Systematic Review and Meta-Analysis

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# Association between APE1 rs1760944 and rs1130409 polymorphism with prostate cancer risk

## A systematic review and meta-analysis

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**Abstract**

**Background:** Recently, some studies have suggested that the association of apurinic/apyrimidinic endonuclease 1 (APE1) gene polymorphism with prostate cancer (PCa) risk, but there are still some controversies. Hence, we elaborated the relationship between APE1 rs1760944 and rs1130409 gene and PCa risk through systematic literature review and meta-analysis.

**Methods:** As of March 2020, EMBASE, PubMed, the Cochrane Library, Science Direct/Elsevier, MEDLINE and CNKI were used for systematic literature retrieval to investigate the correlation between APE1 rs1760944 and rs1130409 gene polymorphism with PCa risk. Meta-analysis was performed using Review Manager and Stata software.

**Results:** Seven studies were distinguished, consists of 1769 cases of PCa patients and 2237 normal controls. Our results illustrated that there are significant correlation between the APE1 rs1760944 gene polymorphism and PCa in all genetic models ($P < .05$). The combined odds ratios and 95% confidence intervals were as follows: Additive model (ORs 0.62, 95%, CI [0.39, 0.97]); Codominant model (ORs 0.74, 95% CI [0.58, 0.95]); Dominant model (ORs 0.75, 95%, CI [0.59, 0.95]); Recessive model (ORs 0.63, 95% CI [0.41, 0.96]); Allele model (ORs 0.78, 95% CI [0.65, 0.94]). There also have significant associations between APE1 rs1130409 polymorphisms and PCa in all genetic models ($P < .05$). The combined odds ratios and 95% confidence intervals were as follows: Additive model (ORs 1.37, 95%, CI [1.01, 1.85]); Codominant model (ORs 1.21, 95% CI [1.01, 1.44]); Dominant model (ORs 1.33, 95%, CI [1.02, 1.73]); Recessive model (ORs 1.74, 95% CI [1.06, 2.85]); Allele model (ORs 1.14, 95% CI [1.00, 1.29]).

**Conclusion:** This study suggests that APE1 rs1760944 polymorphisms might be a protective factor of PCa, and APE1 rs1130409 is suggested to be a risk factor of PCa. APE1 rs1760944 and rs1130409 polymorphisms may be used in the risk assessment of PCa.

**Abbreviations:** BER = base excision repair, CI = confidence interval, DRC = DNA repair ability, GWAS = Genome-wide association study, NOS = Newcastle-Ottawa Quality Assessment scale, OR = odds ratio, PCa = Prostate cancer, SNPs = single nucleotide polymorphisms.

**Keywords:** APE1 rs1130409, APE1 rs1760944, polymorphism, prostate cancer

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*The authors have no conflicts of interest to disclose.*

*The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.*

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## 1. Introduction

Prostate cancer (PCa) is one of the most common tumors in men, causing more than 250,000 deaths every year.[1,2] At present, the etiology and pathogenesis of PCa are still unclear.[3,4] Therefore, it is of great significance to identify the risk factors of PCa for the development of intervention and protection measures. Currently, much evidence suggests that complex interactions between genetic and environmental factors are involved in the development of PCa.[5–8] A genome-wide association study (GWAS) found that at least 35 loci were associated with PCa.[6,7] About 42% of PCa risk can be explained by genetic factors. It is of great value and significance to test these risk alleles in the population.[8]

The difference of DNA repair ability (DRC) among individuals is an important factor affecting individual's cancer risk.[9] DNA repair gene polymorphism may cause this variation. Apurinic/apyrimidinic endonuclease 1 (APE1) in human is located on chromosome 14q11.2, which consists of five exons and spans about 2.5 to 3 kb of DNA.[10,11] In addition to its role in DNA repair, APE1 is also known as a transcriptional coactivator of many transcription factors, such as AP-1 HIF-1 α, p53 and

NF-κB, which are involved in cancer promotion and progression.[12] APE1 is a promising target for pharmacological treatment of some cancer types.[13] To date, epidemiological studies have shown that single nucleotide polymorphisms (SNPs) in APE1 may confer an individual's susceptibility to PCa.[14,15] Some related studies have reported the correlation between the SNP variation of APE1 rs1760944 and rs1130409 and PCa risk, but the results on this issue are contradictory. Some studies reported that this polymorphism may increase the risk of PCa, but other studies did not.[16–22] Therefore, we systematically reviewed the available literature and performed a meta-analysis to evaluate the the relationship between APE1 rs1760944 and rs1130409 gene polymorphisms and PCa risk, which may provide valuable insights for the risk assessment of PCa.

## 2. Materials and methods

### 2.1. Literature search

Published studies on the association between APE1 rs1760944 and rs1130409 gene polymorphisms and PCa risk were restricted to a meta-analysis. Two independent researchers retrieved documents from Science Direct/Elsevier, Embase, CNKI, PubMed, the Cochrane Library and Medline with a search deadline of March 2020 and no language or learning type restrictions. The retrieval terms consisted of MeSH terms and text words. For example, the retrieval terms for the APE1 rs1760944 and rs1130409 gene were "APE1 rs1760944 gene ", "rs1760944 ", "APE1 rs1130409 gene", "rs1130409", "Apurinic/apyrimidinic (AP) endonuclease", or "APEX1 gene"; those for PCa were "prostate cancer," "prostatic neoplasms", "cancer of prostate", "cancer of the prostate", "neoplasms, prostate", "neoplasms, prostatic", "prostate neoplasms", "prostatic cancer", or "PCa"; and those for the polymorphism were "SNP", "single-nucleotide polymorphism", "polymorphism", "variation", or "mutation". All abstracts and relevant documents were retrieved. At the same time, the references in related articles are manually searched, and only full-text documents were included. This study was approved by the Ethics Committee of Chongqing Traditional Chinese Medicine Hospital.

### 2.2. Eligibility criteria

Inclusion criteria: If case-control studies tested the relationship between APE1 rs1760944 and rs1130409 gene variants and PCa, the study was included. The case group was PCa patients The criteria for PCa were suspicious findings on a digital rectal examination (DRE) and/or elevated PSA serum levels (>4.0 ng/ml), followed by histopathological confirmation of prostate cancer. And the control groups were normal people. The SNPs of APE1 rs1760944 and rs1130409 were genotyped by polymerase chain reaction-restriction fragment length polymorphism. Effective data were extracted from the article, including eligible and genotype cases and controls, as well as the number of cases and controls of each APE1 rs1760944 and rs1130409 genotype.

