OncoTargets and Therapy

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ORIGINAL RESEARCH

Effect of *XPC* polymorphisms on the response to platinum-based chemotherapy: a meta-analysis

This article was published in the following Dove Press journal:
OncoTargets and Therapy

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Objective: As an important DNA repair gene, the xeroderma pigmentosum complementation group C (XPC) gene and its functional genetic variants' relationship with chemotherapy response has been extensively studied. To quantitatively elucidate the genetic impact of the *XPC* rs2228000 and rs2228001 polymorphisms on the response to platinum-based chemotherapy, the present meta-analysis was conducted.

Materials and methods: A systematic literature search was performed in seven cyber databases until February 20, 2019, for all relevant studies that assessed the relationship between *XPC* polymorphisms and the response to platinum-based chemotherapy. Odds ratios (ORs) with a 95% confidence interval (95% CI) were measured to assess the strength of the association. R programs were developed to perform the statistical analyses, including calculations of pooled estimates, publication bias and sensitivity analyses, and heterogeneity interpretations.

Results: A total of 1,615 patients from 10 studies for the rs2228001 polymorphism were winnowed for further statistical analysis. For the rs2228000 polymorphism, 858 samples from six datasets were included. However, this meta-analysis indicated no significant effect of these two *XPC* polymorphisms on the response to platinum-based chemotherapy. When stratified according to sample size, country or cancer type, no statistical significance for association was identified in all subgroups. Further sensitivity analysis and publication bias assessment ensured the reliability of the meta-analysis.

Conclusions: The pooled estimates suggest that neither the rs2228000 polymorphism nor the rs2228001 polymorphism contributes to the genetic predisposition for an altered response to platinum-based chemotherapy. Considering the limitations of our present meta-analysis, more studies with large-scale cohorts and rigorous methods are needed to validate our results.

Keywords: XPC, polymorphism, meta-analysis, platinum-based chemotherapy

Introduction

As a mainstay of chemotherapy, platinum-based regimens are still widely employed for the treatment of a wide spectrum of advanced-stage cancers. Unfortunately, in clinical practice, a significant proportion of patients exhibit intrinsic or acquired resistance to platinum-based therapies. Genome structural variations, such as single nucleotide polymorphisms (SNPs), are genetic factors that may influence chemotherapy response.[1] Therefore, extensive studies have been conducted on the genetic loci associated with sensitivity to platinum-based regimens.

As an important DNA damage recognition protein, xeroderma pigmentosum complementation group C (XPC) plays a key role in nucleotide excision repair. In vitro

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http://doi.org/10.2147/OTT.S202617

experiments suggest that XPC overexpression could lead to enhanced sensitivity to cisplatin treatment,[2] and its defect could result in reduced p53 responses to cisplatin treatment.[3] Two common polymorphic loci of the *XPC* gene, rs2228000 (G>A, Ala499Val) and rs2228001 (G>T, Lys939Gln), have been investigated for the effectiveness of carcinogenesis.[4–6] Scattered evidence has demonstrated that the G allele homozygotes of these two polymorphisms could lead to significantly increased *XPC* mRNA expression in the Asian population.[4,7] Given the obvious importance of the XPC gene, it is reasonable to hypothesize that the *XPC* rs2228000 and rs2228001 polymorphisms can affect responses to platinum-based therapy.

Several previous association studies tried to quantitatively assess the relationship between the *XPC* polymorphism and the response to platinum-based chemotherapy. However, their results were incongruous, and those scattered datasets were also plagued by small sample sizes and consequently led to very restricted statistical power. The aim of this meta-analysis was to comprehensively evaluate the diagnostic value of the *XPC* genotypes of the rs2228000 and rs2228001 polymorphisms as a biomarker for chemotherapy response in cancer patients subjected to platinum-based treatments.

