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RESEARCH ARTICLE

# Assessment of the association between XRCC1 Arg399Gln polymorphism and lung cancer in Chinese

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**Abstract** X-ray repair cross-complementing group 1 (XRCC1) is one of the major DNA repair proteins involved in the base excision repair and plays an important role in the maintenance of genomic integrity. Polymorphisms in XRCC1 may alter the function and repair capacity of XRCC1 protein which further results in the genetic instability and lung carcinogenesis. Previous studies investigating the relationship between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese yielded contradictory results. A meta-analysis was performed to clarify the effect of XRCC1 Arg399Gln polymorphism on lung cancer. The association was assessed by calculating the pooled odds ratio (OR) with 95 % confidence intervals (95 %CI). Nineteen studies with a total of 12,835 participants were included into this meta-analysis. Overall, there was an obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer under three genetic models (Gln vs. Arg: OR=1.13, 95 %CI 1.01–1.25, $P$=0.029; GlnGln vs. ArArg: OR=1.41, 95 %CI 1.07–1.84, $P$=0.013; GlnGln vs. ArArg/ArgGln: OR=1.37, 95 %CI 1.07–1.76, $P$=0.013). Meta-analysis of 18 studies with high quality also found that there was an obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer under three genetic models. There was no obvious risk of bias in the meta-analysis. Data from the current meta-analysis support the obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer in Chinese.

**Keywords** XRCC1 Arg399Gln · Polymorphism · Lung cancer

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## Introduction

Lung cancer incidence has increased rapidly in China in the past years [1, 2]. Mortality from lung cancer has increased by 465 % in China during the past 30 years, and it has become the main cause of death [1, 2]. Although cigarette smoking remains the predominant cause of lung cancer, it cannot fully explain epidemiologic characteristics of lung cancer in nonsmokers [3]. Many lung cancers occur in nonsmoker which suggests that genetic factors also play important roles in the development of lung cancer [4]. Currently, the genetic polymorphisms in DNA repair genes are increasingly studied as possible risk factors of lung cancer because of their roles in maintaining the genome integrity [5, 6]. Genomic instability has been considered to play key roles in the multistage carcinogenesis and a hallmark of the carcinogenesis of many cancers including lung cancer [7, 8]. Genetic variations in DNA repair genes have been reported to be associated with the genomic instability and increasing risk of genomic damages [9]. X-ray repair cross-complementing group 1 (XRCC1) is one of the major DNA repair proteins involved in the base excision repair (BER) and plays an important role in the maintenance of genomic integrity [5, 6]. Polymorphisms in XRCC1 may alter the function and repair capacity of XRCC1 protein which further results in the genetic instability and lung carcinogenesis [5, 6]. Previous studies investigating the association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese reported contradictory results [10–19].

A meta-analysis was performed to clarify the effect of XRCC1 Arg399Gln polymorphism on lung cancer.

## Methods

### Search strategy and inclusion criteria

A systemic literature search of PubMed and China National Knowledge Infrastructure (CNKI) databases was conducted from their inception to 06 January 2013. A search strategy combining both the Medical Subject Heading and text words was used. There was no language restriction. The search words included XRCC1, Arg399Gln, polymorphisms, polymorphism, lung cancer, and lung carcinoma. Reference lists of all the included articles, the related articles, and relevant reviews were also screened to avoid omitting any potentially relevant studies. Studies were included for the meta-analysis if they satisfied the following criteria: (1) Investigating the association between XRCC1 Arg399Gln polymorphism and lung cancer risk; (2) Participants were from China; (3) Baseline characteristics were comparable between the cases and controls; and (4) Distributions of XRCC1 Arg399Gln genotype were all reported.

### Data extraction and quality assessment

Two investigators independently extracted data from each study with a predefined review form, and discrepancies were resolved by consensus of all investigators. Information extracted included author, year of publication, study design, age of participants, selection of control (population or hospital based), sample size, distributions of XRCC1 Arg399Gln genotype, and genotyping method. The quality of each study was assessed by the judgment of the deviation from Hardy–Weinberg equilibrium (HWE) in the control group. Studies without the deviation from HWE in the control group were defined as high-quality studies.

