

Nucleotide excision repair gene polymorphisms and prognosis of non-small cell lung cancer patients receiving platinum-based chemotherapy: A meta-analysis based on 44 studies

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Abstract. Genetic variations are linked to DNA repair ability and varied drug metabolism that largely affects the prognosis of antineoplastic agents, including platinum. The purpose of the present meta-analysis was to determine the roles of the genetic variants of the nucleotide excision repair genes on the prognosis of platinum-based chemotherapy in patients with non-small cell lung cancer (NSCLC). A meta-analysis was performed, including 44 original studies with a total number of 5,944 patients with NSCLC according to the search strategy. The tumor responses [complete response, partial response, stable disease (SD) and progressive disease (PD)] were estimated and the Stata package was used for the comprehensive quantitative analyses. The results showed that the *XPG C46T* polymorphism was significantly associated with tumor chemotherapy when SD or PD was considered as a non-response [TT vs. CC: risk ratio (RR), 1.31; 95% confidence interval (CI), 1.14-1.5; and P=0.00; TT/CT vs. CC: RR, 1.23; 95% CI, 1.11-1.36; and P=0.00; and TT vs. CC/CT: RR, 1.22; 95% CI, 1.11-1.36; and P=0.00]. No significant association between the *ERCC1 C118T/C8092A XPD Lys751Gln* and *XPA A23G* polymorphisms and tumor response was found. There was also no evidence found to support the use of the *ERCC1 C118T/C8092A XPD Lys751Gln* and *XPA A23G* polymorphisms as prognostic predictors of platinum-based chemotherapies in NSCLC in the meta-analysis. For the *XPG C46T* polymorphisms, a significant association with an objective response was detected. Multiple and large-scale studies are required to further investigate the association between biomarkers and tumor prognosis.

Introduction

Lung cancer is currently the most common malignancy and is a leading cause of mortality worldwide (1-2). The mechanism of this type of carcinogenesis remains to be fully elucidated. Tobacco smoking has been suspected to be the most significant cause of lung cancer. However, only 1 in 10 smokers develop lung cancer, demonstrating that it is likely that genetic susceptibility also plays a significant role (3). Therefore, the detection of genetic polymorphisms should be taken into consideration to explain individual differences in lung cancer susceptibility. Non-small cell lung cancer (NSCLC) represents ~80% of primary lung cancer cases and approximately two-thirds of these patients are diagnosed at an advanced stage (4). Several effective chemotherapeutic agents are available for treatment and platinum-based chemotherapy, including cisplatin and carboplatin, is the standard initial treatment regimen for NSCLC (5). Evidence from NSCLC trials involving unselected patients has shown that the efficacy of the regimen used is reported to be only 30-40% (6). Although the disease stage at diagnosis is the major prognostic predictor, there are variations in survival rates among patients who begin treatment at a similar disease status and undergo similar treatment regimens. Findings of a previous study have indicated that genetic factors may also affect the effectiveness of treatment (7).

Pharmacogenetics plays a significant role in current cancer chemotherapy and it has been reported that the prognosis can be partly influenced by genes (8). These antineoplastic agents contribute to the inhibition of DNA replication and transcription due to the formation of adducts and covalent cross-links between DNA-double strands that lead to DNA damage. These adduct and cross-links can be repaired by complex molecules in the nucleotide excision repair (NER) pathway, including *ERCC1*, *XPD*, *XPF* and *XPG* gene-encoded proteins. Therefore, NER gene polymorphisms may be able to predict the outcome and prognosis in individual patients with NSCLC undergoing platinum chemotherapy.

Mutations are early events in carcinogenesis and for various types of cancer the defect of DNA repair is a risk factor (9). The maintenance of genome integrity is extremely significant for the survival of all organisms, but DNA is regularly damaged by various types of endogenous and exogenous mutagens.

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The DNA repair gene system is crucial in protecting against gene mutation caused by carcinogenesis. The deficiency in the capacity of DNA repair may result in birth defects, cancer and a reduced lifespan (10). DNA repair consists of at least four types, including damaged base excision repair, DNA-NER, mismatch repair and double-strand break repair (11). Among these, NER is a highly adaptable and advanced DNA damage removal pathway that impedes the deleterious effects of a multitude of DNA lesions, including major types of environmental-induced damage. In eukaryotic cells, the process requires >30 proteins to perform at various steps (12).

In recent years, an increasing body of epidemiological studies (1,3,5) have demonstrated that the potential role of polymorphisms of the genes in the NER pathway may be associated with the clinical prognosis of patients with NSCLC receiving platinum-based chemotherapies in China. However, the results were shown to be inconclusive. In order to investigate the effect of these genetic factors, including *ERCC1*, *XPD/ERCC2*, *XPA* and *XPG*, on the prognosis of platinum-based chemotherapy, a meta-analysis was performed, to the best of our knowledge, for the first time with regards to the key genes of DNA repair and metabolism in the Chinese population.

Materials and methods

Literature search strategy and selection criteria. A comprehensive literature search was performed using the PubMed, Embase, Chinese National Knowledge Infrastructure (CNKI) (<http://www.cnki.net/>) and Wanfang databases (<http://www.wanfangdata.com.cn/>) to identify the studies investigating the associations between the NER gene variants and NSCLC risk in the Chinese population that were published prior to October 1, 2013. The following terms were used in the search: Lung cancer, non-small cell lung cancer or NSCLC; in combination with polymorphisms, variants or mutation; *ERCC1*, *XPD/ERCC2*, *XPA* or *XPG*; platinum or cisplatin and carboplatin; and in combination with China or Chinese. The searches were limited to human studies and the Chinese population. The gender and average ages of patients in each original study were not taken into consideration. All the references of the review and original articles on this topic were also checked. When multiple publications reported the same or overlapping data, only the most updated study with the largest sample size was selected.

The studies included in the meta-analysis had to meet all the following inclusion criteria: i) Cancer should be confirmed as NSCLC; ii) treatment regimens were platinum-based chemotherapies; and iii) the original data were presented with the calculation of risk ratios (RRs) with corresponding 95% confidence intervals (CIs) or other available data for estimating RR (95% CI).