Exclusion criteria: Case reports, only abstracts, meeting reports, and studies lacking a control population were excluded. Additionally, literature reviews that duplicated previous publications were excluded.

### 2.3. Study selection and validity assessment

Two independent researchers searched the titles and abstracts of the literature, and all relevant studies that met the research criteria were screened. If the title and abstract of the literature could not be used to judge whether the study should be included, the full text was retrieved for analysis. If there were differences in the literature included, it was assessed by consensus or by a third reviewer. In meta-analysis, two reviewers conducted quality assessments based on the main criteria for nonrandomized and observational studies of the Newcastle-Ottawa Quality Assessment scale (NOS).

### 2.4. Data extraction and statistical analysis

Data were collected from the literatures by three reviewers and contained demographic statistics (authors, publishing year, nation, number and average age of participants) and number of cases and controls for each APE1 rs1760944 and rs1130409 genotype. Differences were settled by consensus. Two researchers conducted quantitative meta-analyses using RevMan and Stata software. The combined odds ratio (OR) and its 95% confidence interval (CI) were calculated. Heterogeneity was assessed using p-values and the I-square statistic ($I^2$) in the pooled analysis, which represents the percentage of total variation in all studies. If the $P$ value is less than 0.1 or the $I^2$ value is more than 50%, the random effect model is used to analyze and summarize the estimated values. Otherwise, the fixed effect model is applied. The association between APE1 rs1760944 and rs1130409 polymorphisms and the risk of PCa was studied in an allele model (G vs T) (Both elements of each subject's genotype are considered to correspond to the same value of the dependent variable. The associations with these individual alleles are then tested.), additive model (GG vs TT) (testing is designed specifically to reveal associations that depend additively upon the minor allele – that is, where having two minor alleles (GG) rather than having no minor alleles (TT)) is twice as likely to affect the outcome in a certain direction as is having just one minor allele (TG) rather than no minor alleles (TT)), dominant model (GG and TG vs TT) (This model specifically tests the association of having at least one minor allele G (either TG or GG) vs not having it at all (TT)), recessive model (GG vs TG and GG) (This model specifically tests the association of having the minor allele D as both alleles (DD) vs having at least one major allele G (TG or TT)), and codominant model (TG vs TT) (testing on the genotypes TT, GG, and TG without regard to any "order" or allelic count or allelic pairing that they might have). The $P < .05$ suggest significant associations between the APE1 rs1760944 and rs1130409 gene polymorphism and PCa. In addition, publication bias was detected by visual symmetry of funnel plots, with asymmetry suggesting possible publication bias. This was also assessed by the Begg's and Egger's test in the meta-analysis. If the $P$-value was less than .05, publication bias existed.

## 3. Results

### 3.1. Characteristics of the included studies

The detailed check procedure is exhibited in Figure 1. A total of447 unduplicated studies were reviewed. seven studies were ultimately screened out. Table 1 summarizes the data from the seven studies. All retrieved researches involved 1769 cases of PCa patients and 2237 normal controls. All these studies reported exclusion/inclusion criteria.[16–22]

Four studies explored the relationship between APE1 rs1760944 gene polymorphism and PCa, And six studies have studied the relationship between APE1 rs1130409 gene

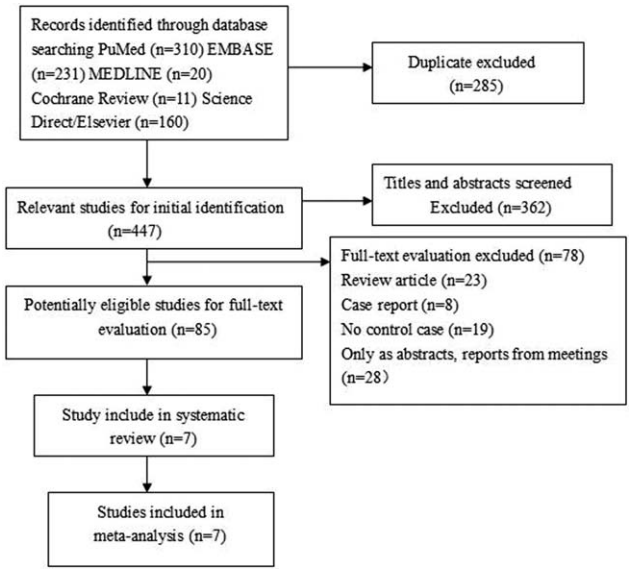


**Figure 1.** Flow diagram of the selection of eligible studies.

polymorphism and PCa. In addition, restriction fragment length polymorphism analysis was used to detect APE1 gene polymorphism in all these studies.

### 3.2. Meta-analysis

The meta-analysis revealed significant associations between the APE1 rs1760944 gene polymorphism and PCa in all genetic models ($P < .05$). Suggests that APE1 rs1760944 polymorphisms might be a protective factor of PCa, The combined ORs and 95% CIs were as follows: Additive model (ORs 0.62, 95%, CI [0.39, 0.97]) (Fig. 2); Codominant model (ORs 0.74, 95% CI [0.58, 0.95]) (Fig. 3); Dominant model (ORs 0.75, 95%, CI [0.59, 0.95]) (Fig. 4); Recessive model (ORs 0.63, 95% CI [0.41, 0.96]) (Fig. 5); Allele model (ORs 0.78, 95% CI [0.65, 0.94]) (Fig. 6). There also have significant associations between APE1 rs1130409 polymorphisms and PCa in all genetic models ($P < .05$). APE1 rs1130409 is suggested to be a risk factor of PCa. The combined odds ratios and 95% confidence intervals were as follows: Additive model (ORs 1.37, 95%, CI [1.01, 1.85]) (Fig. 2); Codominant model (ORs 1.21, 95% CI [1.01, 1.44]) (Fig. 3); Dominant model (ORs 1.33, 95%, CI [1.02, 1.73]) (Fig. 4); Recessive model (ORs 1.74, 95% CI [1.06, 2.85]) (Fig. 5); Allele model (ORs 1.14, 95% CI [1.00, 1.29]) (Fig. 6). Begg's funnel plots were largely symmetric (Figures 7A, 8A, 9A,10A, 11A), suggesting that there was no publication bias in the meta-analysis. Egger's regression test also indicated little evidence of publication bias in all genetic models ($P > .05$) (Table 2). We also conducted a sensitivity analysis of the meta-analysis. We omitted one study at a time, and the calculated combined ORs for the remaining studies yielded consistent results. In the overall meta-analysis, no single study significantly changed the combined results, which indicated that the results were statistically stable and reliable (Figures 7B, 8B, 9B, 10B, 11B).