### Statistical analysis

Deviation from HWE in the control group was examined using a two-tailed $\chi^2$ test. The strength of association between XRCC1 Arg399Gln polymorphism and lung cancer risk was assessed using the pooled odds ratio (OR) with 95 % confidence intervals (95 %CI). We evaluated the risk using the allele model (Gln vs. Arg), the additive model (GlnGln vs. ArArg), the dominant model (GlnGln/ArgGln vs. ArArg), and the recessive model (GlnGln vs. ArArg/ArgGln). The statistical heterogeneity among studies was assessed with the $I^2$ test was used to quantify inconsistency [20]. A $I^2$ value ≥ 50 % was considered to represent significant heterogeneity, and the random (DerSimonian–Laird method) [21] effect model was used to calculate the pooled OR. A $I^2$ value < 50 % was considered to represent less heterogeneity, and the fixed (Mantel–Haenszel method) [22] effect model was used to calculate the pooled OR. To explore the potential effect of study quality on the overall effect estimates, sensitivity analysis was performed by excluding studies with the deviation from HWE in the control group. Funnel plot was generated as a visual aid to detect bias. Statistical analyses were undertaken using Stata version 11.0 (StataCorp, College Station, TX, USA).

## Results

### Description of included studies

A total of 85 potentially abstracts were identified from those two databases. After screening the abstracts and reviewing the full-texts, 66 studies were excluded because of case reports, or reviews, or non-relevant studies. Finally, 19 studies with a total of 12,835 participants were included into this meta-analysis [10–19, 23–31]. All studies included in the meta-analysis used a hospital-based case–control design, with a total of 6,288 cancer cases and 6,547 controls [10–19, 23–31]. Fifteen studies

**Table 1** Meta-analysis of the association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese

| Groups | Studies (participants) | OR(95 %CI) | *P* value | $I^2$ value |
|---|---|---|---|---|
| Total studies | | | | |
| Gln vs. Arg | 19(12,835) | 1.13(1.01–1.25) | 0.029 | 66.6 % |
| GlnGln vs. ArArg | 19(12,835) | 1.41(1.07–1.84) | 0.013 | 67.1 % |
| GlnGln/ArgGln vs. ArArg | 19(12,835) | 1.03(0.96–1.11) | 0.334 | 48.1 % |
| GlnGln vs. ArArg/ArgGln | 19(12,835) | 1.37(1.07–1.76) | 0.013 | 63.7 % |
| High-quality studies | | | | |
| Gln vs. Arg | 18(11,549) | 1.12(1.00–1.26) | 0.045 | 67.5 % |
| GlnGln vs. ArArg | 18(11,549) | 1.35(1.02–1.77) | 0.033 | 64.5 % |
| GlnGln/ArgGln vs. ArArg | 18(11,549) | 1.08(0.96–1.22) | 0.179 | 50.9 % |
| GlnGln vs. ArArg/ArgGln | 18(11,549) | 1.31(1.02–1.67) | 0.034 | 59.5 % |

*OR* odds ratio, *95 %CI* 95 % confidence interval

(78.9 %) used polymerase chain reaction–restriction fragment length polymorphisms (RFLP) to test the genotype of XRCC1 Arg399Gln polymorphism. All studies reported data enabling formal testing of whether genotype frequencies in the control group deviated from HWE, and the genotype distribution of XRCC1 Arg399Gln polymorphism in the control group was not consistent with HWE only in one study [19].

