Polymorphisms in XPD Gene Could Predict Clinical Outcome of Platinum-Based Chemotherapy for Non-Small Cell Lung Cancer Patients: A Meta-Analysis of 24 Studies

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Abstract

Objective: Xeroderma pigmentosum group D (XPD) is an essential gene involved in the nucleotide excision repair (NER) pathway. Two commonly studied single nucleotide polymorphisms (SNPs) of XPD (Lys751Gln, A>C, rs13181; Asp312Asn, G>A, rs1799793) are implicated in the modulation of DNA repair capacity, thus related to the responses to platinum-based chemotherapy. Here we performed a meta-analysis to better evaluate the association between the two XPD SNPs and clinical outcome of platinum-based chemotherapy in non-small cell lung cancer (NSCLC) patients.

Methods: A comprehensive search of PubMed database was conducted to identify relevant articles. Primary outcomes included objective response (i.e., complete response + partial response vs. stable disease + progressive disease), progression-free survival (PFS) and overall survival (OS). The pooled and 95% confidence intervals (CIs) of ORs (odds ratios) and HRs (hazard ratios) were estimated using the fixed or random effect model.

Results: Twenty-four studies were eligible according to the inclusion criteria. None of the XPD Lys751Gln/Asp312Asn polymorphisms was associated with objective response, PFS or OS in NSCLC patients treated with platinum drugs. However, stratified analysis by ethnicity, the XPD Lys751Gln (A>C) polymorphism was not significantly associated with increased response in Caucasians (OR = 1.35, 95%CI = 1.0–1.83, P = 0.122 for heterogeneity) but was associated with decreased PFS in Asians (HR = 1.39, 95%CI = 1.07–1.81, P = 0.079 for heterogeneity). Furthermore, a statistically significant difference existed in the estimates of effect between the two ethnicities (P = 0.014 for TR; P<0.001 for PFS).

Conclusions: XPD Lys751Gln (A>C) may have inverse predictive and prognostic role in platinum-based treatment of NSCLC according to different ethnicities. Further studies are needed to validate our findings.

Introduction

Lung cancer remains the most frequent human malignancy worldwide and represents a leading cause of cancer related death with only 15% of patients surviving five years or more [1]. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of primary lung cancer and most patients have suffered from advanced disease at the time of diagnosis [2]. Currently, the standard chemotherapeutic regimen for the treatment of advanced NSCLC patients is based on the combination of platinum compounds and a third-generation cytotoxic agent [3]. However, there is considerable heterogeneity in therapeutic efficacy of platinum-based chemotherapy between different patients, and the response rate of platinum doublets is only 25–30% in NSCLC [4]. Apart from clinical factors including patient age, performance status and pathologic stages, genetic variance contributes significantly to the variability in individual response to platinum based chemotherapy in NSCLC patients [5,6]. In addition, recent evidence has suggested that genetic polymorphisms are associated with the development and progression of lung cancer [7,8]. Therefore, there is an urgent need to identify genetic markers that
could predict the risk of lung cancer and the response of patients to platinum based chemotherapy.

Platinum agents exert anti-cancer activity mainly through the formation of DNA adducts, which inhibit DNA replication and eventually hinder cell division [9].

Nucleotide excision repair (NER) is a predominant pathway responsible for removing platinum-induced DNA lesions [10]. Thus the modification of NER pathway may have impact on tumor sensitivity to platinum based chemotherapy, and consequently influence clinical outcome and patient survival [11–13]. The *xeroderma pigmentosum group D* (*XPD*, also named *excision repair cross-complementing group 2, ERCC2*) gene encodes for an ATP-dependent DNA helicase, a subunit of the basal transcription factor II H (TFII H) which mediates DNA unwinding for the initiation of NER [14]. *XPD* Asp312Asn and Lys751Gln are two common nonsynonymous single nucleotide polymorphisms (SNPs) in coding region of *XPD* gene and have been associated with impaired DNA repair capacity [12,15,16]. In recent years, a great number of molecular epidemiological studies have investigated the relationship of *XPD* polymorphisms with treatment response in NSCLC. While a possible role of the two SNPs as the predictor of response in advanced NSCLC is indicated, the results available in individual literature are inconsistent [17,18]. Thus, we performed this meta-analysis to evaluate the effects of *XPD* Asp312Asn (G>A) and Lys751Gln (A>C) polymorphisms on the efficacy of platinum-based chemotherapy in advanced NSCLC by assessing therapeutic response (TR), progression-free survival, and overall survival.