Exclusion criteria were: Studies without genotype or allele data, case reports, studies pertaining to small cell lung cancer, studies containing overlapping data, non-human studies, interim analyses, comparisons of laboratory methods, editorials and review articles (including meta-analyses). Any missing information was obtained by contacting the corresponding authors in all cases and the studies were not considered if critical missing information could not be obtained following repeated requests. The method for how the polymorphism was detected was not limited and the evaluation criteria

for the tumor response were accepted for all subjects [the World Health Organization (WHO) criteria or the Response Evaluation Criteria in Solid Tumors (RECIST)]. In terms of the definition of the tumor response, two different standards were allowed and they were based on the aforementioned evaluation. If certain studies did not obtain the crucial information of drug response and/or state of survival rate, the corresponding authors were contacted to request the relevant data.

Data extraction. Data were extracted and entered into a database. Two investigators (DH and YZ) searched the initially relevant literature with keywords in the titles or abstracts and eligible studies were determined. When extracting data from each eligible study independently to ensure the accuracy of data, any discordance with regard to results was resolved when agreement was reached by the two investigators. All the studies were evaluated by titles and abstracts initially, prior to further evaluation for particular studies.

Data were collected with regards to the genotypes of *ERCC1 C118T/C8092A*, *ERCC2/XPD A751C*, *XPA G23A* and *XPG C46T*, and the following information was extracted from each of the eligible studies: First author, year of publication, sample size of genotyped cases, gender (male/female), median (or mean) age and (range) year, smoking/no-smoking, genotyping methods, chemotherapy regimens, evaluation criteria, histology, clinical stage and genotype studied.

Statistical analysis. The RR for the tumor response [complete response (CR) + partial response (PR) vs. stable disease (SD) + progressive disease (PD) or CR + PR + SD vs. PD] by adopting the WHO or the RECIST criteria (13) was estimated subsequent to accepting the aforementioned chemotherapy treatment.

Two models of meta-analysis, the random-effects [DerSimonian and Laird (14)] and the fixed-effects models (Mantel-Haenszel), were performed to calculate the pooled RRs in the present study. For each comparison, statistical heterogeneity among the studies was evaluated by calculating the χ^2 -based Q statistical test (Cochran's Q statistics), when $P < 0.1$ heterogeneity existed (15). I^2 statistics were calculated to assess the degree of between-study inconsistency due to heterogeneity rather than by chance when $I^2 > 50\%$ indicated the statistical significance (16). When heterogeneity existed, the random-effects model was chosen to evaluate the overall or pooled estimate of risk (RRs). The fixed-effects model was chosen when heterogeneity detected between studies had no significance.

An evaluation of potential publication bias was performed by visual inspection with the funnel plots and statistical evaluation with Begg and Egger's unweighted regression tests (17-18). Possible publication bias was indicated by an asymmetric plot. Stata version 9.0 (StataCorp, College Station, TX, USA) was implemented for statistical analyses. All the P-values were two-tailed and $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Identification and characteristics of included studies. There were 102 relevant publications identified through the literature

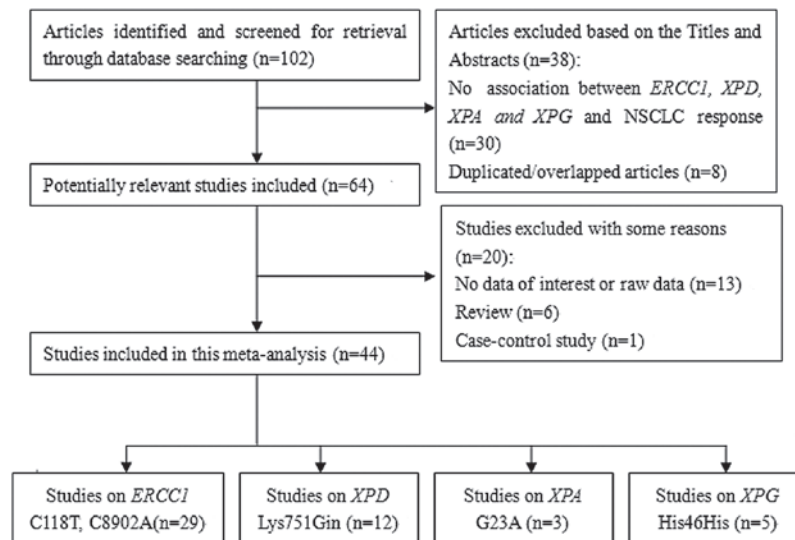


Figure 1. Process of inclusion and exclusion of studies for *ERCC1*, *XPD*, *XPA* and *XPG* and the concise reasons for all selections.

search and selection was based on the inclusion criteria following the initial screening. Among these, 64 potentially relevant studies were identified subsequent to carefully reading titles and abstracts. A total of 20 studies were excluded for the following reasons: One was a case-control study, six were reviews, 13 had no data of interest or raw data and eight studies were excluded due to duplicated/overlapping studies. No additional studies were identified from the references cited in the published studies that were searched for manually. Twenty-nine studies concerning the *ERCC1 C118T/C8092A* polymorphism (19-47), eight with the *C8092A* polymorphism (19,22,24,31,39,40,48-49), 12 with the *XPD A751C* polymorphism (26,27,39,47,49-56), three with *XPA G23A* (57-59) and five studies with *XPG His46His* (58-62). The specific process of the inclusion and exclusion of eligible studies is shown in Fig. 1. The main characteristics of the studies identified are shown in Table I.