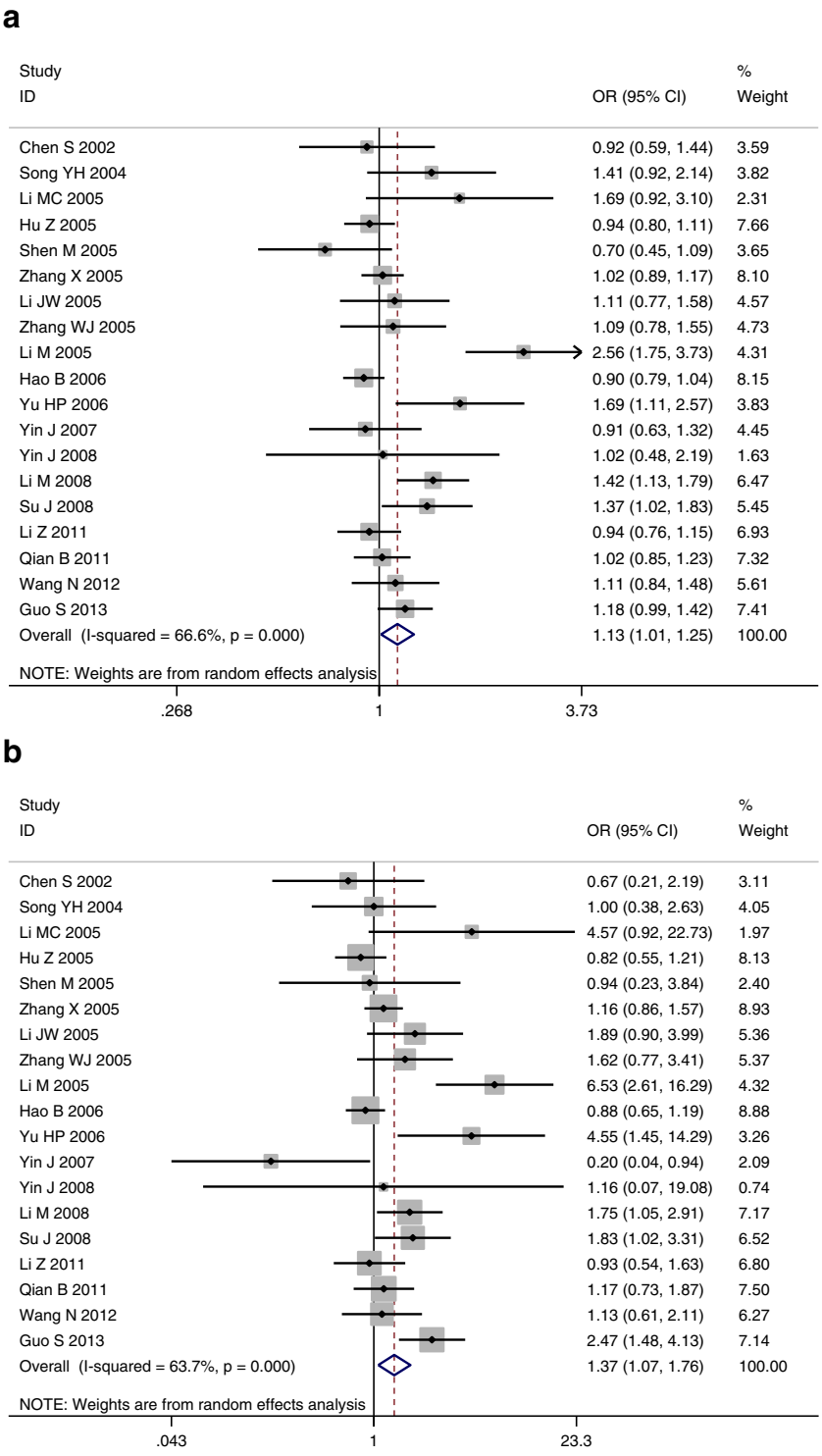


**Fig. 1** Results of the association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese. **a** The allele model (Gln vs. Arg); **b** the recessive model (GlnGln vs. ArArg/ArgGln)

### Meta-analysis

Table 1 shows the main results from the meta-analysis on the association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese. Overall, there was an obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer under three genetic models (Gln vs. Arg: OR=1.13, 95 %CI 1.01–1.25, $P$=0.029; GlnGln vs. ArArg: OR=1.41, 95 %CI 1.07–1.84, $P$=0.013; GlnGln vs. ArArg/ArgGln: OR=1.37, 95 %CI 1.07–1.76, $P$=0.013) (Fig. 1, Table 1).