Materials and methods

Literature search

For this study, a comprehensive literature screening was conducted to identify relevant datasets published in the China Knowledge Resource Integrated Database (http://www.cnki.net/), the Wanfang Data Resource System of Digital Periodicals (http://www.wanfangdata.com.cn/), the VIP Chinese Technology Periodical Database (http://qikan.cqvip.com/), the Wiley Cochrane Library (http://onlinelibrary.wiley.com/cochranelibrary/search/), PubMed from the National Center for Biotechnology Information (http://www.ncbi.nlm.nih.gov/pubmed), Excerpta Medica Database (https://www.embase.com/), and the Web of Science from Clarivate Analytics (http://isiknowledge.com/). A search string was constructed as a Boolean expression and built with the following terms and known synonyms: cancer ("cancer", "adenocarcinoma", and "carcinoma"), polymorphism ("polymorphism", "SNP", and "variant"), XPC gene ("RAD4" and "XPC"), and platinum-based chemotherapy ("chemotherapy", "platinum", "carboplatin", "cisplatin", "oxaliplatin", "lobaplatin", and "nedaplatin"). In our literature search, language was limited to English for PubMed, Web of Science, Cochrane, and Excerpta Medica Database. In the CNKI, Wanfang, and

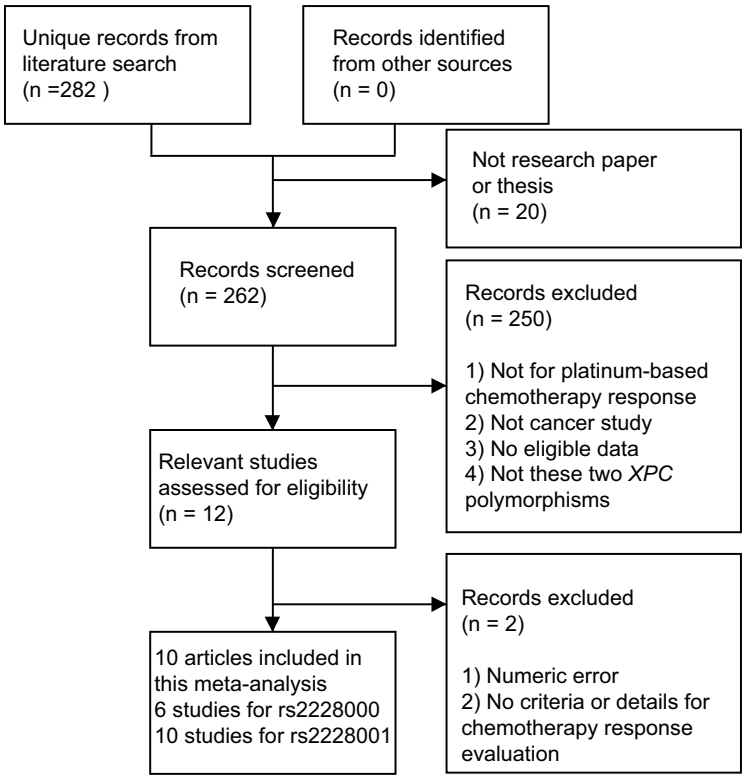

Figure 1 Flowchart showing the detailed processes of literature screening and study selection.

Table 1 Principal characteristics of studies included in this meta-analysis

Author (year)	Ref	Country (region)	Cancer type	Chemotherapy strategy	Criteria	NOS	Good responder	Poor responder
rs2228000								
Zhu X.(2010)	[19]	China(Asia)	Non-small cell lung cancer	Cisplatin/ Carboplatin-based	WHO	5	25	71
Zhang F.(2010)	[22]	China(Asia)	Ovarian cancer	Cisplatin/ Carboplatin-based	WHO	6	82	48
Zhai Y.(2011)	[23]	China(Asia)	Non-small cell lung cancer	Vinorelbine & Cisplatin	WHO	6	57	106
Sun H.(2013)	[20]	China(Asia)	Ovarian cancer	Platinum-based	TFI	4	139	73
Lawania S.(2018)	[15]	India (Asia)	Lung cancer	Platinum-based	RECIST	5	89	78
Mlak R.(2018)	[16]	Poland(Europe)	Non-small cell lung cancer	Platinum & Gemcitabine	RECIST	4	17	73
rs2228001								
Wang L.(2010)	[24]	China(Asia)	Ovarian cancer	Cisplatin-based	WHO	6	41	22
Zhu X.(2010)	[19]	China(Asia)	Non-small cell lung cancer	Cisplatin/ Carboplatin-based	WHO	5	27	69
Zhang F.(2010)	[22]	China(Asia)	Ovarian cancer	Cisplatin/ Carboplatin-based	WHO	6	82	48
Zhai Y.(2011)	[23]	China(Asia)	Non-small cell lung cancer	Vinorelbine & Cisplatin	WHO	6	57	106
Sun X.(2013)	[17]	China(Asia)	Bone malignant tumor	Cisplatin-based	EORTC	6	94	88
Sun H.(2013)	[20]	China(Asia)	Ovarian cancer	Platinum-based	TFI	5	140	73
Xue M.(2015)	[18]	China(Asia)	Gastric cancer	FOLFOX	RECIST	7	269	141
Qi L.(2016)	[21]	China(Asia)	Cervical cancer	Cisplatin-based	RECIST	6	78	36
Lawania S.(2018)	[15]	India (Asia)	Lung cancer	Platinum-based	RECIST	5	89	78
Mlak R.(2018)	[16]	Poland(Europe)	Non-small cell lung cancer	Platinum & Gemcitabine	RECIST	4	15	62