## 4. Discussion

In this study, we focused on seven studies reported to elucidate the relationship between APE1 rs1760944 and rs1130409 gene polymorphisms and PCa risk. Four studies explored the relationship between APE1 rs1760944 gene polymorphism and PCa, the data indicate that APE1rs1760944 gene polymorphism might a protective factor of PCa. For APE1 rs1130409, six studies have studied the relationship between APE1 rs1130409 gene polymorphism and PCa. However, the data indicate that APE1 rs1130409 gene polymorphism might one of the risk factors of PCa.

Human exposure to a variety of environmental carcinogens and endogenous/exogenous reactive oxygen species may lead to DNA damage, which ultimately increases the susceptibility of men to prostate cancer (PCa).[23,24] The body's complex DNA repair system has evolved to correct DNA damage caused by the environment.[25] There are many DNA repair pathways, each responsible for repairing specific types of damage.[26] The base excision repair (BER) pathway mainly eliminates DNA damage caused by ionizing radiation, reactive oxygen radicals and methylation agents.[27] Apurinic/apyrimidinic (AP) endonuclease APE1 gene is located at chromosome 14q11.2, which encodes one of the main enzymes in BER pathway and accounts for almost all the cleavage activity of abasic sites observed in cell extract.[28–32] In addition, APE1 is also a multifunctional protein, which participates in other important cell processes, including response to oxidative stress, regulation of transcription factors, cell cycle control and apoptosis. Therefore, the abnormal expression of APE1 gene may lead to the repair of defects in these lesions and give individuals the susceptibility to cancer.[33–38]

**Table 1**

**Characteristics of the included studies.**

| | | Case | | | | | | Control | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Author | Country | N | T | G | TT | TG | GG | N | T | G | TT | TG | GG | genotype |
| Lan C 2006[a] | America | 124 | 148 | 101 | 42 | 64 | 17 | 116 | 143 | 81 | 42 | 59 | 11 | rs1130409 |
| Lan C 2006[b] | America | 228 | 252 | 204 | 65 | 122 | 41 | 219 | 254 | 180 | 73 | 108 | 36 | rs1130409 |
| Lan C 2006[c] | America | 124 | 219 | 29 | 98 | 23 | 3 | 116 | 194 | 38 | 82 | 30 | 4 | rs1760944 |
| Lan C 2006[d] | America | 228 | 431 | 25 | 204 | 23 | 1 | 219 | 403 | 33 | 186 | 31 | 1 | rs1760944 |
| Kuasne H 2011 | Brazil | 172 | 251 | 93 | 84 | 83 | 5 | 172 | 276 | 68 | 106 | 64 | 2 | rs1130409 |
| Lavender NA 2010 | America | 208 | 252 | 120 | 82 | 88 | 16 | 665 | 817 | 445 | 274 | 269 | 88 | rs1130409 |
| Mandal RK 2012 | India | 192 | 283 | 101 | 106 | 71 | 15 | 224 | 330 | 118 | 118 | 94 | 12 | rs1760944 |
| Mittal RD 2012 | India | 195 | 288 | 104 | 108 | 72 | 15 | 250 | 373 | 127 | 136 | 101 | 13 | rs1130409 |
| Jing B 2013 | China | 198 | 228 | 147 | 78 | 93 | 27 | 156 | 170 | 142 | 47 | 76 | 33 | rs1760944 |
| Pournourali M 2015 | Iran | 100 | 90 | 110 | 15 | 60 | 25 | 100 | 110 | 90 | 30 | 50 | 20 | rs1130409 |