Meta-analysis of 18 studies with high quality also found that there was an obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer under three genetic models (Gln vs. Arg: OR=1.12, 95 %CI 1.00–1.26, $P$=0.045; GlnGln vs. ArArg: OR=1.35, 95 %CI 1.02–1.77, $P$=0.033; GlnGln vs. ArArg/ArgGln: OR=1.31, 95 %CI 1.02–1.67, $P$=0.034) (Table 1).

### Publication bias

The shape of funnel plots in all four genetic models was symmetrical, which suggested no risk of publication bias in the meta-analysis. For example, the shape of funnel plot was symmetrical in the allele genetic model suggesting no risk of publication bias in the allele model of the meta-analysis (Fig. 2). Thus, there was no obvious risk of bias in the meta-analysis.

## Discussion

Although cigarette smoking remains the predominant cause of lung cancer, it cannot fully explain epidemiologic characteristics of lung cancer in nonsmokers [3]. Many lung cancers occur in nonsmokers, which suggest that genetic factors also play important roles in the development of lung cancer [4, 32]. Some polymorphisms have been identified as risk factors of lung cancer, such as microsomal epoxide hydrolase 1 T113C polymorphism [33].

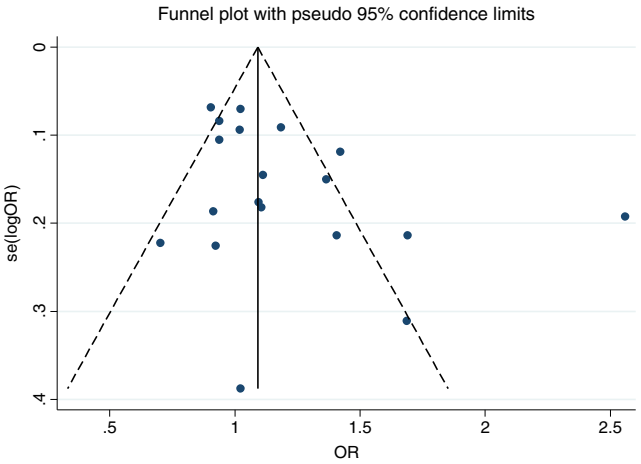


**Fig. 2** Funnel plot of publication bias in the meta-analysis of the association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese under the allele genetic model

XRCC1 is one of the major DNA repair proteins involved in the base excision repair and plays an important role in the maintenance of genomic integrity. Polymorphisms in XRCC1 may alter the function and repair capacity of XRCC1 protein which further results in the genetic instability and lung carcinogenesis. Previous studies investigating the relationship between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese reported contradictory results [10–19, 23–31]. A meta-analysis was performed to clarify the effect of XRCC1 Arg399Gln polymorphism on lung cancer. Nineteen studies with a total of 12,835 participants were included into this meta-analysis. Overall, there was an obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer under three genetic models (Table 1). Meta-analysis of 18 studies with high quality also found that there was an obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer under three genetic models. There was no obvious risk of bias in the meta-analysis. Data from the current meta-analysis support the obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer in Chinese.

Currently, the genetic polymorphisms in DNA repair genes are increasingly studied as possible risk factors of lung cancer because of their roles in maintaining the genome integrity [5, 6]. XRCC1 Arg399Gln polymorphism is the most studied polymorphism in XRCC1 [5, 6]. However, previous meta-analyses of all possible studies from total populations showed that there was no association between XRCC1 Arg399Gln polymorphism and lung cancer [34, 35]. All those two meta-analyses showed obvious heterogeneity among the included studies [34, 35]. Though there were many possible sources of heterogeneity, the race-special effect usually was the main source of heterogeneity. Currently, there were many studies on the relationship between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese, so we performed a meta-analysis only in Chinese. The findings from this meta-analysis showed that there was an obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer in Chinese. Thus, our meta-analysis provided new findings in the relationships between XRCC1 Arg399Gln polymorphism and cancers.