Abbreviations: FOLFOX, combination of Leucovorin Calcium (Folinic Acid), Fluorouracil and Oxaliplatin; RECIST, response evaluation criteria in solid tumors; TFI, treatment-free interval; EORTC, evaluation criteria from European Organization for Research and Treatment of Cancer; WHO response evaluation criteria introduced by the World Health Organization; NOS, The Newcastle–Ottawa Scale score.

Chinese VIP databases, the search language was set to Chinese. All other default parameters in these databases we used were left unchanged. The published literature was searched from the database's inception to 20 February 2019.

Study selection

For a dataset to be included in this meta-analysis, full-text content should be accessible, and the corresponding relevant study had to meet the following predefined inclusion criteria: (1) study for the *XPC* polymorphism (rs2228000 or rs2228001); (2) study for the response to platinum-based cancer chemotherapy; and (3) enough genotype data to construct at least one genetic comparison model. Studies were taken out from further processing when failing any of the prespecified exclusion criteria: (1) nonplatinum-based chemotherapy; (2) no data for chemotherapy response; (3) no data for the *XPC* polymorphisms; (4) duplicated data; (5) noncancer study; or (6) no chemotherapy response evaluation criteria or details in responder definition.

Data extraction and processing

The name of the author and the publication year were extracted from individual studies to mark the corresponding dataset used in further meta-analyses. Information regarding the features of the study design and patient characteristics were included. We recorded cancer type, chemotherapy regimens, geographical region, and criteria in the assessment of treatment outcomes. Furthermore, the numbers of patients with good and poor response for different polymorphism genotypes were extracted to construct 2×2 contingency tables for statistical analysis. The

methodological quality assessment for the eligible studies was conducted according to the 9-point Newcastle–Ottawa Scale (NOS, http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm. Accessed 24 Mar 2019). The NOS scores, ranging from 0 to 9, indicated a low, moderate, and high quality for 0–3, 4–6, and 7–9 points, respectively.

Statistical analysis

Statistical meta-analyses were conducted with our in-house R pipeline (R version: 3.5.1, http://cran.r-project.org/), which integrated the analysis modules of the "meta" package (version: 4.9–2, http://cran.r-project.org/web/packages/meta/).[8] Differences in the response to platinum-based chemotherapies between the *XPC* genotypes of the rs2228000 and rs2228001 polymorphisms were assessed for statistical significance and were expressed as an odds ratio (OR) with corresponding 95% confidence interval (95% CI). Cochran's Chi-square-based Q-test was adopted to evaluate between-study heterogeneity. A fixed effect model based on the Mantel–Haenszel algorithm[9] was used for the circumstances under which no significant heterogeneity was detected ($P \geq 0.10$). Otherwise, a random effects model employing the DerSimonian and Laird algorithm[10] was used. Stratified analyses were conducted separately according to chemotherapy response criteria [WHO criteria and response evaluation criteria in solid tumors (RECIST) versus others], sample size (≥200 versus <200), country (China versus others), and cancer type (lung cancer versus others) to explore the impact of these characteristics on the pooled estimates. The strength of the association between the *XPC* polymorphisms and chemotherapy response was evaluated under a homozygote model (aa versus AA, allele A represents the major allele and allele a represents the minor allele), heterozygote model (Aa versus AA), dominant model (aa+Aa versus AA), and recessive model (aa versus AA+Aa). To address significant heterogeneity, a Galbraith plot was generated to spot outliers as possible sources.[11] Publication bias was assessed according to the asymmetry of the funnel plot. Neither the Egger's test[12] nor the Begg and Mazumdar's test[13] would be conducted to quantitatively evaluate the publication bias when no more than ten datasets were included in one genetic comparison model. To determine the robustness of the pooled estimate, leave-one-out sensitivity analysis was employed to assess the effect of every single study on statistical significance.