Overall analysis of data

Tumor response of *ERCC1 C118T/C8092A* polymorphisms (non-response: SD or PD). A total of 24 studies were eventually included with a total sample size of 2,585 patients. Data showed that there was no significant association between *ERCC1 C118T* polymorphisms and tumor response in the present study analyses under the four comparison models [TT vs. CC: RR (95% CI), 1.01 (0.7-1.45), $P=0.976$; CT vs. CC: RR (95% CI), 0.91 (0.78-1.05), $P=0.199$; CT/TT vs. CC: RR (95% CI), 0.95 (0.85-1.06), $P=0.386$; and TT vs. CC/CT: RR (95% CI), 1.06 (0.91-1.23), $P=0.463$; Table II and Fig. 2]. There was significant heterogeneity observed between studies in the initial fixed model in three genetic contrasts for which a random model was required (TT vs. CC: $I^2=61\%$; CT vs. CC: $I^2=51.1\%$; and CT/TT vs. CC: $I^2=66.9\%$; Table II), except for the recessive model (TT vs. CC/CT: $I^2=39.8\%$; Table II). In addition, publication bias was detected in Egger's test (TT vs. CC: $P=0.028$; and TT vs. CC/CT: $P=0.029$), but not in the other models (CT vs. CC: $P=0.251$; and CT/TT vs. CC: $P=0.973$) (data not shown).

Eight studies were included with a total sample size of 1,102 patients. Data showed that the *ERCC1 C8092A* polymorphism was not associated with tumor response in this

analysis [AA vs. CC: RR (95% CI), 1.09 (0.88-1.35), $P=0.412$; CA vs. CC: RR (95% CI), 0.94 (0.81-1.1), $P=0.431$; AA/CA vs. CC: RR (95% CI), 1.11 (0.91-1.35), $P=0.328$; and AA vs. CC/CA: RR (95% CI), 0.96 (0.88-1.05), $P=0.377$; Table II]. No significant between-study heterogeneity was observed in the initial fixed model and therefore a random model was not performed, resulting in P -values of 0. In addition, no publication bias was detected in Egger's test (AA vs. CC: $P=0.53$; CA vs. CC: $P=0.106$; and AA vs. CC/CA: $P=0.397$), but not in the dominant model (AA/CA vs. CC: $P=0.044$) (data not shown).

Tumor response of *ERCC1 C118T* polymorphisms (non-response: PD). Seven studies were included with a total sample size of 729 patients. Data showed that *ERCC1 C118T* polymorphisms were not associated with the tumor response in this analysis under the four comparison models (TT vs. CC: RR (95% CI), 0.65 (0.3-1.41), $P=0.276$; CT vs. CC: RR (95% CI), 1 (0.5-2), $P=0.995$; CT/TT vs. CC: RR (95% CI), 0.83 (0.64-1.07), $P=0.149$; and TT vs. CC/CT: RR (95% CI), 0.67 (0.31-1.44), $P=0.304$; Table III). Significant between-study heterogeneity was observed in the initial fixed model and then a random model was performed ($I^2=75\%$) under the heterozygote comparison model. In addition, no publication bias was detected with a $P>0.05$ in Egger's test, and no significant outcome of influence analysis was observed (data not shown).

Tumor response of *XPD A751C* polymorphisms (non-response: SD or PD). Twelve studies were included with a total sample size of 2,043 patients. Overall, the meta-analysis showed that there was no statistically significant association between the *XPD A751C* polymorphism and tumor response for all the genetic models (GlnGln vs. LysLys: RR=1.21, 95% CI: 0.92-1.59, $P=0.183$, $I^2=0.0\%$ for heterogeneity test; LysGln vs. LysLys: RR=1.08, 95% CI: 0.96-1.22 $P=0.182$, $I^2=33.1\%$ for heterogeneity test; the recessive model, GlnGln vs. LysLys/LysGln: RR=1.16, 95% CI: 0.89-1.52, $P=0.272$, $I^2=0\%$ for heterogeneity test; and the dominant model, GlnGln/LysGln vs. LysLys: RR=1.02, 95% CI: 0.92-1.13, $P=0.714$, $I^2=43.7\%$ for heterogeneity test; Table II and Fig. 3). In addition, no publication bias

Table I. Characteristics of the studies on platinum-based chemotherapy for *ERCC1*, *XPB*, *XPA* and *XPB* polymorphisms about NSCLC identified in the meta-analysis.

