An updated meta-analysis of 37 case-control studies on the association between NFKB1 -94ins/del ATTG promoter polymorphism and cancer susceptibility

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Keywords: NFKB1; polymorphism; cancer; meta-analysis
Received: April 10, 2016 Accepted: July 10, 2016 Published: July 24, 2016

ABSTRACT

As a cell survival signal, nuclear factor-kappa B (NFkB) is associated with the pathogenesis of numerous malignancies. According to several studies, NFKB1 -94ins/del ATTG promoter polymorphism is associated with the risk of different malignancies, but the results were not consistent. Therefore, we performed an updated meta-analysis based on 37 case-control studies from 33 articles (16,271 cases and 22,781 controls) to clarify the relationship. The odds ratio (OR) and 95% confidence interval (CI) were used to determine the strength of the association. We found that the NFKB1 -94ins/del ATTG promoter polymorphism was significantly associated with increased susceptibility to cancer in the recessive (II vs. ID+DD, OR = 1.140, 95% CI = 1.029–1.263, p = 0.012), homozygote (II vs. DD, OR = 1.259, 95% CI = 1.068–1.485, p = 0.006), and allele (I vs. D, OR = 1.109, 95% CI = 1.025–1.199, p = 0.010) genetic models. The subgroup analysis for ethnicity found that the NFKB1 -94ins/del ATTG promoter polymorphism was significantly associated with an increased susceptibility to cancer in Asians and with a decreased susceptibility in Caucasians. The stratified analyses revealed significant associations between the polymorphism and increased susceptibility to ovarian cancer, oral squamous cell carcinoma, and nasopharyngeal carcinoma.

INTRODUCTION

Cancer is the result of complex interactions between inherited and environmental factors, which threatens people worldwide due to high morbidity and mortality [1]. Although the aetiology of this disease remains unclear, genetic susceptibility is one known explanation for the inter-individual variation in cancer risk [2]. Many researchers have been studying the aetiology of oncogenesis, and have identified the relationship between genetic polymorphism and cancer risk, especially for the NFKB1 -94ins/del ATTG promoter polymorphism.

NFkB is responsible for regulating the expression of many genes for immune response, cell adhesion, differentiation, proliferation, angiogenesis and apoptosis [3]. NFkB was first identified by Sen and Baltimore in 1986 [4]. As a transcription factor, NFkB binds to a 10 bp DNA element in kappa immunoglobulin light-chain enhancer in B cells [5]. The NFkB family consists of p50/ p105, p65/Rel A, c-Rel, Rel B, and p52/p100. Among them, the major form of NFkB is a heterodimer of the p50/p105 and p65/Rel A subunits that are encoded by the NFKB1 and NFKB2 genes, respectively [49]. The human NFKB1 gene, located on chromosome 4q24, encodes a 50 kDa DNA-binding protein that can act as a master regulator of inflammation and cancer development [6,7].

A common insertion/deletion polymorphism in the promoter region of the NFKB1 gene elicits a regulatory effect on the NFKB1 gene [8] and an increasing number of studies have assessed the association between the NFKB1
### Table 1: Characteristics of studies included in the meta-analysis