**Materials and Methods**

**Search strategy and study selection**

The identification of potentially relevant studies was performed through a search in electronic database PubMed using the following terms “*XPD* or *ERCC2*” and “lung neoplasm or non-small cell lung cancer” and “prognosis or outcome or survival or efficacy or response”. The latest search was updated on August 20, 2013. Bibliographies of eligible studies, review articles and other relevant publications were also reviewed to identify all potential studies.

Articles published in English peer-reviewed journals that provided outcome data stratified by *XPD* polymorphic variants were included. The detailed eligible criteria were as follows: (1) patients with histologically or pathologically confirmed advanced, recurrent, or metastatic NSCLC; (2) the patients were treated with platinum-based chemotherapy; (3) *XPD* Lys751Gln (rs13181) or Asp312Asn (rs1799793) single nucleotide polymorphism was genotyped; (4) studies provided primary outcomes of interest including objective response, progression-free survival or overall survival. The studies were excluded from the analysis if any of the cases occurred: (a) platinum-based chemotherapy was used as neoadjuvant treatment; (b) critical information was missing or could not be obtained by our repeated requests.

**Data extraction**

Two investigators (Qin Qin and Chi Zhang) independently screened the studies and extracted the data from included studies by using standard data-abstraction forms. Disagreements were resolved through discussion with another investigator (Hongcheng Zhu). For each study, the following characteristics and information were collected: name of the first author, year of publication, country of origin, ethnicity, the number of enrolled patients, treatment protocol, clinical stage, outcome, and SNPs included in each study. In addition, response to chemotherapy according to genotypes, hazard ratios (HRs) for OS and PFS, and their 95% confidence intervals (CIs) were collected for statistical analysis. If a direct report of HR and 95% CI was not available [19], estimated value was derived indirectly from Kaplan-Meier curves using the methods described by Tierney et al. [20]. Survival rates on Kaplan-Meier curves were read by Engauge Digitizer version 4.1
Table 1. Studies included in this meta-analysis.

| Study            | Year | Country | Ethnicity | Drug                  | Case N | Stage   | Outcome | SNPs of XPD | HWE |
|------------------|------|---------|-----------|-----------------------|--------|---------|----------|-------------|-----|
| Cheng et al.[29] | 2013 | China   | Asian     | Platinum-based        | 115    | IIIB-IV | OS/PFS   | Lys751Gln   | 0.76|
| Li et al.[30]    | 2013 | China   | Asian     | Platinum-based        | 496    | IIIA-IV | TR/OS/PFS| Lys751Gln and Asp312Asn |
| Chen et al.[31]  | 2012 | China   | Asian     | Platinum-based        | 355    | IIIB-IV | TR       | Lys751Gln   | >0.05|
| Li et al.[32]    | 2012 | China   | Asian     | Platinum-based        | 89     | IIIA-IV | TR       | Lys751Gln   | 0.53|
| Liao et al.[33]  | 2012 | China   | Asian     | Gemcitabine+platinum  | 62     | IIIB-IV | TR/OS    | Lys751Gln and Asp312Asn | 0.74/0.89|
| Provencio et al.[34] | 2012 | Spain   | Caucasian | Vinorelbine+cisplatin | 180    | IIIB-IV | TR/PFS   | Lys751Gln and Asp312Asn | <0.05/0.48|
| Wu et al.[35]    | 2012 | China   | Asian     | Platinum-based        | 353    | IIIA-IV | TR/OS    | Lys751Gln and Asp312Asn | >0.05|
| Ren et al.[36]   | 2012 | China   | Asian     | Platinum-based        | 340    | IIII-IV | OS       | Lys751Gln   | >0.05|
| Zhang et al.[37] | 2012 | China   | Asian     | Gemcitabine+cisplatin | 632    | I-IV    | OS       | Lys751Gln and Asp312Asn | 0.83/0.58|
| Ludovini et al.[38] | 2011 | Italy   | Caucasian | Cisplatin+ gemcitabine/ taxol/vinorelbine | 192    | IIIB-IV | TR/OS/PFS| Lys751Gln   | >0.05|
| Mathiaux et al.[19] | 2011 | France  | Caucasian | Platinum-based        | 85     | IIIA-IV | PFS      | Lys751Gln   | -   |
| Viñoles et al.[39] | 2011 | Spain   | Caucasian | Cisplatin+vinorelbine  | 94     | IIIB-IV | TR/OS/PFS| Lys751Gln and Asp312Asn | 0.07/0.19|
| Liu et al.[40]   | 2011 | China   | Asian     | Platinum-based        | 199    | IIIIA-IV| OS/PFS   | Lys751Gln   | 0.22|
| Li et al.[41]    | 2010 | China   | Asian     | Platinum-based        | 115    | IIIB-IV | TR       | Lys751Gln   | >0.05|
| Kalikaki et al.[42] | 2009 | Greece  | Caucasian | Platinum-based        | 119    | IIIA-IV | TR/OS    | Lys751Gln and Asp312Asn | >0.05|
| Yao et al.[43]   | 2009 | China   | Asian     | Platinum-based        | 108    | IIIB-IV | TR/OS    | Lys751Gln   | 0.28|
| Gandara et al.[44] | 2009 | USA     | Both      | Paclitaxel+carboplatin | 381    | IIIB-IV | TR/OS/PFS| Lys751Gln   | >0.05|
| Tibaldi et al.[18] | 2008 | Italy   | Caucasian | Gemcitabine+cisplatin  | 65     | IIIB-IV | TR/OS/PFS| Lys751Gln and Asp312Asn | >0.05|
| Booton et al.[45] | 2006 | UK      | Caucasian | Carboplatin+docetaxel | 108    | III-IV  | TR/OS    | Lys751Gln and Asp312Asn | 0.89/0.39|
| Penas et al.[20] | 2006 | Spain   | Caucasian | Gemcitabine+cisplatin  | 132    | IIIB-IV | OS/PFS   | Lys751Gln and Asp312Asn | >0.05|
| Isla et al.[17]  | 2004 | Spain   | Caucasian | Cisplatin+docetaxel   | 62     | IIIB-IV | TR/OS/PFS| Lys751Gln and Asp312Asn | 0.95|
| Ryu et al.[46]   | 2004 | Korea   | Asian     | Cisplatin+paclitaxel/ docetaxel/ gemcitabine | 107    | IIIB-IV | TR       | Lys751Gln and Asp312Asn | 0.54/0.69|
| Gurubhagavatula et al.[12] | 2004 | USA     | Caucasian | Platinum-based        | 103    | IIIA-IV | OS       | Asp312Asn   | >0.05|
| Camps et al.[47] | 2003 | Spain   | Caucasian | Gemcitabine+cisplatin  | 33     | IIIB-IV | TR       | Lys751Gln   | <0.05|