First author (year) (ref.)	Sample size	Male/ female	Median (or mean) (range) year	Smoking/ no-smoking	Genotyping methods	Chemotherapy	Evaluation criteria ^a	Histology	Clinical stage	Genotype studied
Ren <i>et al</i> (2010) (19)	117	88/29	61 (21-81)	NA	PCR-RFLP	DDP + NVB, DDP + TXT, DDP + GEM	WHO	SCC, 28; ACA, 80; other, 9	III: 84, IV: 33	ERCC1C8092A/ C118T
Han <i>et al</i> (2011) (20)	91	55/36	56 (NA)	NA	Direct sequencing	DDP + TAX, DDP + GEM	RECIST	SCC, 43; ACA, 48	NA	ERCC1 C118T
Chen and Wang (2011) (21)	54	38/16	56 (30-73)	NA	PCR-RFLP	DDP + TAX, DDP + DOC	RECIST	SCC, 34; ACA, 16; other, 4	III: 20, IV: 34	ERCC1 C118T
Zhang and Li (2009) (22)	68	NA	NA	NA	Direct sequencing	GP or TP	RECIST	NA	NA	ERCC1C8092A/ C118T
Cheng <i>et al</i> (2012) (23)	142	89/53	62 (43-81)	NA	Direct sequencing	DDP + NVB, DDP + TAX	RECIST	SCC, 82; ACA, 60	III: 96, IV: 46	ERCC1 C118T
Wang <i>et al</i> (2012) (24)	130	90/40	62 (28-83)	NA	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM	RECIST	SCC, 46; ACA, 76; other, 8	III: 58, IV: 72	ERCC1C8092A/ C118T
Lu <i>et al</i> (2013) (25)	100	54/46	61 (41-82)	NA	PCR-RFLP	DDP + NVB, DDP + TAX	RECIST	SCC, 60; ACA, 40	III: 44, IV: 56	ERCC1 C118T
Zhang <i>et al</i> (2013) (26)	78	52/26	58 (29-81)	48/30	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM	RECIST	SCC, 33; ACA, 42; other, 3	III: 49, IV: 29	ERCC1 C118T, XPDLys751Gin
Li <i>et al</i> (2012) (27)	89	64/25	59 (21-84)	NA	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM, DDP + DOC	RECIST	SCC, 30; ACA, 43; other, 16	III: 18, IV: 59	ERCC1 C118T, XPDLys751Gin
Wang <i>et al</i> (2011) (28)	142	89/53	62 (43-81)	79/63	PCR-RFLP	DDP + NVB, DDP + TAX	RECIST	SCC, 82; ACA, 60	III: 96, IV: 46	ERCC1 C118T
Yang and Hang (2011) (29)	62	44/16	59 (35-77)	NA	PCR-LDR	DDP + GEM	RECIST	SCC, 23; ACA, 37	III: 26, IV: 34	ERCC1 C118T
Xu <i>et al</i> (2012) (30)	149	99/50	62 (28-83)	NA	PCR-LDR	DDP + NVB, DDP + TAX, DDP + GEM, DDP + DOC	RECIST	SCC, 52; ACA, 83; other, 14	III: 57, IV: 92	ERCC1 C118T
Wang <i>et al</i> (2010) (31)	90	63/27	55 (33-73)	NA	Direct sequencing	DDP + NVB, DDP + TAX, DDP + GEM, DDP + DOC	RECIST	SCC, 20; ACA, 69; other, 1	III: 30, IV: 60	ERCC1C8092A/ C118T
Chen and Xu (2009) (32)	95	76/19	58 (35-77)	67/28	PCR-LDR	DDP + NVB, DDP + TAX, DDP + GEM	RECIST	SCC, 51; ACA, 39; other, 5	III: 40, IV: 55	ERCC1 C118T
Ren <i>et al</i> (2009) (33)	130	74/56	61 (30-78)	NA	Direct sequencing	DDP + NVB, DDP + TAX, DDP + GEM	RECIST	SCC, 49; ACA, 81	III: 40, IV: 90	ERCC1 C118T
Hua <i>et al</i> (2011) (34)	64	42/22	58 (31-78)	NA	Direct sequencing	NA	RECIST	SCC, 22; ACA, 40; other, 2	III: 18, IV: 46	ERCC1 C118T
Zhou <i>et al</i>	130	74/56	61 (30-78)	73/57	TaqMan	DDP/CBP + NVB,	RECIST	SCC, 49; ACA, 81	III: 40,	ERCC1 C118T

Table I. Continued.

First author (year) (ref.)	Sample size	Male/ female	Median (or mean) (range) year	Smoking/ no-smoking	Genotyping methods	Chemotherapy	Evaluation criteria ^a	Histology	Clinical stage	Genotype studied
(2010) (35)						DDP/CBP + TAX, DDP/CBP + GEM			IV: 90	
Zhong <i>et al</i> (2008) (36)	210	158/51	57 (25-81)	NA	MALDI-TOF	DDP + NVB, DDP + TAX, DDP + GEM, DDP + DOC, DDP + GEM	RECIST	SCC, 38; ACA, 121; other, 40	III: 80, IV: 129	ERCCI C118T
Li <i>et al</i> (2010) (37)	115	78/37	60 (NA)	68/47	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM, DDP + DOC	WHO	SCC, 30; ACA, 82; other, 3	IIIb-IV: 115	ERCCI C118T, XPDLys751Gin
Liu <i>et al</i> (2008) (38)	94	71/23	60 (32-79)	NA	PCR-RFLP	DDP + TAX	WHO	SCC, 33; ACA, 42; other, 19	I-II: 12, III-IV: 82	ERCCI C118T
Liao <i>et al</i> (2012) (39)	62	35/27	57 (36-78)	NA	TaqMan	DDP + GEM	RECIST	SCC, 4; ACA, 52; other, 6	III: 10, IV: 52	ERCCI C118T/ C8092A, XPDLys751Gin
Hong <i>et al</i> (2013) (40)	135	90/45	56 (25-72)	77/58	TaqMan	DDP + GEM	RECIST	SCC, 39; ACA, 80; other, 16	III: 12, IV: 123	ERCCI C8092A/ C118T
Gao <i>et al</i> (2010) (41)	57	44/13	59 (38-77)	NA	PCR-RFLP	DDP + GEM	WHO	SCC, 12; ACA, 40; other, 5	II: 1, III: 22, IV: 34	ERCCI C118T
Jin <i>et al</i> (2010) (42)	73	59/14	59 (24-82)	NA	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM, DDP + DOC	WHO	SCC, 42; ACA, 28; other, 3	III: 30, IV: 43	ERCCI C118T
Su and Cao (2012) (43)	161	108/53	NA	88/73	TaqMan	DDP/CBP + NVB, DDP/CBP + DOC/TAX, DDP + GEM, DDP + PEM	WHO	SCC, 52; ACA, 82; other, 27	III: 55, IV: 106	ERCCI C118T
Wang <i>et al</i> (2012) (44)	101	60/41	53 (36-76)	54/47	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM	RECIST	SCC, 31; ACA, 68; other, 2	III: 17, IV: 84	ERCCI C118T
Li <i>et al</i> (2010) (45)	60	41/19	NA	37/23	TDI-FP	DDP + NVB, DDP + TAX, DDP + GEM	RECIST	SCC, 19; ACA, 37; other, 4	III: 35, IV: 25	ERCCI C118T
Zhou <i>et al</i> (2013) (46)	204	120/84	61 (45-75)	NA	MALDI- TOF-MS	DDP	RECIST	SCC, 89; ACA, 115	NA	ERCCI C118T
Sun <i>et al</i> (2009) (47)	113	76/37	60 (34-84)	NA	PCR-gene chip	DDP/CBP + GEM, DDP/CBP + NVB, DDP/CBP + TAX/TXT/DOC	WHO	SCC, 30; ACA, 80; other, 3	NA	ERCCI C118T, XPDLys751Gin
KimCurran <i>et al</i> (2011) (48)	300	201/99	60 (33-78)	157/143	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM	RECIST	SCC, 88; ACA, 168; other, 44	NA	ERCCI C8092A
Yuan <i>et al</i>	200	130/70	56 (30-74)	NA	PCR-RFLP	DDP + NVB, CBP + NVB,	WHO	SCC, 37; ACA, 143;	III: 49,	XPDLys751Gin,

Table I. Continued.