| Author       | Year | Ethnicity | Country | Cases | Control | Method       | Cancer type | Case | HWE  | Control | HWE  |
|--------------|------|-----------|---------|-------|---------|--------------|-------------|------|------|---------|------|
| Liu          | 2006 | Asian     | China   | 212   | 201     | PCR          | OSCC        | 59   | 103 | 50      | 0.993|
| Riemann      | 2006 | Caucasian | Germany | 139   | 307     | PCR-RFLP     | CRC         | 54   | 58  | 27      | 0.586|
| Riemann      | 2006 | Caucasian | Germany | 72    | 307     | PCR-RFLP     | B cell CLL  | 18   | 41  | 13      | 0.586|
| Riemann      | 2006 | Caucasian | Germany | 140   | 307     | PCR-RFLP     | RCC         | 47   | 76  | 17      | 0.586|
| Riemann      | 2007 | Caucasian | Germany | 242   | 307     | PCR-RFLP     | BC          | 88   | 124 | 30      | 0.586|
| Lo           | 2009 | Asian     | China   | 182   | 116     | PCR          | GC          | 62   | 89  | 31      | 0.361|
| He           | 2009 | Asian     | China   | 202   | 404     | PCR-RFLP     | HCC         | 83   | 84  | 35      | 0.07 |
| Zhang        | 2009 | Asian     | China   | 117   | 143     | PCR-PAGE     | PC          | 46   | 57  | 14      | 0.624|
| Zhou         | 2009 | Asian     | China   | 163   | 203     | PCR-RFLP     | NPC         | 74   | 67  | 22      | 0.177|
| Zhou         | 2010 | Asian     | China   | 233   | 365     | PCR-PAGE     | CSCC        | 108  | 105 | 20      | 0.297|
| Andersen      | 2010 | Caucasian | Denmark | 378   | 756     | TaqMan       | CRC         | 121  | 195 | 62      | 0.801|
| Tang         | 2010 | Asian     | China   | 207   | 228     | PCR-PAGE     | BC          | 89   | 92  | 26      | 0.565|
| Song         | 2011 | Asian     | China   | 1001  | 1005    | PCR-RFLP     | CRC         | 363  | 500 | 138     | 0.102|
| Fan          | 2011 | Asian     | China   | 179   | 223     | PCR-CE       | OC          | 78   | 84  | 17      | 0.396|
| Vangsted     | 2012 | Caucasian | Denmark | 348   | 1700    | Taqman       | MM          | 110  | 163 | 55      | 0.303|
| Ungerback    | 2012 | Caucasian | Sweden  | 344   | 622     | TaqMan       | CRC         | 114  | 187 | 43      | 0.079|
| Liu          | 2012 | Asian     | China   | 906   | 906     | PCR          | NPC         | 269  | 467 | 170     | 0.289|
| Lin          | 2012 | Asian     | China   | 462   | 520     | TaqMan       | OSCC        | 116  | 246 | 100     | 0.099|
| Kopp         | 2013 | Caucasian | Denmark | 334   | 334     | TaqMan       | PC          | 128  | 152 | 54      | 0.741|
| Huo          | 2013 | Asian     | China   | 187   | 221     | PCR          | OC          | 83   | 82  | 22      | 0.399|
| Cheng        | 2013 | Asian     | China   | 135   | 520     | RT-PCR       | HCC         | 42   | 64  | 29      | 0.099|
| Li           | 2013 | Asian     | China   | 609   | 640     | TaqMan       | BC          | 189  | 269 | 151     | 0.156|
| Öltulu       | 2014 | Caucasian | Turkey  | 95    | 99      | PCR-RFLP     | NSCLC       | 35   | 44  | 16      | 0.18 |
| Hua          | 2014 | Asian     | China   | 401   | 433     | HapMap       | GC          | 92   | 182 | 127     | 0.144|
| Zhang        | 2014 | Asian     | China   | 624   | 1606    | PCR          | HCC         | 205  | 312 | 107     | 0.63 |
| Liu          | 2015 | Asian     | China   | 1590  | 1979    | HapMap       | NPC         | 552  | 769 | 269     | 0.169|
| Wang         | 2015 | Asian     | China   | 421   | 425     | PCR-RFLP     | NSCLC       | 113  | 219 | 89      | 0.595|
| Lu           | 2015 | Asian     | China   | 687   | 687     | PCR-RFLP     | OC          | 115  | 351 | 221     | 0.271|
| Kopp         | 2015 | Caucasian | Denmark | 915   | 1719    | KASP         | CRC         | 320  | 449 | 146     | 0.311|
| Chen         | 2015 | Asian     | China   | 410   | 442     | PCR          | OC          | 120  | 195 | 95      | 0.136|
| Li           | 2015 | Asian     | China   | 730   | 780     | TaqMan       | BC          | 227  | 316 | 187     | 0.208|
| Li           | 2015 | Asian     | China   | 1216  | 1588    | TaqMan       | RCC         | 451  | 577 | 188     | 0.152|
| Li           | 2015 | Asian     | China   | 820   | 945     | TaqMan       | PC          | 299  | 377 | 144     | 0.371|
| Wang         | 2015 | Asian     | China   | 352   | 459     | PCR          | PTC         | 106  | 186 | 60      | 0.273|
| Li           | 2015 | Asian     | China   | 220   | 222     | PCR-RFLP     | Osteosarcoma| 60   | 114 | 46      | 0.55 |
| Han          | 2015 | Asian     | China   | 936   | 936     | PCR-RFLP     | PC          | 63   | 339 | 534     | 0.23 |
| Rybka        | 2016 | Caucasian | Poland  | 62    | 126     | PCR          | AML         | 25   | 30  | 7       | 0.079|