Several limitations should be acknowledged in the meta-analysis. Firstly, lung cancer is a complex disease, and there are complex interactions between genetic background and environmental factors especially tobacco smoking. However, our meta-analysis did not analyze the interactions between XRCC1 Arg399Gln polymorphism and tobacco smoking in the development of lung cancer because there was not enough data from the included studies. Secondly, gene–gene interactions were also possible in the association between XRCC1 Arg399Gln

polymorphism and lung cancer risk. Therefore, further studies are needed to assess the possible gene–gene interactions. Finally, our meta-analysis was pooled at the study's level because of the lack of individual patient data from the original studies. A meta-analysis of individual patient data may provide a more precise estimation on the association between XRCC1 Arg399Gln polymorphism and lung cancer risk in Chinese. Therefore, a meta-analysis of individual patient data is needed in the future.

In conclusion, data from the current meta-analysis support the obvious association between XRCC1 Arg399Gln polymorphism and increased risk of lung cancer in Chinese. Besides, further studies are needed to assess the possible gene–gene or gene–environment interactions in the association above.

**Conflicts of interest** None

## References


1. Wen C, Dehnel T. China wrestles with lung cancer. Lancet Oncol. 2011;12:15.
2. She J, Yang P, Hong Q, Bai C. Lung cancer in China: challenges and interventions. Chest. 2013;143:1117–26.
3. Herbst RS, Heymach JV, Lippman SM. Lung cancer. N Engl J Med. 2008;359:1367–80.
4. Brennan P, Hainaut P, Boffetta P. Genetics of lung-cancer susceptibility. Lancet Oncol. 2011;12:399–408.
5. Hao B, Wang H, Zhou K, Li Y, Chen X, Zhou G, et al. Identification of genetic variants in base excision repair pathway and their associations with risk of esophageal squamous cell carcinoma. Cancer Res. 2004;64:4378–84.
6. Ginsberg G, Angle K, Guyton K, Sonawane B. Polymorphism in the DNA repair enzyme xrcc1: utility of current database and implications for human health risk assessment. Mutat Res. 2011;727:1–15.
7. Hoeijmakers JH. DNA damage, aging, and cancer. N Engl J Med. 2009;361:1475–85.
8. Negrini S, Gorgoulis VG, Halazonetis TD. Genomic instability—an evolving hallmark of cancer. Nat Rev Mol Cell Biol. 2010;11:220–8.
9. Bristow RG, Hill RP. Hypoxia and metabolism. Hypoxia, DNA repair and genetic instability. Nat Rev Cancer. 2008;8:180–92.
10. Chen S, Tang D, Xue K, Xu L, Ma G, Hsu Y, et al. DNA repair gene xrcc1 and xpd polymorphisms and risk of lung cancer in a Chinese population. Carcinogenesis. 2002;23:1321–5.
11. Hu Z, Ma H, Lu D, Zhou J, Chen Y, Xu L, et al. A promoter polymorphism (-77t>c) of DNA repair gene xrcc1 is associated with risk of lung cancer in relation to tobacco smoking. Pharmacogenet Genomics. 2005;15:457–63.
12. Shen M, Berndt SI, Rothman N, Mumford JL, He X, Yeager M, et al. Polymorphisms in the DNA base excision repair genes apex1 and xrcc1 and lung cancer risk in Xuan Wei, China. Anticancer Res. 2005;25:537–42.
13. Zhang X, Miao X, Liang G, Hao B, Wang Y, Tan W, et al. Polymorphisms in DNA base excision repair genes adprt and xrcc1 and risk of lung cancer. Cancer Res. 2005;65:722–6.
14. Yin J, Vogel U, Ma Y, Qi R, Sun Z, Wang H. The DNA repair gene xrcc1 and genetic susceptibility of lung cancer in a northeastern Chinese population. Lung Cancer. 2007;56:153–60.
15. Li M, Yin Z, Guan P, Li X, Cui Z, Zhang J, et al. Xrcc1 polymorphisms, cooking oil fume and lung cancer in Chinese women nonsmokers. Lung Cancer. 2008;62:145–51.