First author (year) (ref.)	Sample size	Male/ female	Median (or mean) age and (range) year	Smoking/ no-smoking	Genotyping methods	Chemotherapy	Evaluation criteria ^a	Histology	Clinical stage	Genotype studied
(2006) (49)						CBP + TAX, DDP + TAX/TXT		other, 20	IV: 151	ERCC1C8092A
Chen <i>et al</i> (2012) (50)	355	248/107	60 (32-78)	202/153	TaqMan	DDP/CBP + NVB, DDP/CBP + GEM, DDP/CBP + TAX/TXT	RECIST	SCC, 99; ACA, 201; other, 55	III: 118, IV: 237	XPDLys751Gin
Yao <i>et al</i> (2009) (51)	108	71/37	61 (39-79)	NA	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM, DDP + TXT	WHO	SCC, 28; ACA, 77; other, 3	III: 37, IV: 71	XPDLys751Gin
Wu <i>et al</i> (2012) (52)	353	246/107	57 (32-80)	199/154	Direct sequencing	DDP + NVB, DDP + TAX, DDP + GEM, DDP + TXT	NA	SCC, 75; ACA, 213; other, 67	III: 141, IV: 212	XPDLys751Gin
Zhang <i>et al</i> (2013) (53)	62	38/24	58 (37-72)	NA	Direct sequencing	DDP + NVB, DDP + TAX, DDP + GEM, DDP + MTA	RECIST	SCC, 13; ACA, 39; other, 10	NA	XPDLys751Gin
Fan <i>et al</i> (2008) (54)	81	63/18	63 (55-80)	NA	PCR-RFLP	DDP + NVB, DDP + TAX/TXT, DDP + GEM	WHO	SCC, 21; ACA, 44; other, 16	III: 34, IV: 47	XPDLys751Gin
Chen <i>et al</i> (2011) (55)	87	54/33	60 (43-81)	NA	PCR-RFLP	DDP + NVB, DDP + TAX, DDP + GEM, DDP + MTA	WHO	SCC, 52; ACA, 35	III: 58, IV: 29	XPDLys751Gin
Ren <i>et al</i> (2012) (56)	340	232/108	60 (30-78)	184/156	TaqMan	DDP + NVB, DDP + GEM, DDP + TAX/TXT	RECIST	SCC, 145; No-SCC, 195	III: 111, IV: 229	XPDLys751Gin
Sun <i>et al</i> (2007) (57)	96	62/34	58 (34-77)	NA	PCR-cDNA chip	NA	WHO	SCC, 39; ACA, 57	NA	XPAG23A
Jia <i>et al</i> (2011) (58)	89	45/44	NA	NA	DNA sequencing	DDP/CBP + DOC, DDP/CBP + GEM	RECIST	SCC, 39; ACA, 44; other, 6	III: 22, IV: 67	XPAG23A, XPGHis46His
Feng <i>et al</i> (2009) (59)	115	78/37	60 (34-84)	NA	DNA microarray genotyping	DDP/CBP + TAX, DDP/CBP + GEM, DDP/CBP + NVB	WHO	SCC, 30; ACA, 82; other, 3	NA	XPAG23A, XPGHis46His
Zhang <i>et al</i> (2013) (60)	475	306/145	64 (32-76)	NA	TaqMan	DDP + DOC, DDP/CBP + GEM, DDP/CBP + NVB	EORTC	SCC, 169; ACA, 256; other, 27	III: 159, IV: 292	XPGHis46His
Lv <i>et al</i> (2012) (61)	85	49/36	56 (36-71)	NA	DNA sequencing	DDP + DOC, DDP + GEM, DDP + NVB, DDP + MTA	RECIST	SCC, 34; ACA, 43; other, 8	NA	XPGHis46His
Sun <i>et al</i> (2009) (62)	82	53/29	59 (34-79)	NA	DNA microarray genotyping	DDP/CBP + TAX/TAT/DOC, DDP/CBP + GEM, DDP/CBP + NVB	WHO	SCC, 16; ACA, 61; other, 5	IV: 82	XPGHis46His

^aTumor response adopting to Response Evaluation Criteria in Solid Tumors (RECIST) or World Health Organization (WHO) criteria. NSCLC, non-small cell lung cancer; NA, ; PCR, polymerase chain reaction; RFLP, restriction fragment length polymorphism; DDP, cisplatin; NVB, vinorelbine; TXT, docetaxel; GEM, gemcitabine; SCC, squamous cell carcinoma; ACA, adenocarcinoma; TAX, paclitaxel; DOC, taxotere or docetaxel; GP, ; TP, ; LDR, ; CBP, carboplatin; MALDI, ; TOF, ; TDI, ; FP, ; MS, ; MTA, pemetrexed; EORTC, European Organization for Research and Treatment of Cancer.

Table II. Summary of the risk ratios (RRs) and 95% confidence intervals (CIs) of the non-small cell lung cancer risk for contrasts (non-response, stable disease or progressive disease).