PTC papillary thyroid carcinoma, CRC colorectal cancer, BC bladder cancer, OC ovarian cancer, PC prostate cancer, HCC hepatocellular carcinoma, GC gastric cancer, OSCC oral squamous cell carcinoma, NSCLC none small cell lung cancer, NPC nasopharyngeal carcinoma, RCC renal cell carcinoma, MM multiple myeloma, AML acute myeloid leukaemia.
NFKB1-94ins/del ATTG promoter polymorphism and cancer risk [9-11]. However, some researchers could not replicate this association. Previous meta-analysis [45-48] focused on the relationship between the NFKB1-94ins/del ATTG promoter polymorphism and cancer, but the results were inconsistent. Since then, several other studies [36-44] performed on large case and control groups have assessed the relationships between the NFKB1-94ins/del ATTG promoter polymorphism and susceptibility to a variety of cancers. Therefore, to better understand the precise relationships, we performed a comprehensive updated meta-analysis with increased statistical power.

RESULTS

Characteristics of eligible studies

Our electronic database search resulted in 202 articles and 2 articles were available manually, we scanned all of the abstracts, and there were 45 articles that conformed to the inclusion criteria, we excluded 9 articles [52-60] that did not conform to HWE, 2 studies [61,62] were excluded as they were duplications of previous publications and 1 study [63] did not have completely extractable data. Thus, we included 33 independent records [14-44, 50-51]. Riemann et al [15] was treated as three independent case groups because three cancer types were studied along with a control sample. Li et al [39] conducted their research in three types of urinary cancer (renal cancer, bladder cancer and prostate cancer), so we treated the data as three separate comparisons. Finally, a total of 37 separate studies involving 16,271 cases and 22,781 controls were available for our updated meta-analysis. Figure 1 describes the process for the study. Characteristics of the eligible studies are summarized in Table 1. Among them, 26 studies were performed in Asian populations and 11 studies in Caucasian populations. In total, this meta-analysis included 5 studies on colorectal cancer studies, 4 on bladder cancer studies, 4 on ovarian cancer studies, 4 on prostate cancer studies, 3 on hepatocellular carcinoma studies, 3 on nasopharyngeal carcinoma studies, 2 on gastric cancer studies, 2 on oral squamous cell carcinoma studies, 2 on non-small cell lung cancer studies, 2 on renal cell cancer studies and 5 on other cancers. All cases were clinically pathologically confirmed.

Figure 1: Flow chart of the process for study identification and selection.
Table 2: Associations between the NFKB1 -94ins/del ATTG promoter polymorphism and cancer risk