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(http://digitizer.sourceforge.net/), then the data read from Kaplan-Meier curves were entered in the calculation spreadsheet appended to Tierney’s paper.

Statistical methods

The odds ratio (OR) with its 95% CI were estimated to show the strength of the association between XPD polymorphism and objective response [CR (complete response) +PR (partial response)] in each study. Response to chemotherapy was assessed with RECIST [21] (Response Evaluation Criteria in Solid Tumors) criteria or WHO criteria every 2 or 3 treatment cycles. Stata SE 11.0 software was used to obtain pooled statistics for HRs of survival or ORs of chemotherapy response. The statistical significance of the pooled estimates was examined by Z test. The initial analyses were performed with a fixed effect model assuming homogeneity of the individual HRs. The assumption was tested by performing Cochran Q-test for heterogeneity. The effect of heterogeneity was tested by performing I2 test. A significant I2 test (P<0.05) or I2>50% indicated the heterogeneity among the studies, and the random-effect model was applied for meta-analysis.

Sub-group analyses were performed according to ethnicities. The differences in the effect estimates between subgroups were compared as described by Altman et al. [22]. Begger’s funnel plots and the Egger’s linear regression tests were used to evaluate the potential publication bias. All P values were 2-sided, and all analyses were carried out with Stata SE 11.0 software package.

Results

A total of 61 related papers were identified by initial screening (as of August 20, 2013), and 28 reports were identified after further
Figure 2. Forest plot of objective response and survival in NSCLC patients treated with platinum-based chemotherapy according to XPD Lys751Gln polymorphism (A/C/C vs. A/A). (A) objective response; (B) OS; (C) PFS.

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examined. Two studies were excluded because all patients were not treated with platinum-based chemotherapy. Moreover, two studies were excluded from the analysis because the data were inestimable and the authors were unreachable. As a result, 24 studies including 4,468 NSCLC patients were eligible for inclusion in our meta-analysis. The process of selecting publications was presented in Fig. 1 and the characteristics of the included studies were listed in Table 1. A total of 17 studies including 2,919 patients reported the correlation between XPD polymorphisms and treatment response, 11 studies including 2,001 patients reported XPD polymorphisms and PFS, and 17 studies including 3,561 patients reported XPD polymorphisms and OS.