Genetic model	No. of studies	Pooled RR (95% CI)	P-value	Heterogeneity		Begg's test (P-value)	Egger's test (P-value)
				P-value	I ² (%)		
ERCC1 C118T							
Homozygote comparison (TT vs. CC)	8	1.01 (0.70-1.45)	0.976	0.0112	61.00	0.174	0.028
Heterozygote comparison (CT vs. CC)	8	0.91 (0.78-1.05)	0.199	0.046	51.10	0.711	0.251
Dominant (CT/TT vs. CC)	21	0.95 (0.85-1.06)	0.386	0.0	66.90	0.786	0.973
Recessive (TT vs. CC/CT)	11	1.06 (0.91-1.23)	0.463	0.083	39.80	0.213	0.029
ERCC1 C8092A							
Homozygote comparison (AA vs. CC)	3	1.09 (0.88-1.35)	0.412	0.899	0.0	1.000	0.53
Heterozygote comparison (CA vs. CC)	3	0.94 (0.81-1.1)	0.431	0.447	0.0	0.296	0.106
Dominant (AA/CA vs. CC)	8	1.11 (0.91-1.35)	0.328	0.754	0.0	0.296	0.044
Recessive (AA vs. CC/CA)	3	0.96 (0.88-1.05)	0.377	0.959	0.0	0.266	0.397
XPD Lys751Gln							
Homozygote comparison (GlnGln vs. LysLys)	3	1.21 (0.92-1.59)	0.183	0.9	0.00	1.000	0.065
Heterozygote comparison (LysGln vs. LysLys)	7	1.08 (0.96-1.22)	0.182	0.175	33.10	0.548	0.828
Dominant (GlnGln/LysGln vs. LysLys)	12	1.02 (0.92-1.13)	0.714	0.052	43.70	0.837	0.665
Recessive (GlnGln vs. LysLys/LysGln)	3	1.16 (0.89-1.52)	0.272	0.925	0.0	1.000	0.022

was detected in Egger's test with $P > 0.05$ (Table II). The shape of the funnel plot did not reveal any evidence of clear asymmetry (data not shown).

Tumor response of XPA A23G and XPG C46T polymorphisms (non-response: SD or PD). Three studies were included with a total sample size of 300 patients. Overall, this meta-analysis showed that there was no statistically significant association between the XPA A23G polymorphism and tumor response for the recessive model (GG/AG vs. AA: RR=0.99, 95% CI: 0.65-1.52, $P=0.969$, $I^2=80.8\%$ for heterogeneity test; Table IV). The other three models were not performed as there was no data of interest or raw data.

For the XPG C46T polymorphism, five studies were included with a total sample size of 846 patients. Overall, the meta-analysis showed that there was an increase in the statistically significant association between the XPG C46T polymorphism and tumor response for the three genetic models (TT vs. CC: RR=1.31, 95% CI: 1.14-1.5, $P=0.00$, $I^2=0\%$ for heterogeneity test; the recessive model, TT vs. CC/CT: RR=1.22, 95% CI: 1.11-1.36, $P=0.00$, $I^2=0\%$ for heterogeneity test; and the dominant model, TT/CT vs. CC: RR=1.23, 95% CI: 1.11-1.36, $P=0.00$, $I^2=0\%$ for heterogeneity test, Table IV). The XPG C46T polymorphism had no association with tumor response in the heterozygote comparison (CT vs. CC: RR=1.1, 95% CI: 0.97-1.25, $P=0.136$, $I^2=0\%$ for heterogeneity test). In addition, no publication bias was detected in Egger's test with all $P > 0.05$ (Table IV). The shape of the funnel plot did not reveal any evidence of clear asymmetry (data not shown).

Discussion

A total of 44 studies with 5,944 NSCLC patients were included that examined the ERCC1 C118T/C8092A, ERCC2/XPB A751C,

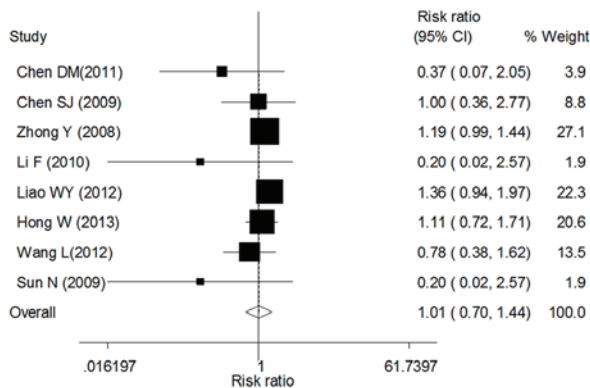
XPA G23A and XPG C46T polymorphisms. To the best of our knowledge, this is the first meta-analysis elaborating the role of NER gene polymorphisms on the prognosis of platinum-based chemotherapy in Chinese NSCLC patients. However, the overall combined RRs did not support any appreciable association between the ERCC1 C118T/C8092A, XPB A751C and XPA G23A polymorphisms on the prognosis of platinum-based chemotherapy under the four genetic contrast models when SD or PD was defined as non-response, which was consistent with previous meta-analyses (63,64). Additionally, no significant association was obtained for the ERCC1 C118T polymorphisms when only PD was considered as non-response. However, elevated associations were observed for the homozygote, dominant and recessive comparisons in the XPG C46T polymorphism, indicating that such gene carriers were more susceptible to platinum-based chemotherapy in Chinese patients with NSCLC.

NER is a highly versatile pathway that is primarily responsible for repairing DNA damage by removing the majority of DNA damage through incisions on both sides of the lesion. The NER pathway is a significant defense mechanism in humans for protection from two major carcinogens; sunlight and cigarette smoke (65). NER has two systems: The repair of strand distortions of the genome by global genome repair and the removal of distorted lesions that block elongating RNA polymerases by transcription-coupled repair (66). There are >30 proteins involved in the NER pathway (67). The removal of these platinum adducts, which results in resistance to chemotherapy, is mainly carried out through NER and due to the deficiency of NER, cells are hypersensitive to platinum (68). For the platinum-chemotherapy resistance of NSCLC, there is still no definite predictive biomarker. Regarding the ERCC1 C118T/C8092A and XPB A751C polymorphisms on the prognosis of platinum-based chemotherapy in patients with NSCLC, several meta-analyses are available although with inconsistent conclusions from each other (1,63-64,69-70),

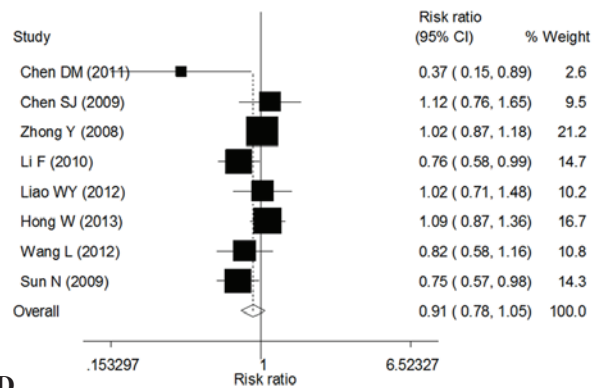
Table III. Summary of the risk ratios (RRs) and 95% confidence intervals (CIs) of the non-small cell lung cancer risk for contrasts (non-response, progressive disease).