| Cancer types          | Ethnicity | Cancer types          | Ethnicity |
|-----------------------|-----------|-----------------------|-----------|
| Other cancers         | Caucasian | Other cancers         | Caucasian |
| Bladder cancer        | Asian     | Bladder cancer        | Asian     |
| Ovarian cancer        | Asian     | Ovarian cancer        | Asian     |
| Prostate cancer       | Asian     | Prostate cancer       | Asian     |
| Gastric cancer        | Asian     | Gastric cancer        | Asian     |
| Oral squamous cell carcinoma | Asian | Oral squamous cell carcinoma | Asian |
| None small cell lung cancer | Asian | None small cell lung cancer | Asian |
| Hepatocellular carcinoma | Asian | Hepatocellular carcinoma | Asian |
| Nasopharyngeal Carcinoma | Asian | Nasopharyngeal Carcinoma | Asian |
| Rental cell cancer    | Asian     | Rental cell cancer    | Asian     |
| Other cancers         | Asian     | Other cancers         | Asian     |
| Overall               | Ethnicity | Overall               | Ethnicity |
| Variables             | N         | II+ID vs. DD          | OR (95% CI) |
| Case/Control          |           | II vs. DD             | OR (95% CI) |
| ID                     |           | ID vs. DD             | OR (95% CI) |

The bold values indicate that the association is significant

* Number of comparisons

Meta-analysis of the overall population

The main meta-analysis results of the association between the NFKB1 -94ins/del ATTG promoter polymorphism and cancer risk are shown in Table 2. All P values displayed obvious heterogeneity between the selected research studies under five genetic models of the updated meta-analysis. Thus, the random-effect model was used. We found that the NFKB1 -94ins/del ATTG promoter polymorphism was significantly increased cancer risk in homozgygote (II vs. DD, OR = 1.259, 95% CI = 1.068-1.485), recessive (II vs. ID+DD, OR = 1.140, 95% CI = 1.029-1.263) and allele (I vs. D, OR = 1.109, 95% CI = 1.025-1.199) genetic models. However, the association was not found in II+ID vs. DD (OR = 1.139, 95% CI = 0.994-1.305) and ID vs. DD (OR = 1.118, 95% CI = 0.977-1.253). (Figure 2)

Subgroup analyses

The subgroup analysis for ethnicity revealed significant increases in susceptibility for cancer risk in the four models among Asians (II+ID vs. DD, OR = 1.223, 95% CI = 1.031-1.451; II vs. ID+DD, OR = 1.280, 95% CI = 1.142-1.435; II vs. DD, OR = 1.463, 95% CI = 1.196-1.788; I vs. D, OR = 1.199, 95% CI = 1.092-1.317) and decreases in susceptibility in three models among Caucasians (II vs. ID+DD, OR = 0.824, 95% CI = 0.752-0.893; II vs. DD, OR = 0.855, 95% CI = 0.748-0.979; I vs. D, OR = 0.899, 95% CI = 0.844-0.958). (Figure 3, Table 2). The stratified analyses revealed a significant association between the polymorphism and ovarian cancer (II+ID vs. DD, OR = 1.481, 95% CI = 1.128-1.943; II vs. ID+DD, OR = 1.503, 95% CI = 1.265-1.786; II vs. DD, OR = 1.761, 95% CI = 1.420-2.184; ID vs. DD, OR = 1.246, 95% CI = 1.048-1.482; I vs. D, OR = 1.109, 95% CI = 1.025-1.199), oral squamous cell carcinoma (II+ID vs. DD, OR = 1.593, 95% CI = 1.253-2.026; II vs. ID+DD, OR = 1.420, 95% CI = 1.199-2.100). (Figure 2)
95% CI = 1.102-1.829; I vs. D, OR = 1.427, 95% CI = 1.229-1.657) and nasopharyngeal carcinoma (II vs. DD, OR = 1.339, 95% CI = 1.040-1.724; ID vs. DD, OR = 1.257, 95% CI = 1.092-1.447; I vs. D, OR = 1.158, 95% CI = 1.002-1.337) in the models. However, we did not find associations in hepatocellular carcinoma, colorectal cancer, bladder cancer, prostate cancer, non-small cell lung cancer and renal cell cancer (Table 2).