XPD Lys751Gln (rs13181A>C)

**Objective response.** Fifteen studies including 2,383 patients were qualified for analyzing the association between XPD Lys751Gln polymorphism and TR in NSCLC patients. In the dominant model, the minor variant C was not associated with objective response in all patients (Table 2, Fig. 2). The ORs in homozygous and heterozygous models were similar to those in dominant model (Table 2). However, stratified analysis by ethnicity showed a significant difference in the estimates of effect between Caucasians and Asians in dominant model (P = 0.014). The C/C and A/C genotypes of XPD751 were borderline associated with favorable objective response in Caucasian patients treated with platinum-based regimen (C/C + A/C vs. A/A: OR = 1.35, P = 0.05; Fig. 3); while the variant allele appeared to show an inverse association in Asian patients (C/C + A/C vs. A/A: OR = 0.80, P = 0.129; Fig. 3). No publication bias was detected according to the results of funnel plot and the Egger’s test (C/C + A/C vs. A/A: P_{Begg} = 0.767; P_{Egger} = 0.748; Fig. 4).

**Overall survival.** Data from 16 included studies (including 3,456 patients) were applicable for the analysis. As shown in Fig 2B, the variant genotype of XPD751 was associated with a nonsignificant increase of hazard for death in all patients (C/C + A/C vs. A/A: HR = 1.03, P = 0.631; C/C vs. A/A: HR = 1.29, P = 0.198; A/C vs. A/A: HR = 1.09, P = 0.369; Table 2). Likewise, stratified analysis by ethnicity showed no significant correlation between XPD Lys751Gln polymorphism and overall survival in Asian or Caucasian patient (Fig. 3). No publication bias was detected by either the funnel plot or Egger’s test (C/C + A/C vs. A/A: P_{Begg} = 0.246; P_{Egger} = 0.512; Fig. 4).

**Progression-free survival.** A total of 11 studies (including 2,001 patients) were eligible for inclusion in the analysis. The pooled results showed no significant association between XPD Lys751Gln polymorphism and PFS under either kinds of genetic model (Table 2, Fig. 2). Nevertheless, subgroup analysis by ethnicity showed a significant increase in the hazard of progression in Asian patients (C/C + A/C vs. A/A: HR = 1.39, P = 0.015; Fig 3). Further comparison indicated remarkably significant difference in the estimate of effect between Asian and Caucasian populations (P<0.001). No significant publication bias was detected by either the funnel plot or Egger’s test (C/C + A/C vs. A/A: P_{Begg} = 0.118; P_{Egger} = 0.131; Fig. 4).

**XP**D Asp312Asn (rs1799793G>A)

**Objective response.** Ten studies including 1,588 patients were eligible for the final analysis. Pooled data from all patients indicated that the variant A allele was not associated with objective response under either genetic model (Fig. 5; Table 2). In addition, stratified analysis by ethnicity did not demonstrate significant difference (A/A vs. A/G vs. G/G: OR = 0.95, P = 0.233 for Asians; OR = 0.95, P = 0.761 for Caucasians). No publication bias was detected by either the funnel plot or the Egger’s test (A/A vs. A/G vs. G/G: P_{Begg} = 0.602; P_{Egger} = 0.353).

**Overall survival.** Nine studies including 2,053 subjects were included for the final analysis. Among them, 4 studies used dominant model, 5 studies used homozygous model, and 6 used heterozygous model. The data of included studies were combined according to the genetic model, respectively. The pooled outcome indicated that the A/A genotype was marginally associated with a poorer OS compared with G/G genotype (A/A vs. G/G: HR = 1.29, P = 0.055). No association was found in the other two genetic models (Fig 5; Table 2). There was no publication bias given the symmetrical distributions of the funnel plot or the Egger’s test (A/A vs. A/G: P_{Begg} = 0.308; P_{Egger} = 0.259).

**Progression-free survival.** Only three studies were eligible for the analysis of the association between XPD Asp312Asn polymorphism and PFS. In homozygous and heterozygous models, the HRs were 0.97 (P = 0.92) and 0.90 (P = 0.437), respectively (Table 2). No publication bias was detected in the funnel plots or Egger’s test (A/G vs. G/G: P_{Begg} = 1.0; P_{Egger} = 0.387).

**Discussion**

In this meta-analysis, we found no statistical evidence for an association between two XPD SNPs (Asp312Asn/Lys751Gln) and overall clinical outcomes of NSCLC patients treated with platinum-based chemotherapy. However, stratified analysis indicated an ethnic difference by showing that the A/C and C/C genotypes of XPD751 polymorphism were significantly associated with favorable objective response in Caucasian patients while a higher progression risk in Asian patients.