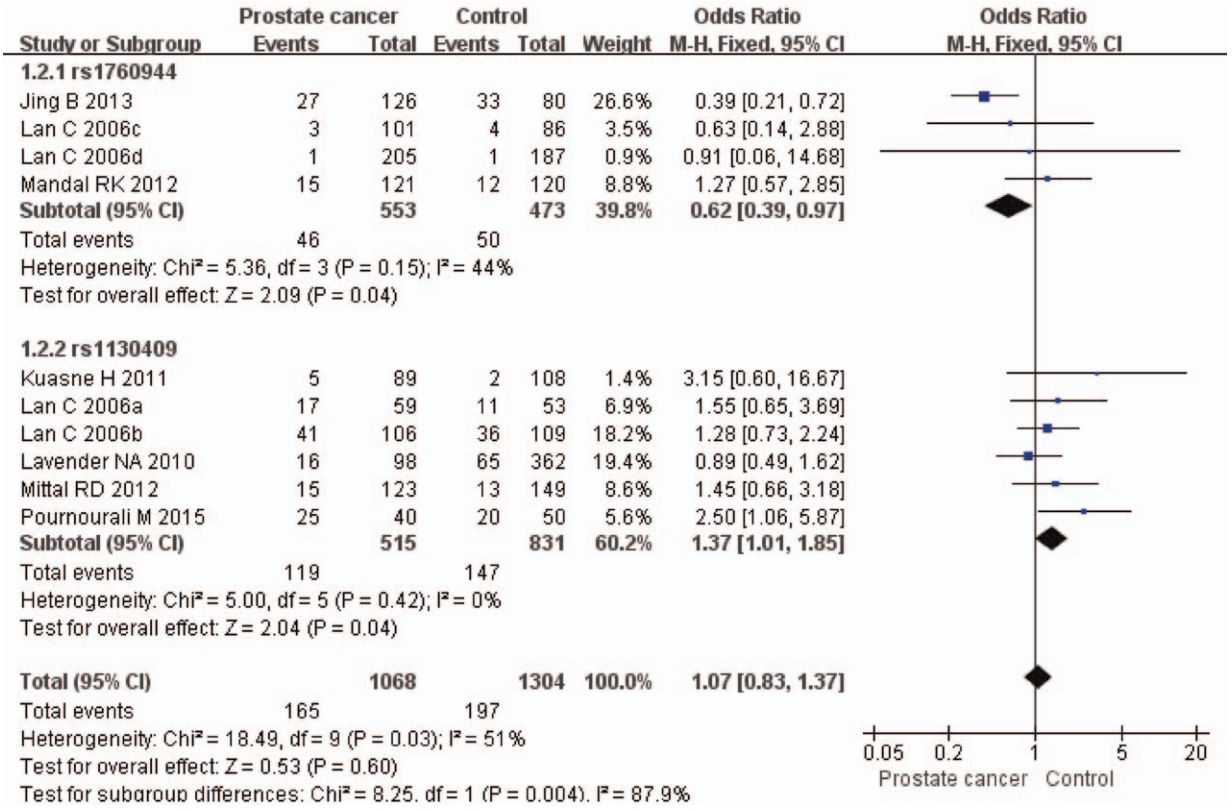


**Figure 2.** Forest plot showing the meta-analysis outcomes of the additive model.

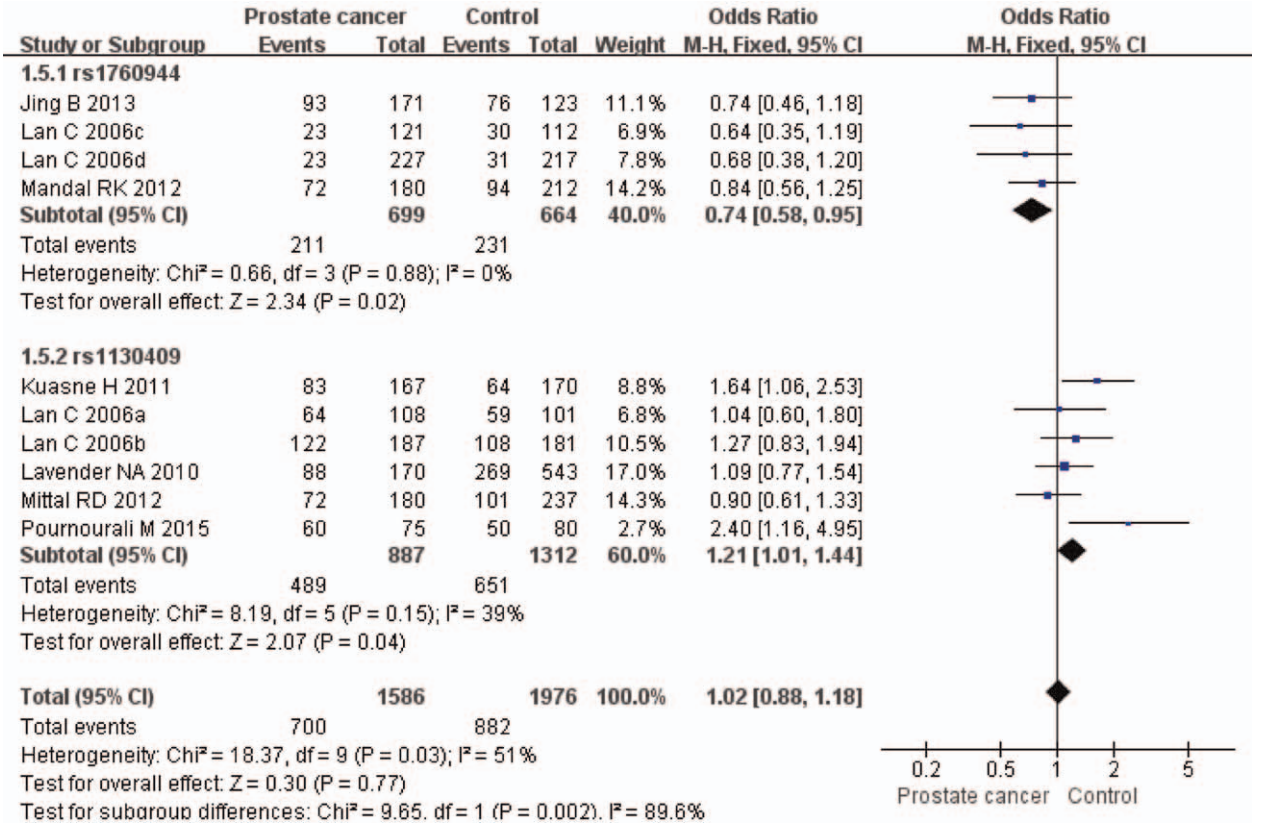


**Figure 3.** Forest plot showing the meta-analysis outcomes of the codominant model.

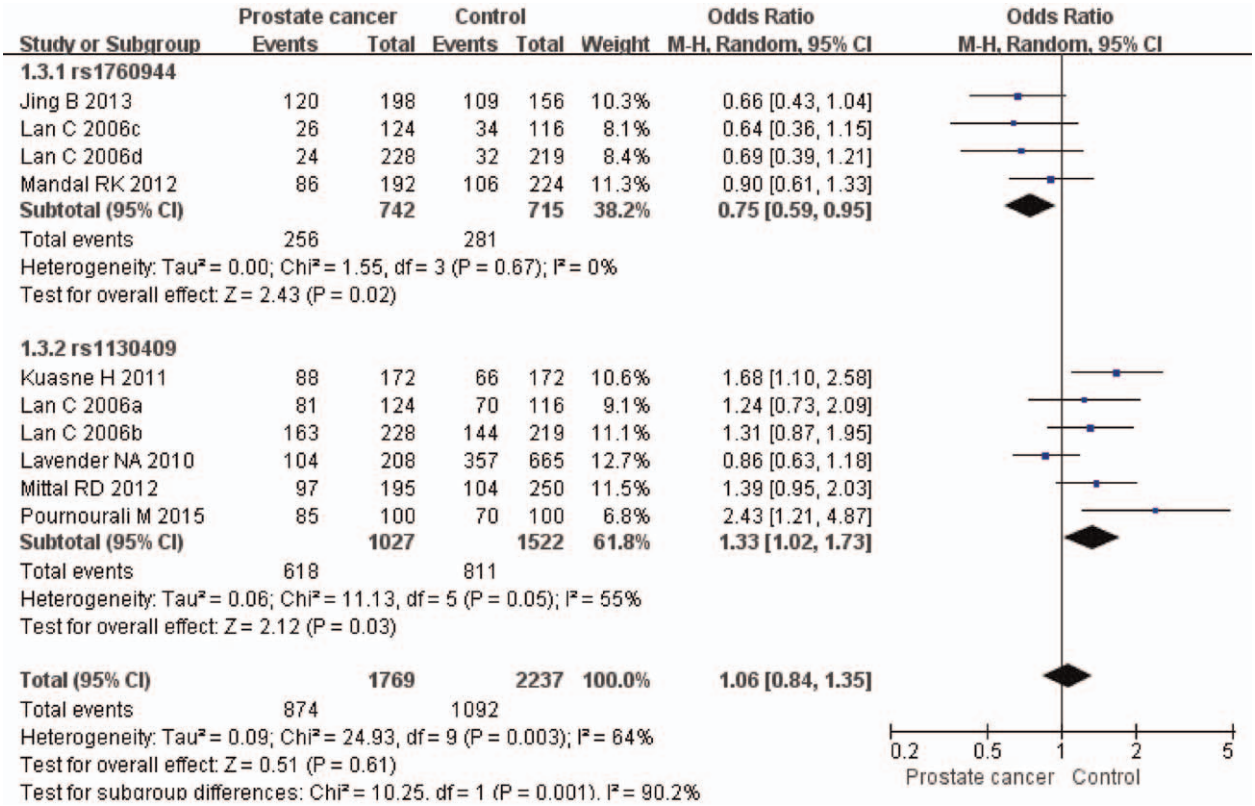


**Figure 4.** Forest plot showing the meta-analysis outcomes of the dominant model.

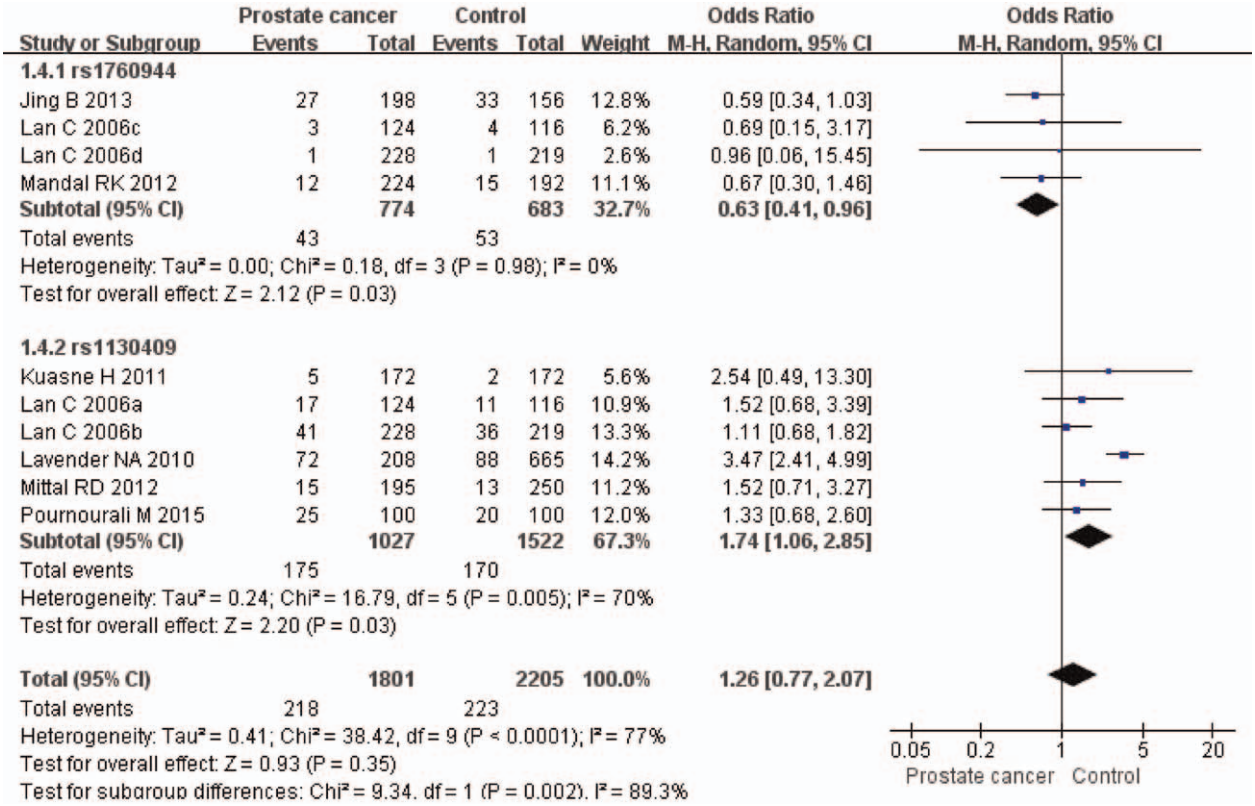


**Figure 5.** Forest plot showing the meta-analysis outcomes of the recessive model.

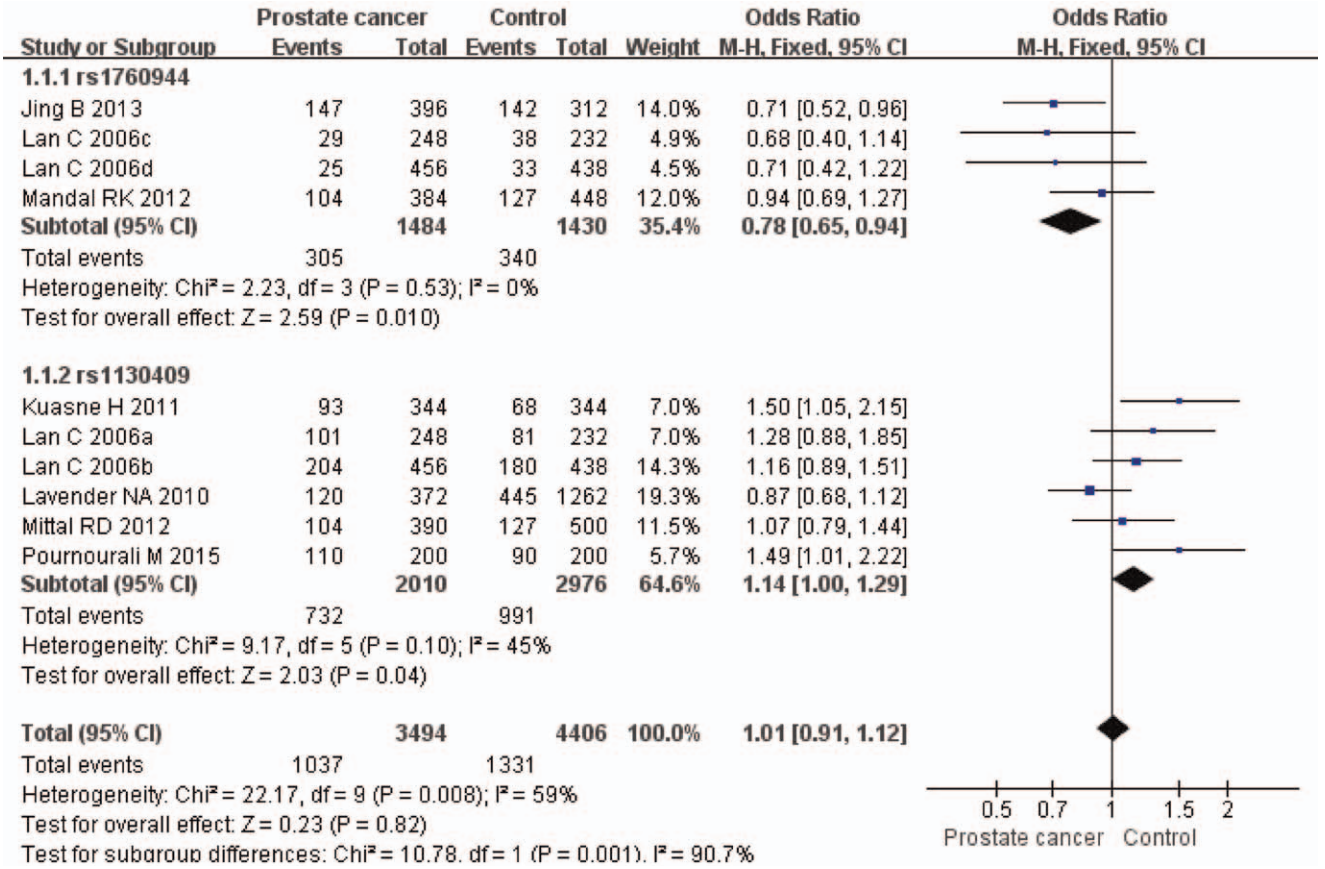


**Figure 6.** Forest plot showing the meta-analysis outcomes of the allele model.

Epidemiological studies have found that APE1 gene polymorphism is related to the risk of lung cancer, breast cancer, colorectal cancer and bladder cancer.[35,36] 18 SNPs were identified in APE1, including two functional SNPs rs1760944 in the promoter region and rs1130409 in the fifth exon. These two functional SNPs have been widely studied. It is reported that APE1 rs1760944 T > G polymorphism is related to the change of promoter activity in