Figure 2: Forest plots of ORs with 95% CI for the NFKB1 -94ins/del ATTG promoter polymorphism and risk of cancer in the overall population (II vs. ID + DD).
Publication bias

The publication bias analysis was performed by Beggs’ funnel plot and Egger’s test. The shape of the Beggs’ funnel plots seemed symmetrical (Figure 4) and Egger’s test suggested no evidence of significant publication bias ($p = 0.161$ for the dominant model, $p = 0.056$ for the recessive model, $p = 0.092$ for the homozygote model, $p = 0.239$ for the heterozygote model, and $p = 0.117$ for the allele model) in this updated meta-analysis.

**Table 1:** ORs and 95% CIs for the $NFKB1$ -94ins/del ATTG promoter polymorphism and risk of cancer in ethnicity (I vs. D).

| Study ID | OR (95% CI) | % Weight |
|---------|-------------|----------|
| Asian | | |
| Lin (2006) | 1.26 (0.96, 1.66) | 2.45 |
| Zhou (2009) | 1.45 (1.07, 1.96) | 2.30 |
| Lo (2009) | 1.80 (1.29, 2.51) | 2.15 |
| Zhang (2009) | 1.46 (1.03, 2.08) | 2.04 |
| He (2009) | 1.86 (1.45, 2.37) | 2.61 |
| Tang (2010) | 1.46 (1.11, 1.93) | 2.45 |
| Zhou (2010) | 1.49 (1.17, 1.91) | 2.60 |
| Fan (2011) | 1.52 (1.14, 2.03) | 2.37 |
| Song (2011) | 1.27 (1.12, 1.44) | 3.20 |
| Lin (2012) | 1.50 (1.26, 1.80) | 2.96 |
| Liu (2012) | 1.03 (0.90, 1.17) | 3.18 |
| Li (2013) | 0.75 (0.64, 0.88) | 3.05 |
| Huo (2013) | 1.58 (1.19, 2.10) | 2.39 |
| Cheng (2013) | 1.70 (1.30, 2.23) | 2.47 |
| Zhang (2014) | 0.98 (0.86, 1.12) | 3.17 |
| Hua (2014) | 0.71 (0.58, 0.86) | 2.88 |
| Wang (2015) | 1.37 (1.13, 1.65) | 2.89 |
| Li (2015) | 1.31 (1.01, 1.71) | 2.50 |
| Wang (2015) | 0.87 (0.71, 1.06) | 2.85 |
| Li (2015) | 0.98 (0.88, 1.09) | 3.27 |
| Liu (2015) | 1.18 (1.07, 1.30) | 3.32 |
| Li (2015) | 0.93 (0.81, 1.07) | 3.16 |
| Han (2015) | 1.19 (1.02, 1.38) | 3.09 |
| Lu (2015) | 1.17 (1.00, 1.36) | 3.08 |
| Chen (2015) | 1.34 (1.10, 1.62) | 2.89 |
| Li (2015) | 0.78 (0.68, 0.90) | 3.12 |
| Subtotal (I-squared = 86.0%, $p = 0.000$) | 1.20 (1.09, 1.32) | 72.46 |

Caucasian

| Study ID | OR (95% CI) | % Weight |
|---------|-------------|----------|
| Riemann (2006) | 0.97 (0.73, 1.30) | 2.37 |
| Riemann (2006) | 0.72 (0.50, 1.04) | 1.99 |
| Riemann (2006) | 0.93 (0.70, 1.24) | 2.37 |
| Riemann (2007) | 1.02 (0.80, 1.31) | 2.60 |
| Andersen (2010) | 0.79 (0.66, 0.94) | 2.96 |
| Ungerback (2012) | 0.90 (0.74, 1.09) | 2.89 |
| Vangstedt (2012) | 0.85 (0.72, 1.01) | 3.00 |
| Kopp (2013) | 1.20 (0.96, 1.49) | 2.75 |
| Olufiu (2014) | 0.64 (0.42, 0.97) | 1.75 |
| Kopp (2015) | 0.89 (0.79, 0.99) | 3.24 |
| Rybka (2016) | 1.14 (0.73, 1.78) | 1.64 |
| Subtotal (I-squared = 84.1%, $p = 0.110$) | 0.90 (0.83, 0.99) | 27.54 |

| Overall (I-squared = 84.2%, $p = 0.000$) | 1.11 (1.02, 1.20) | 100.00 |

NOTE: Weights are from random effects analysis.