Although platinum-based doublet chemotherapy is currently considered as the standard care for first-line treatment of advanced NSCLC, a large proportion of patients display varying levels of resistance, indicating a remarkable individual variability in the therapeutic efficacy and prognosis. The heterogeneity could not be fully explained by currently used prognostic parameters in clinical setting such as TNM stage, performance status, and weight loss. Thus, identifying new biomarkers for better predictive and prognostic assessment is urgently needed. Single nucleotide polymorphisms are now considered as potential candidate biomarkers for cancer prognosis due to their modification of functions of critical genes involved in phenotypic drug sensitivity.

Mechanisms of platinum mediated cytotoxicity include the formation of bulky DNA adducts resulting in both inter- and intra-strand cross-links that block DNA replication and lead to cancer cell death. The platinum-DNA adducts are recognized and removed by the nucleotide excision repair (NER) pathway, which modulates platinum-based chemotherapeutic efficacy by removing platinum-produced DNA damage [23,24]. The DNA repair protein XPD has been identified as a critical molecular in DNA lesion removal by NER through exerting two primary functions (i) stabilization of the transcription factor complex TFIIH; and (ii) 5'→3' helicase function. Experimental evidence has indicated that XPD overexpression leads to bifunctional alkylating agent drug resistance and accelerated removal of interstrand cross-links [25]. Several common and putatively functional SNPs have been found

Figure 3. Subgroup analysis by ethnicity of objective response and survival in NSCLC patients treated with platinum-based chemotherapy according to XPD Lys751Gln polymorphism (A/C+C/C vs. A/A). (A) objective response; (B) OS; (C) PFS.

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Figure 4. Beggar’s funnel plot for the dominant model (A/C+C/C vs. A/A) of XPD Lys751Gln polymorphism. (A) objective response; (B) OS; (C) PFS. doi:10.1371/journal.pone.0079864.g004
Table 2. The association between XPD Lys751Gln and Asp312Asn polymorphisms and objective response, OS and PFS.

| XPD     | Objective response | Overall survival | Progression-free survival |
|---------|--------------------|------------------|--------------------------|
|         |                    | Study           | Pooled OR | P/Phet* | Study           | Pooled HR | P/Phet* | Study           | Pooled HR | P/Phet* |
| Lys751Gln |                    |                 |            |         |                |            |         |                |            |         |
| A/C vs. A/A | 10                | 1.05 (0.77–1.44) | 0.742/0.894 | 6       | 1.09 (0.91–1.30) | 0.369/0.446 | 4       | 1.02 (0.81–1.28) | 0.873/0.345 |
| C/C vs. A/A | 7                | 1.09 (0.49–2.44) | 0.828/0.059 | 5       | 1.29 (0.87–1.91) | 0.198/0.011 | 4       | 0.99 (0.64–1.53) | 0.948/0.084 |
| A/C+C/C vs. A/A |       |                |            |         |                |            |         |                |            |         |
| All       | 16                | 1.02 (0.83–1.26) | 0.818/0.104 | 13      | 1.03 (0.91–1.18) | 0.631/0.199 | 9       | 1.09 (0.94–1.27) | 0.267/0.287 |
| Asian     | 8                 | 0.80 (0.60–1.07) | 0.129/0.597 | 7       | 1.11 (0.94–1.31) | 0.217/0.062 | 3       | 1.39 (1.07–1.81) | 0.015/0.879 |
| Caucasian | 8                 | 1.35 (1.0–1.83)  | 0.050/0.122 | 6       | 0.92 (0.74–1.13) | 0.430/0.860 | 5       | 0.92 (0.74–1.13) | 0.418/0.477 |
| Asp312Asn |                    | Study           | Pooled OR | P/Phet* | Study           | Pooled HR | P/Phet* | Study           | Pooled HR | P/Phet* |
| A/G vs. G/G | 7                | 0.93 (0.63–1.37) | 0.718/0.665 | 6       | 1.03 (0.70–1.50) | 0.894/0.016 | 3       | 0.90 (0.69–1.17) | 0.437/0.609 |
| A/A vs. G/G | 5                | 0.98 (0.51–1.90) | 0.952/0.339 | 5       | 1.29 (0.99–1.69) | 0.055/0.324 | 2       | 0.97 (0.53–1.78) | 0.920/0.469 |
| A/G+A/A vs. G/G |       |                |            |         |                |            |         |                |            |         |
| All       | 10                | 0.87 (0.68–1.12) | 0.284/0.770 | 4       | 1.76 (0.89–3.55) | 0.101/0.001 | -       | -               | -            | -       |
| Asian     | 4                 | 0.81 (0.57–1.14) | 0.233/0.275 | -       | -               | -            | -       | -               | -            | -       |
| Caucasian | 6                 | 0.95 (0.67–1.35) | 0.761/0.905 | -       | -               | -            | -       | -               | -            | -       |