Genetic model	No. of studies	Pooled RR (95% CI)	P-value	Heterogeneity		Begg's test (P-value)	Egger's test (P-value)
				P-value	I ² (%)		
ERCC1 C118T							
Homozygote comparison (TT vs. CC)	3	0.65 (0.30-1.41)	0.276	0.234	31.20	1.000	0.687
Heterozygote comparison (CT vs. CC)	3	1.00 (0.50-2.00)	0.995	0.018	75.00	0.296	0.245
Dominant (CT/TT vs. CC)	7	0.83 (0.64-1.07)	0.149	0.142	37.60	0.368	0.283
Recessive (TT vs. CC/CT)	3	0.67 (0.31-1.44)	0.304	0.545	0.00	1.000	0.803

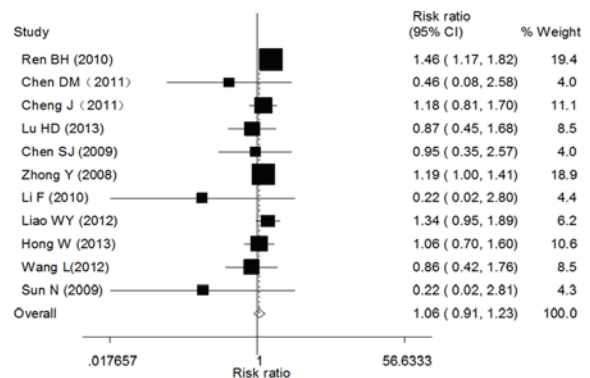
A



B



C



D

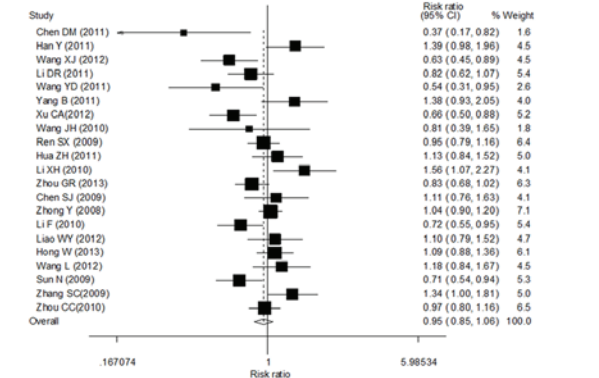


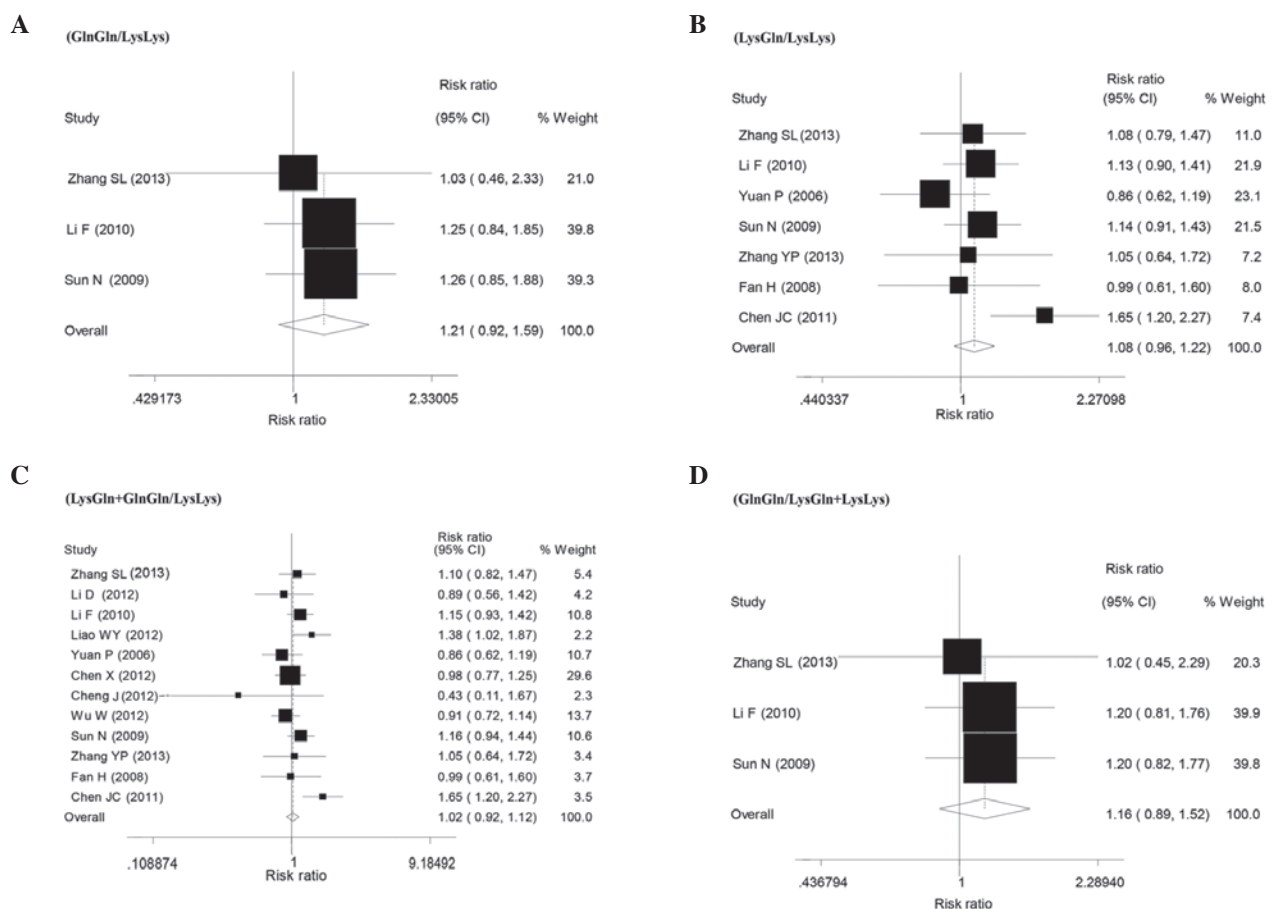
Figure 2. Risk ratios (RRs) and 95% confidence intervals (CIs) of the individual studies and pooled data for the association between the *ERCC1 C118T* gene polymorphism and non-small cell lung cancer. The summary of the pooled RR is indicated by a diamond and horizontal lines represent the 95% CI. (A) T/T vs. C/C; (B) C/T vs. C/C; (C) T/T+C/T vs. C/C; and (D) T/T vs. C/T+C/C.