Figure 3: Forest plots of ORs with 95% CI for the $NFKB1$ -94ins/del ATTG promoter polymorphism and risk of cancer in ethnicity (I vs. D).
Sensitivity analysis

The sensitivity analysis was performed by the sequential omission of individual studies. After excluding each study sequentially, we obtained statistically similar results (data not shown), suggesting that the data of our meta-analysis are relatively stable and credible. In addition, the random-effects model was compared with the fixed-effects model, and the statistically similar results were obtained in all genetic models.

DISCUSSION

In recent years, several investigators reported the association between the \textit{NFKB1 -94ins/del ATTG} promoter polymorphism and risk of cancers [14-35] such as bladder, ovarian, prostate, gastric and breast cancers as well as non-small cell lung, hepatocellular and nasopharyngeal carcinomas, but the results are inconclusive. Previous meta-analyses [45-48] had the drawback of a limited number of studies included and small sample sizes, or studies that were not in HWE were not excluded, which may affect the validity of the conclusions. Many relevant case-control studies were published recently [36-44], including more ethnicities and cancer types. However, the results of these articles were not consistent in previous meta-analyses. To provide a more comprehensive conclusion, we expanded the sample size to more than double through the addition of new studies that were published since the previous meta-analyses.

We performed a meta-analysis of 37 case-control studies from 33 articles (16,271 cases and 22,781 controls) to clarify the relationship between the \textit{NFKB1 -94ins/del ATTG} promoter polymorphism and cancer susceptibility. We found that the \textit{NFKB1 -94ins/del ATTG} promoter polymorphism was significantly associated with increased risk of cancer; this result was different than a previous meta-analysis [48], which reported that there was no association between the \textit{NFKB1 -94ins/del ATTG} promoter polymorphism and cancer risk. The reasons for this difference could be explained as follows: 1) we included 37 case-control studies, versus only 11 studies (2,743 cases and 2,195 controls) in the previous meta-analysis, and therefore, the results of this meta-analysis were more credible; and 2) there may be some factors among the study populations that could influence the results, including age, gender, life style, and environment. In addition, when compared with the meta-analysis by Wenyuan Duan [45], although we reached the same conclusion in the terms of overall population, our analysis has some advantages: 1) we excluded articles that do not conform to HWE, whereas the previous meta-analyses did not; and 2) we included 37 studies, whereas previous meta-analyses included just 25 studies, which could lead

Figure 4: Begg’s funnel plot of the association between the NFKB1 -94ins/del ATTG promoter polymorphism and risk of cancer (II + ID vs. DD).
This study has several limitations, like any meta-analysis. First, moderate heterogeneity was detected in some comparisons and may distort the meta-analysis. Second, the non-genetic risk factors such as environment are also important in the incidence ratio of cancer. Unfortunately, there were not enough data for further subgroup analysis; therefore, the results of subgroup analysis may affect the validity of the conclusions. Third, in the subgroup analysis, we found that our analysis was limited to Asian and Caucasian populations, so we do not know whether these conclusions can also be adopted in other populations. This may cause publication bias. Finally, the sample sizes for each type of cancer were relatively small, so further research should enlarge the sample sizes to obtain more accurate conclusions.

Despite these limitations, our study has several strengths. First, all of the studies that we chose agreed with HWE, which may increase the validity of the conclusions. Second, the sample size of our study was more than double that of the previous meta-analysis, significantly increasing the statistical power. Although this updated meta-analysis had the above-mentioned shortcomings, we tried to control them through perfected searching, sifting the good ones from the bad and performing the statistical analyses strictly.