*Study: the number of studies included in the analysis.
*Phet: P value of between-study heterogeneity.
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in XPD encoding sequence, of which rs13181 and rs1799793 SNPs [Asp312Asn (G>A) and Lys751Gln (A>C), respectively] are associated with suboptimal DNA repair capacity [15,16]. Therefore, it is conceivable that the two functional SNPs of \textit{XPD} might reveal platinum sensitivity as an inborn trait, and have prognostic values among NSCLC patients treated with platinum agents. A number of molecular epidemiological studies have reported the relationship between \textit{XPD} SNPs and clinical outcome in NSCLC patients treated with platinum based chemotherapy. However, the estimates between the studies differed considerably and no consensus has yet been reached.

By pooling dataset of 24 studies investigating the predictive role of \textit{XPD} Asp312Asn (G>A) and Lys751Gln (A>C) in clinical outcome of NSCLC patients treated with platinum regimen, we
found that none of the two polymorphisms was related to TR, PFS or OS in overall population, which is consistent with the findings of the previous meta-analysis by Ming Yin et al. [26]. On the other hand, in our stratified analysis by ethnicity, it was striking to find that the XPD Lys751Gln polymorphism was significantly associated with favorable objective response in Caucasians but with unfavorable PFS in Asians, which was not reported in the previous meta-analysis. The discrepant results might be due to a significantly larger sample size (2,383 vs. 694 for TR; 2,001 vs. 640 for PFS) of our meta-analysis, which remarkably improves the statistical power to detect a significant association and subsequently draw a more reliable conclusion. Notably, there was an apparent discrepancy between Asians and Caucasians in the prognostic value of XPD rs13181 C allele, and the existence of ethnic difference was confirmed by statistical test (P < 0.05). The discrepancy could be explained by the fact that the treatment outcome of platinum agents may be influenced by gene-gene interaction from different genetic background and gene-environment interaction from different lifestyle. Moreover, other factors such as selection bias and different matching criteria may play a role.

Despite our efforts in performing a comprehensive and accurate analysis, limitations of our meta-analysis need to be pointed out. Firstly, differences in several characteristics of the study designs, including subject selection, chemotherapeutic protocol, and follow-up time may have caused wide heterogeneity in the results among included studies. Stratified analysis by the important host- or treatment-related factors would be helpful to reduce the heterogeneity and improve the quality of meta-analysis. However, few of the studies provided information about genotype distribution by subgroups, thus making such analyses impossible. Secondly, a proportion of estimates used in the analysis were unadjusted because not all included studies reported adjusted estimates. Even they did, the estimates were not adjusted by the uniform potential confounders. Thirdly, although toxicity is an important concern in the combinational therapy with platinum compounds in advanced NSCLC patients, the association between XPD SNPs and platinum toxicities was unable to be evaluated because few studies provided related data; even they did, different toxicity profiles were used in the studies. Finally, the role of gene-gene and gene-environment interactions was not considered in the present analysis due to our lack of access to the original data from the included studies.

Nevertheless, several advantages of our meta-analysis should be acknowledged. First, significant number of subjects pooled from various studies significantly increased statistical power of the analysis. This is the latest meta-analysis on the XPD polymorphisms on platinum-based chemotherapy in NSCLC patients. We have included 24 studies versus 22 studies included in a recent meta-analysis [27], and 12 studies included in a meta-analysis published in 2011 [28]. Second, we analyzed the association of XPD polymorphisms with PFS, which was not addressed in previous meta-analysis studies [27,28]. PFS is an important parameter that provides guidance for tumor chemotherapy. Thus our results will help predict prognosis of NSCLC patients. Third, the quality of studies included in this meta-analysis strictly satisfied our selection criteria, thus limiting the potential bias.

In conclusion, our meta-analysis indicated that XPD Lys751Gln polymorphism may be useful prognostic factors for assessing objective response and progression risk in advanced NSCLC patients treated with platinum-based regimen according to different ethnicities. However, further prospective studies with large sample size and long-term follow-up are required to confirm our findings. In addition, particular attention should be given to the role of gene-gene as well as gene-environment interactions in the modification of chemotherapy efficacy.

Supporting Information

Table S1 PRISMA checklist.