and certain evidence was found to support the use of the *ERCC1 C118T/C8092A* and *XPD A751C* polymorphisms as prognostic predictors of platinum-based chemotherapies in NSCLC. However, its role in Chinese NSCLC patients has not been well-established. Therefore, a meta-analysis of published studies was performed with the aim of clarifying the correlation between five common polymorphisms of four NER genes and prognosis of platinum-based chemotherapy among Chinese NSCLC patients. However, the result showed that the tumor response rate was not significant in patients for *ERCC1 C118T/C8092A*, *XPD A751C*

and *XPA G23A* polymorphisms. More interactions of genetic variations and the gene-environment may also be attributed to the prognosis regarding *ERCC1*, *XPD* and *XPA*. Due to these similar mechanisms, the linkage disequilibrium with other genes should be taken into account. The combination with other gene polymorphisms may result in no significant difference. Additionally, unknown regions may contribute to the potential mechanism of *ERCC1*, *XPD* and *XPA* polymorphisms. Regarding the *XPG* polymorphism, the total sample size was limited and the positive results required further confirmation.

Table IV. Summary of the risk ratios (RRs) and 95% confidence intervals (CIs) of the non-small cell lung cancer risk for contrasts (non-response, stable disease or progressive disease).

Genetic model	No. of studies	Pooled RR (95% CI)	P-value	Heterogeneity		Begg's test (P-value)	Egger's test (P-value)
				P-value	I ² (%)		
XPA A23G							
Recessive (GG/AG vs. AA)	3	0.99 (0.65-1.52)	0.969	0.001	80.80	0.734	0.694
XPG C46T							
Homozygote comparison (TT vs. CC)	3	1.31 (1.14-1.5)	0.000	0.915	0.00	0.296	0.136
Heterozygote comparison (CT vs. CC)	3	1.10 (0.97-1.25)	0.136	0.651	0.00	1.000	0.791
Dominant (TT/CT vs. CC)	5	1.23 (1.11-1.36)	0.000	0.480	0.00	0.806	0.143
Recessive (TT vs. CC/CT)	3	1.22 (1.11-1.36)	0.000	0.564	0.00	1.000	0.907

Figure 3. Risk ratios (RRs) and 95% confidence intervals (CIs) of the individual studies and pooled data for the association between the *XPD Lys751Gln* gene polymorphism and non-small cell lung cancer. The summary of the pooled RR is indicated by a diamond and horizontal lines represent the 95% CI. (A) GlnGln/LysLys; (B) LysGln/LysLys; (C) LysGln + GlnGln/LysLys; and (D) GlnGln/LysGln + LysLys.

Potential limitations of the current study should be acknowledged. First, heterogeneity is a noteworthy issue in a meta-analysis and one of the most significant goals of meta-analysis is identifying the sources of heterogeneity. The study on the *XPD A751C* and *XPA A23G* polymorphism observed evidence of significant heterogeneity. A large heterogeneity between studies was always identified in certain comparisons, which could interfere with the interpretation of the findings of a meta-analysis. There may be additional

potential sources of heterogeneity besides the aforementioned reason, however, owing to a lack of access to original source data, these sources were not investigated further in subgroup analyses according to ethnicity. Second, although evaluation of specific potential confounding factors was attempted, including age distribution, gender, nutrition, alcohol abuse, family history, lifestyle, dietary habits, body mass index, smoking status and stress, the similar environmental conditions and the definition of each stratum varied among studies and were

reported in only a limited number of studies. A more precise analysis should be conducted based on the adjusted estimates. Third, owing to only published studies being included in the meta-analysis, it is extremely possible that other unpublished studies and published studies in languages other than English and Chinese may have been omitted. Therefore, the possibility of a larger sample size and increased statistical power may have been missed. Fourth, the meta-analysis is based on unadjusted estimates, and the availability of individual data potentially allows for more precise analysis. Owing to a lack of interest/complementary data, the opportunity allowing for an adjustment estimate was lost (at least for age and smoking). Fifth, little observation on the gene-gene and gene-environment interactions may be responsible for the unstable results. Notably, the majority of these studies were retrospective studies. Additionally, as a significant impact factor, the tumor description, including classification and stages, may also be accountable for the inconsistent results. The analysis also failed to demonstrate the influence of the *ERCC1*, *XPD*, *XPG* and *XPA* polymorphisms on survival and progression-free survival rates with a lack of interest/complementary data. Taking these potential limitations into consideration, the results may not have enough statistical power to explore the association of these polymorphisms with NSCLC susceptibility.

In conclusion, no evidence was found to support the use of the *ERCC1 C118T/C8092A*, *XPD Lys751Gln* and *XPA A23G* polymorphisms as prognostic predictors of platinum-based chemotherapies in NSCLC treatment based on the current published data in the meta-analysis. For the *XPG C46T* polymorphism, there was a significant association with an objective response detected. However, occasional studies could not be ruled out due to the limited number of subjects examined and observation of between-study heterogeneity. Additional genetic epidemiological investigations that are well designed and have large samples for these findings are required for the association between biomarkers and tumor prognosis.

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