vitro, compared with T allele, rs1760944 G allele is related to reducing cancer risk by enhancing transcription activity. APE1 rs1130409 polymorphism T to G, in the biological significance, APE1 codon T to G polymorphism is associated with the delay of lymphocyte mitosis in healthy subjects, suggesting a higher sensitivity to ionizing radiation.[39] And some authors describe the relationship between allele G and prostate cancer.[40] Some studies have analyzed this transition and support this polymorphism as a low penetrance risk factor for cancer development.[41]

Our findings suggest that APE1 rs1760944 gene polymorphism might be a protective factor of prostate cancer. In this meat-analysis the G/G genotype in control group was significantly higher than prostate cancer group. The transformation from codon T to G at this site, may influenced the enhancing the transcriptional activity, protect DNA from damage, in turns reduce gene mutations, resulting in the decrease risk of prostate cancer. For APE1 rs1130409, our findings suggest that APE1 rs1130409 might a risk factor of prostate cancer, in our meta analysis, G/G genotype in prostate cancer group was significantly higher than in control. The possible mechanisms may the APE1 codon T transversion G polymorphism is have higher sensitivity to ionizing radiation, G alleles are more likely to cause gene damage, resulting in the increase risk of prostate cancer. However, studies with larger sample sizes are needed to better illuminate the mechanisms of the APE1 rs1760944 and rs1130409 in the prostate cancer tumorigenesis.

**Table 2**

**Egger's test of publication bias.**

| | Coeff. | Std. err. | *t* | *P*>\|*t*\| | [95% Conf. interval] |
|---|---|---|---|---|---|
| Allele | 0.40 | 2.41 | 0.17 | .87 | −5.17 5.97 |
| Additive | 1.45 | 1.37 | 1.05 | .32 | −1.72 4.62 |
| Dominant | −2.56 | 1.83 | −1.40 | .20 | −6.77 1.65 |
| Recessive | 2.23 | 2.91 | 0.77 | .46 | −4.49 8.95 |
| Codominant | 1.56 | 2.79 | 0.56 | .59 | −4.86 7.99 |

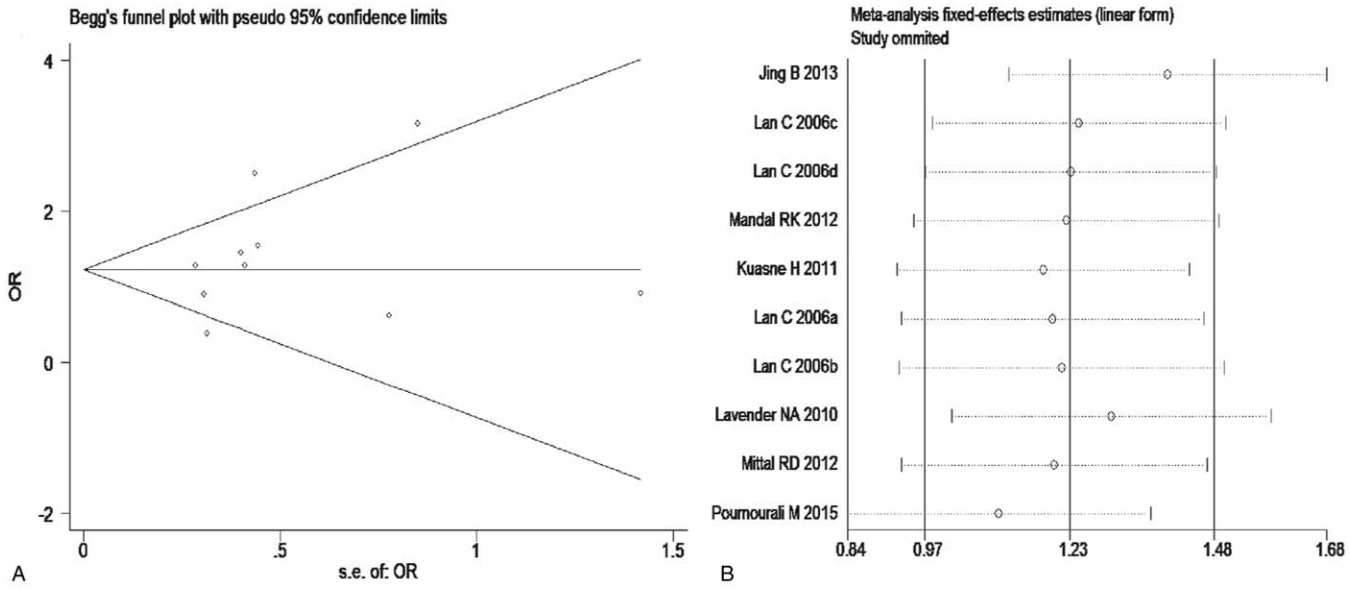


**Figure 7.** Begg's publication bias and Sensitivity analysis plot of Additive model, (A) Begg's publication bias; (B) Sensitivity analysis.