(DOC)

Author Contributions

Conceived and designed the experiments: QQ CZ XY HZ JL LZ XS. Performed the experiments: QQ CZ XY HZ BY JC HC. Analyzed the data: QQ CZ XY HZ JM JL ZL. Contributed reagents/materials/analysis tools: QQ CZ XY HZ BY JC HC JL LZ LX. Wrote the paper: QQ CZ XY XS.

References

1. Jemal A, Thomas A, Murray T, Thun M (2002) Cancer statistics, 2002. CA Cancer J Clin 52: 21–47.
2. Parkin DM, Pisani P, Ferlay J (1999) Estimates of the worldwide incidence of 25 major cancers in 1990. Int J Cancer 80: 827–841.
3. Einhorn LH (2008) First-line chemotherapy for non-small-cell lung cancer: is there a superior regimen based on histology? J Clin Oncol 26: 3485–3496.
4. Ardizzoni A, Boni L, Tiseo M, Fossella FV, Schiller JH, et al. (2007) Cisplatin–gemcitabine chemotherapy in first-line treatment of advanced non-small-cell lung cancer: an individual patient data meta-analysis. J Natl Cancer Inst 99: 847–857.
5. Liu L, Wu C, Wang Y, Zhong R, Duan S, et al. (2011) Combined effect of genetic polymorphisms in P53, P73, and MDM2 on non-small cell lung cancer survival. J Thorac Oncol 6: 1793–1800.
6. Liu L, Wu J, Zhong R, Wu C, Zou L, et al. (2012) Multi-loci analysis reveals the importance of genetic variations in sensitivity of platinum-based chemotherapy in non-small-cell lung cancer. Mol Carcinog.
7. Liu L, Wu J, Wu C, Wang Y, Zhong R, et al. (2011) A functional polymorphism (-1607 1G→2G) in the matrix metalloproteinase-1 promoter is associated with development and progression of lung cancer. Cancer 117: 5172–5181.
8. Ke J, Zhong R, Zhang T, Liu L, Rui R, et al. (2013) Replication study in Chinese population and meta-analysis supports association of the Sp15.33 locus with lung cancer. PLoS One 8: e62485.
9. van de Vaart PJ, Belderbos J, de Jong D, Sneeuw KC, Majoor D, et al. (2000) DNA-adduct levels as a predictor of outcome for NSCLC patients receiving daily cisplatin and radiotherapy. Int J Cancer 89: 160–166.
10. Wu Q, Christiansen LA, Lenerken RJ, Vasques KM (2005) Mismatch repair participates in error-free processing of DNA interstrand crosslinks in human cells. EMBO Rep 6: 551–557.
11. Azuma K, Konoohara Y, Sasada T, Terazaki Y, Berda J, et al. (2007) Excision repair cross-complementation group 1 predicts progression-free and overall survival in non-small cell lung cancer patients treated with platinum-based chemotherapy. Cancer Sci 98: 1336–1343.
12. Gurubhagavatula S, Liu G, Park S, Zhou W, Su L, et al. (2004) XPD and XRCC1 genetic polymorphisms are prognostic factors in advanced non-small-cell lung cancer patients treated with platinum chemotherapy. J Clin Oncol 22: 2594–2601.
13. Lord RV, Brajbinder J, Gandara D, Alberola V, Camps G, et al. (2002) Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res 8: 2296–2299.
14. Spitz MR, Wu X, Wang Y, Wang LE, Shive S, et al. (2001) Modulation of nucleotide excision repair capacity by XPD polymorphisms in lung cancer patients. Cancer Res 61: 1354–1357.
15. Duell EJ, Wiercze JK, Cheng TJ, Varkonyi A, Zuo ZF, et al. (2000) Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. Carcinogenesis 21: 965–971.
16. Lunn RM, Helzlouer KJ, Parshad R, Umbach DM, Harris EL, et al. (2000) XPD polymorphisms: effects on DNA repair proficiency. Carcinogenesis 21: 551–555.
17. Iida D, Sarris C, Rosell R, Alonso G, Domine M, et al. (2004) Single nucleotide polymorphisms and outcome in docetaxel/cisplatin-treated advanced non-small-cell lung cancer. Ann Oncol 15: 1194–1203.
18. Tsuchida G, Giovanetti E, Vasile E, Mey V, Lann AC, et al. (2008) Correlation of CDA, ERCC1, and XPD polymorphisms with response and survival in gemcitabine/cisplatin-treated advanced non-small cell lung cancer patients. Clin Cancer Res 14: 1797–1803.