16. Yin J, Vogel U, Ma Y, Qi R, Wang H. Association of DNA repair gene xrcc1 and lung cancer susceptibility among nonsmoking Chinese women. Cancer Genet Cytogenet. 2009;188:26–31.
17. Li Z, Guan W, Li MX, Zhong ZY, Qian CY, Yang XQ, et al. Genetic polymorphism of DNA base-excision repair genes (ape1, ogg1 and xrcc1) and their correlation with risk of lung cancer in a Chinese population. Arch Med Res. 2011;42:226–34.
18. Qian B, Zhang H, Zhang L, Zhou X, Yu H, Chen K. Association of genetic polymorphisms in DNA repair pathway genes with non-small cell lung cancer risk. Lung Cancer. 2011;73:138–46.
19. Guo S, Li X, Gao M, Li Y, Song B, Niu W. The relationship between xrcc1 and xrcc3 gene polymorphisms and lung cancer risk in northeastern Chinese. PLoS One. 2013;8:e56213.
20. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. 2003;327:557–60.
21. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986;7:177–88.
22. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959;22:719–48.
23. Song Y, Yi L, Pu Y, Liang G, Cui H. Relationship between polymorphisms of DNA repair gene xrcc1 and susceptibility to lung cancer in Nanjing population [article in Chinese]. J Environ Occup Med. 2004;21:18–21.
24. Li J, Mu L, Wei G, Chen C, Zhang Z, Yu S, et al. Relationship between polymorphisms of DNA repair gene xrcc1 and susceptibility to lung cancer [article in Chinese]. China Oncol. 2005;15:335–8.
25. Li M, Cui Z, He Q, Zhou B. Association of genetic polymorphism in the DNA repair gene xrcc1 with susceptibility to lung cancer in non-smoking women [article in Chinese]. Chin J Oncol. 2005;27:713–6.
26. Li MC, Cui ZS, He QC, Zhou BS. Association of genetic polymorphism in the DNA repair gene xrcc1 with susceptibility to lung cancer in non-smoking women. Zhonghua Zhong Liu Za Zhi. 2005;27:713–6.
27. Zhang W, Wu Y, Wu Y. Study on polymorphism of xrcc 1 and susceptibility to lung cancer [article in Chinese]. Chin J Publ Health. 2005;21:561–3.
28. Hao B, Miao X, Li Y, Zhang X, Sun T, Liang G, et al. A novel t-77c polymorphism in DNA repair gene xrcc1 contributes to diminished promoter activity and increased risk of non-small cell lung cancer. Oncogene. 2006;25:3613–20.
29. Yu H, Zeng X, Qiu X, Xu S, Shi L, Zhang X, et al. Polymorphisms in the DNA repair gene xrcc1 and susceptibility to human lung cancer [article in Chinese]. J Guangxi Med Univ. 2006;23:355–8.
30. Su J, Niu R, Liu L, Han X, Shi J. Regression analysis between polymorphisms of DNA repair gene xrcc1 and susceptibility to lung cancer of nonsmoking women [article in Chinese]. J Zhengzhou Univ (Med Sci). 2008;43:234–8.
31. Wang N, Wu YJ, Zhou XL, Wu YM. The polymorphisms of xrcc1 gene and susceptibility to pulmonary cancer. Zhonghua Lao Dong Wei Sheng Zhi Ye Bing Za Zhi. 2012;30:41–4.
32. Liu C, Yin Q, Hu J, Li L, Zhang Y, Wang Y. A meta-analysis of evidences on xpc polymorphisms and lung cancer susceptibility. Tumour Biol. 2013;34:1205–13.
33. Wang S, Zhu J, Zhang R, Gu Z. Association between microsomal epoxide hydrolase 1 t113c polymorphism and susceptibility to lung cancer. Tumour Biol. 2013;34:1045–52.
34. Dai L, Duan F, Wang P, Song C, Wang K, Zhang J. Xrcc1 gene polymorphisms and lung cancer susceptibility: a meta-analysis of 44 case–control studies. Mol Biol Rep. 2012;39:9535–47.
35. Wu J, Liu J, Zhou Y, Ying J, Zou H, Guo S, et al. Predictive value of xrcc1 gene polymorphisms on platinum-based chemotherapy in advanced non-small cell lung cancer patients: a systematic review and meta-analysis. Clin Cancer Res. 2012;18:3972–81.