There are some limitations in our study, which need to be taken into consideration when interpreting the results of this meta-analysis. First, the sample size of each study was relatively small, and a total of 1769 prostate cancer patients and 2237 normal controls were investigated in the seven studies. Second, several studies on this issue were excluded owing to a lack of control data. Furthermore, because of the limited amount of original research, a subgroup of APE1 rs1760944 and rs1130409 gene polymorphism in different race was not conducted. As such, it is difficult to draw definitive conclusions about the clinical value of APE1 rs1760944 and rs1130409 gene variants inPCa.

In summary, the results of this meta-analysis suggest that the current article adds to the evidence of an association between the APE1 gene polymorphisms and prostate cancer progression. These data suggest that APE1 rs1760944 polymorphisms might be a protective factor of prostate cancer, and APE1 rs1130409 is suggested to be a risk factor of prostate cancer. APE1 rs1760944 and rs1130409 polymorphisms may be used in the risk assessment of PCa. However, studies with larger sample sizes are needed to definitively determine the correlation between APE1 rs1760944 and rs1130409 gene polymorphisms and prostate cancer.

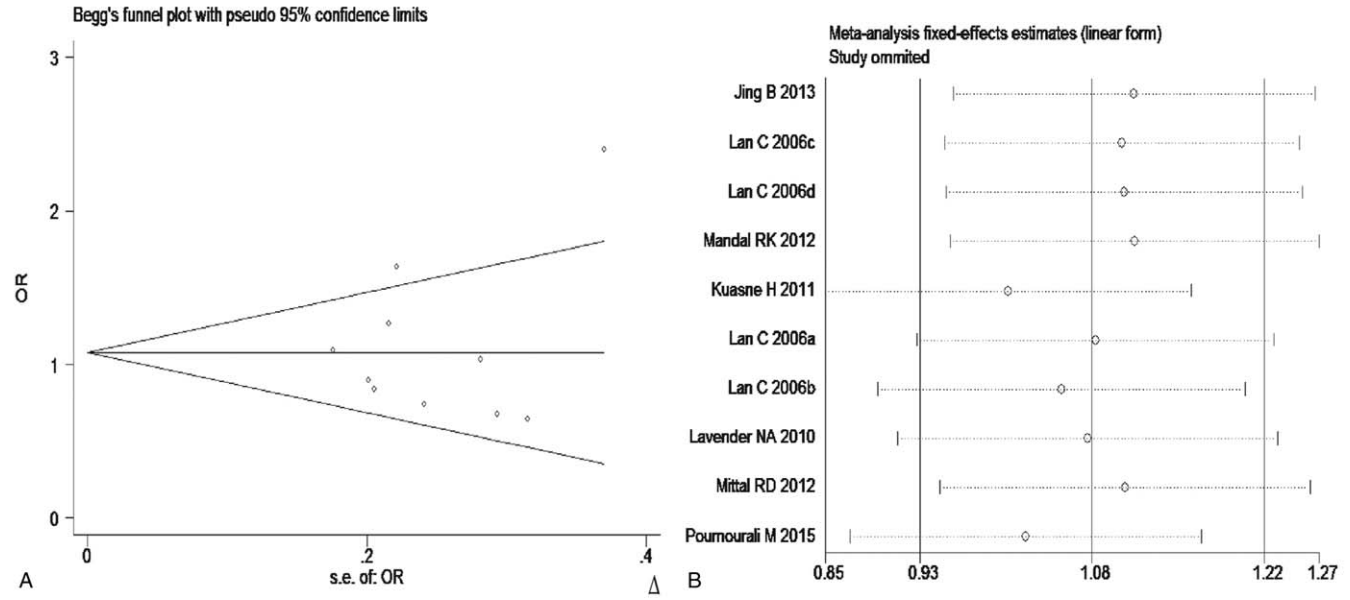


**Figure 8.** Begg's publication bias and Sensitivity analysis plot of Codominant model, (A) Begg's publication bias; (B) Sensitivity analysis.

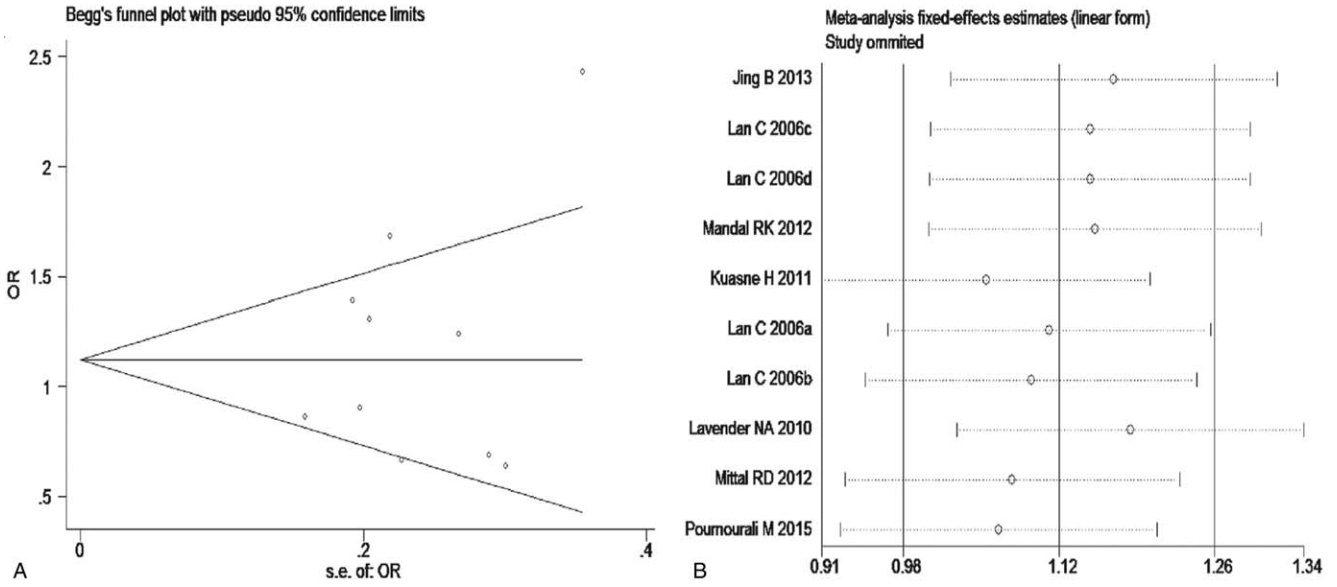


**Figure 9.** Begg's publication bias and Sensitivity analysis plot of Dominant model, (A) Begg's publication bias; (B) Sensitivity analysis.