31. Chen X, Sun H, Ren S, Kim Curran V, Zhang L, et al. (2012) Association of DNA repair gene polymorphisms with survival of advanced NSCLC patients treated with platinum-based chemotherapy. Lung Cancer 71: 191–198.
32. Li F, Sun X, Sun N, Qin S, Cheng H, et al. (2010) Association between XRCC1 and XPD gene polymorphisms on platinum-based chemotherapy in non-small cell lung cancer. Am J Clin Oncol 33: 489–494.
33. Nakahata K, Kase M, Vassalou H, Songakoj K, Voutina A, et al. (2009) DNA repair gene polymorphisms predict favorable clinical outcome in advanced non-small-cell lung cancer. Clin Lung Cancer 10: 118–123.
34. Yao CY, Huang XE, Li C, Shen HB, Shi MQ, et al. (2009) Lack of influence of XRCC1 and XPD gene polymorphisms on outcome of platinum-based chemotherapy for advanced non small cell lung cancer. Clin Lung Cancer 10: 118–123.
35. Wu W, Li H, Wang H, Zhao X, Gao Z, et al. (2012) Effect of polymorphisms in XPD on clinical outcomes of platinum-based chemotherapy for Chinese non-small cell lung cancer patients. PLoS One 7: e33200.
36. Ren S, Zhou S, Wu F, Zhang L, Li X, et al. (2012) Association between polymorphisms of DNA repair genes and survival of advanced NSCLC patients treated with platinum-based chemotherapy. Lung Cancer 73: 102–109.
37. Zhang ZY, Tian X, Wu R, Liang Y, Jin XY (2012) Predictive role of ERCC1 and XPD genetic polymorphisms in survival of Chinese non-small cell lung cancer patients receiving chemotherapy. Asian Pac J Cancer Prev 13: 2583–2586.
38. Ladivini V, Floriani I, Punta L, Minotti V, Meacci M, et al. (2011) Association of cytidine deaminase and xeroderma pigmentosum group D polymorphisms with response, toxicity, and survival in cisplatin/gemcitabine-treated advanced non-small cell lung cancer patients. J Thorac Oncol 6: 2018–2026.
39. Virola N, Provencio M, Reguart N, Cardenal F, Alberola V, et al. (2011) Single nucleotide polymorphisms in MDR1 gen correlates with outcome in advanced non-small-cell lung cancer patients treated with cisplatin plus vinorelbine. Lung Cancer 74: 191–198.
40. Liu L, Yuan F, Wu C, Zhang X, Wang F, et al. (2011) Assessment of XPD Lys751Gln and XRCC1 T-77C polymorphisms in advanced non-small-cell lung cancer patients treated with platinum-based chemotherapy. Lung Cancer 73: 110–115.
41. Li F, Sun X, Sun N, Qin S, Cheng H, et al. (2010) Association between polymorphisms of ERCC1 and XPD and clinical response to platinum-based chemotherapy in advanced non-small cell lung cancer. Am J Clin Oncol 33: 489–494.
42. Nakahata K, Kase M, Vassalou H, Songakoj K, Voutina A, et al. (2009) DNA repair gene polymorphisms predict favorable clinical outcome in advanced non-small-cell lung cancer. Clin Lung Cancer 10: 118–123.
43. Yao CY, Huang XE, Li C, Shen HB, Shi MQ, et al. (2009) Lack of influence of XRCC1 and XPD gene polymorphisms on outcome of platinum-based chemotherapy for advanced non small cell lung cancer. Asian Pac J Cancer Prev 10: 859–864.
44. Gaudara DR, Kawaguchi T, Crowley J, Moon J, Furuse K, et al. (2009) Japanese-US common-arm analysis of paclitaxel plus carboplatin in advanced non-small-cell lung cancer: a model for assessing population-related pharmacogenomics. J Clin Oncol 27: 3540–3546.
45. Booton R, Ward T, Heighway J, Taylor P, Power F, et al. (2006) Xeroderma pigmentosum group D haplotype predicts for response, survival, and toxicity after platinum-based chemotherapy in advanced non-small cell lung cancer. Cancer 106: 2421–2427.
46. Ryu JS, Hong YC, Han HS, Lee JE, Kim S, et al. (2006) Association between polymorphisms of ERCC1 and XPD and survival in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy. Lung Cancer 44: 258–265.
47. Camps C, Sarries C, Roig B, Sanchez JJ, Queralt C, et al. (2003) Assessment of nucleotide excision repair XPD polymorphisms in the peripheral blood of gemcitabine/cisplatin-treated advanced non-small-cell lung cancer patients. Clin Lung Cancer 4: 237–241.