer prevention.

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