CONCLUSIONS

We conclude that the NFKB1 -94ins/del ATTG promoter polymorphism is associated with cancer risk not only in Asian populations, but also in Caucasian populations. Moreover, there might be a significant association with increased susceptibility between the NFKB1 -94ins/del ATTG promoter polymorphism and ovarian cancer, oral squamous cell carcinoma, and nasopharyngeal carcinoma. Well-designed studies with larger representative sample sizes are necessary to confirm our results.

MATERIALS AND METHODS

The systematic review and meta-analysis was in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Publication search

A systematic search of the PubMed, Web of Science, Science Direct, Ovid, China National Knowledge Infrastructure (CNKI) and Wan fang Data electronic databases was performed with the following key words: (“polymorphisms” OR “polymorphism” OR “SNP” OR “single nucleotide polymorphism” OR “variant” OR “mutation”) AND (“neoplasm” OR “cancer” OR “tumor” OR “carcinoma” OR “carcinogenesis”) AND (“NF-κB1” or “NFKB1” or “NFKB1 promoter polymorphism”) AND (“polymorphisms” OR “polymorphism” OR “variant” OR “mutation” OR “SNP”).
OR “Nuclear factor-κB1” OR “Nuclear factor κB1” OR “NFκB1” OR “nuclear factor kappa B1” OR “NF kappa B1” OR “nuclear factor kB1” OR “rs28362491”).

Inclusion criteria

No language or other restrictions were imposed in this study and the inclusion criteria were as follows: 1) case-control design; 2) studies evaluating the association between the NFKB1-94ins/del ATTG promoter polymorphism and cancer risk; 3) studies describing the genotype distributions in detail to calculate the OR and 95%CI in cases and controls; and 4) the distribution data in controls must be consistent with Hardy-Weinberg Equilibrium (HWE).

Exclusion criteria

The exclusion criteria in this meta-analysis were as follows: 1) not concerned with cancer risk; 2) only a case population; 3) duplication of a previous publication; 4) the control group does not conform to HWE; and 5) animal studies.

Data extraction

According to the criteria listed above, information was carefully extracted from eligible studies independently by each investigator (Y. Q. L. and D. W.). The following information was collected from each study: surname of the first author, year of publication, ethnicity of subjects, genotyping method, frequencies of the genotypes in cases and controls, cancer type. The different ethnicities were categorized as Caucasian or Asian. Studies that investigated more than one type of cancer were regarded as individual datasets only in subgroup analyses according to cancer type. Any discrepancy was resolved through discussion.

Statistical analysis

The strength of association between the NFKB1-94ins/del ATTG promoter polymorphism and cancer was estimated through OR with 95% CI. The combined ORs were determined by the Z test, and a P value of < 0.05 was considered to be statistically significant. The NFKB1-94ins/del ATTG promoter polymorphism consists of three genotypes: homozygote insertion or wild-type (II), homozygote deletion or variant (DD), and heterozygous ins/del (ID). We measured the association based on five different genetic models: the dominant (II + ID vs. DD), recessive (II vs. ID + DD), homozygote (II vs. DD), heterozygote (ID vs. DD), and allele (I vs. D) models. To investigate the origin of heterogeneity, subgroup analyses based on ethnicity (Caucasian and Asian) and cancer type were performed to identify the association between the NFKB1-94ins/del ATTG promoter polymorphism and cancer susceptibility.

We used the Q and I^2 statistical tests to check the statistical heterogeneity among studies. If the P value was < 0.05 and I^2 ≥ 50% indicating heterogeneity, then a random-effect model was chosen to calculate the pooled OR; otherwise, a fixed-effect model was selected [12]. A sensitivity analysis was conducted by sequentially excluding each study to evaluate the stability of the results. The publication bias was estimated by Egger’s test and Begg’s funnel plots, with potential publication bias if p<0.05 and the plot was asymmetrical [13]. The statistical analyses were performed using STATA 11.0 software (Stata Corp, College Station, TX, USA).

CONFLICT OF INTERESTS

Authors declare no financial disclosure or conflicts of interest.

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