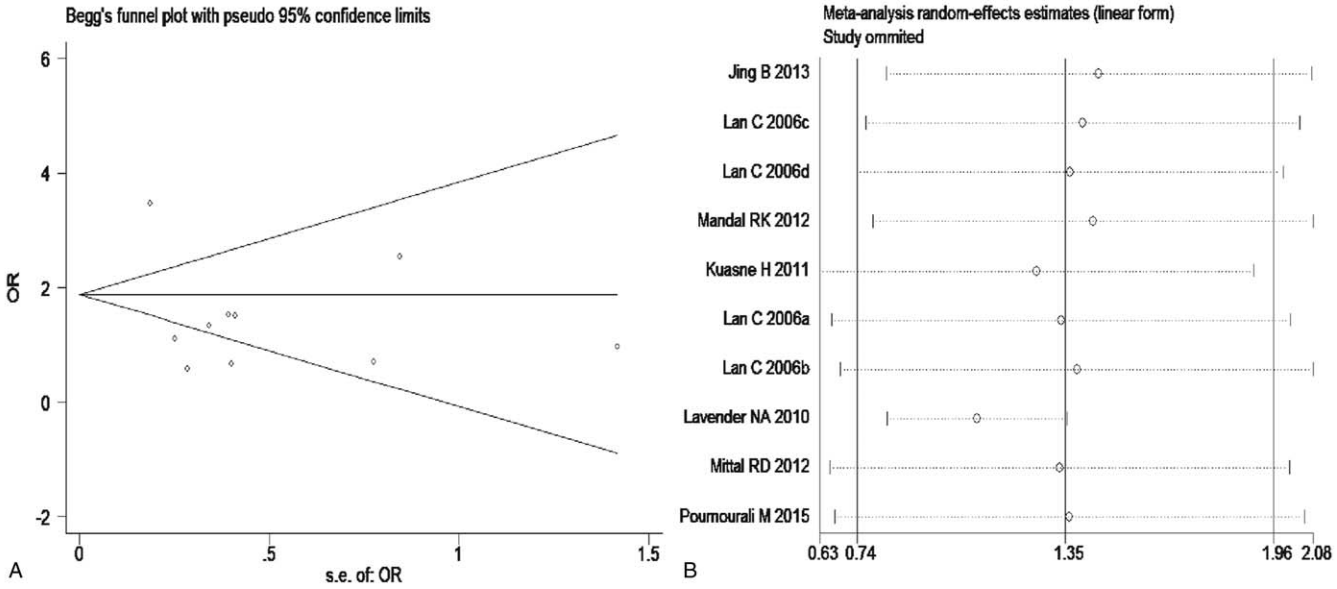


**Figure 10.** Begg's publication bias and Sensitivity analysis plot of Recessive model, (A) Begg's publication bias; (B) Sensitivity analysis.

## Author contributions

**Conceptualization:** Jinnian Liu, Jian Zheng, Yongjian Yin, Shengqiang Qian, Bin Xu, Wei Xiong, Xiangrui Yin.
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**Software:** Jian Zheng, Xia Sheng, Xiangrui Yin.
**Supervision:** Jian Zheng, Yu Guo, Yongjian Yin, Shengqiang Qian, Wei Xiong, Xiangrui Yin.
**Validation:** Jian Zheng, Yongjian Yin, Shengqiang Qian, Xiangrui Yin.
**Visualization:** Jinnian Liu, Yu Guo, Xia Sheng, Shengqiang Qian, Wei Xiong, Xiangrui Yin.

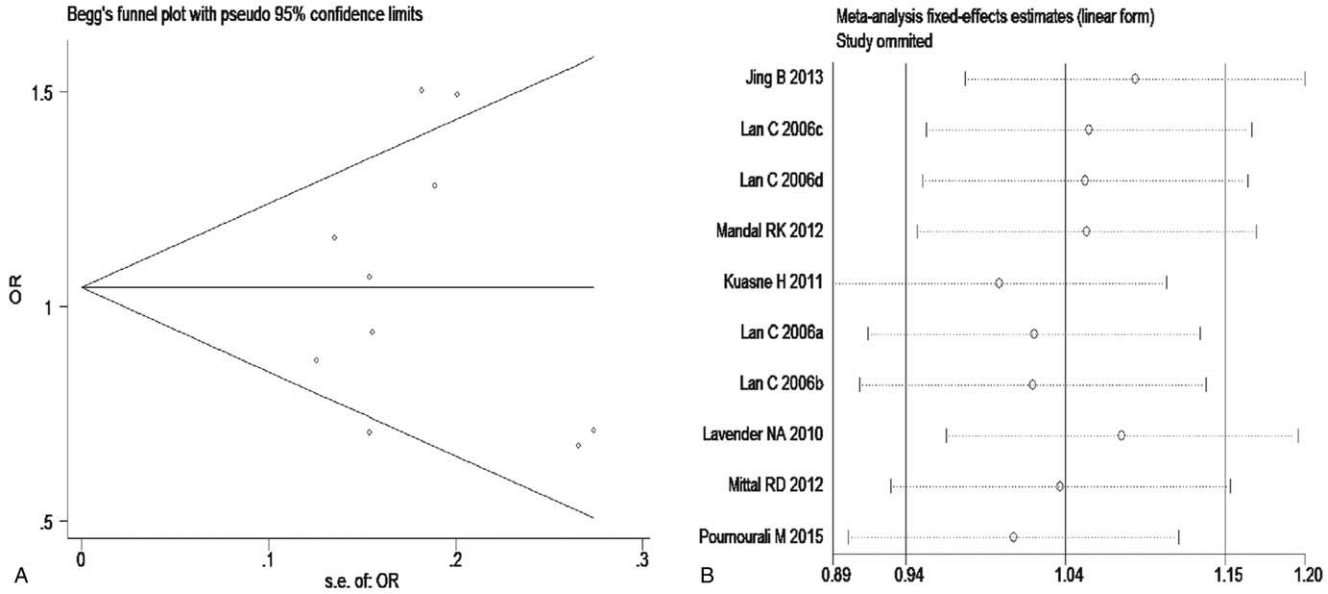


**Figure 11.** Begg's publication bias and Sensitivity analysis plot of Allele model, (A) Begg's publication bias; (B) Sensitivity analysis.

**Writing – original draft:** Jinnian Liu, Yu Guo, Xia Sheng, Yongjian Yin, Wei Xiong, Xiangrui Yin.
**Writing – review & editing:** Jinnian Liu, Jian Zheng, Yu Guo, Yongjian Yin, Xiangrui Yin.

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