All steps involved in this study strictly complied with the principles of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) from the beginning until the end.[14] At least three investigators participated in every step of this meta-analysis. All inconsistencies were resolved by discussion among all investigators.

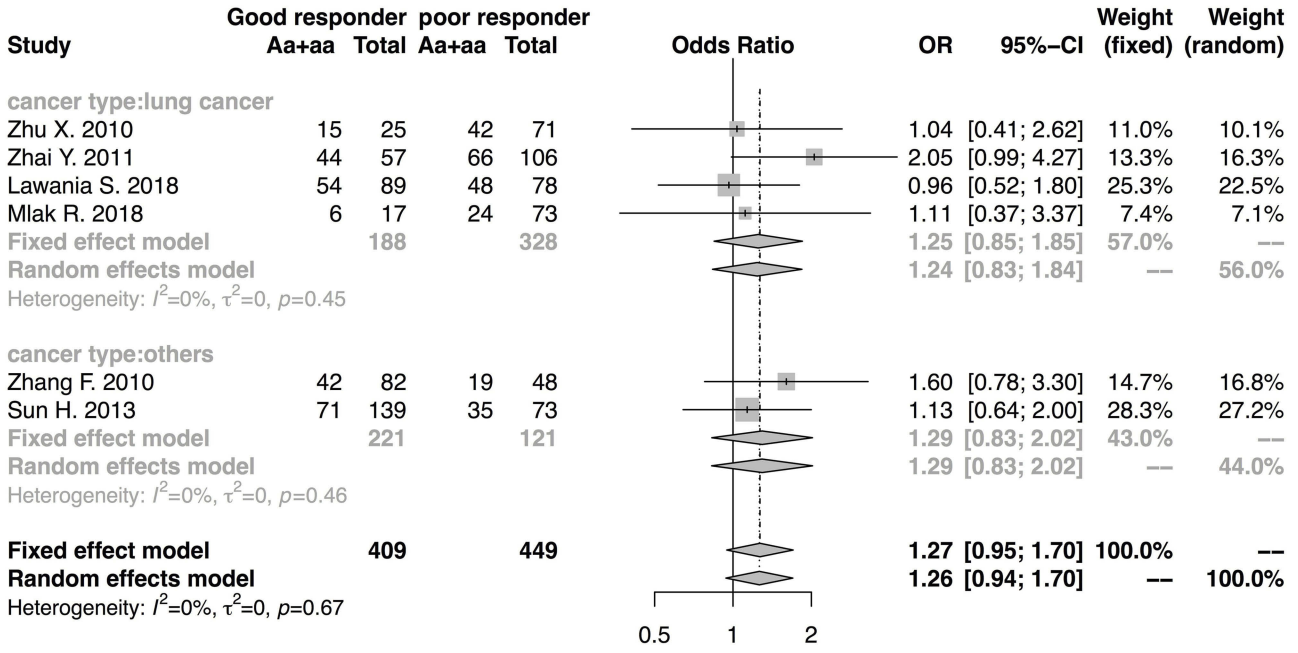

Figure 2 Forest plot showing the association between the *XPC* rs2228000 polymorphism and the response to platinum-based chemotherapy. The odds ratio (OR) and corresponding 95% confidence interval (95% CI) were calculated under the dominant model. Involved studies were stratified according to cancer type. Each study was labeled with the name of the author and the year of publication. The area of the gray box represents the weight of the sample size assigned under the fixed effect model. The lateral points of the gray diamond icon represent the upper and lower bounds of a 95% CI, while the vertical points indicate the point estimate. The solid vertical line represents the null effect (OR=1). A represents the major allele, and a represents the minor allele.

Table 2 Association between the *XPC* rs2228000 polymorphism and the response to platinum-based chemotherapy

	Homozygote model			Heterozygote model			Dominant model			Recessive model		
	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h
Overall	1.46 [0.84, 2.54]	0.18	0.43	1.23 [0.90, 1.67]	0.19	0.58	1.27 [0.95, 1.70]	0.11	0.67	1.35 [0.80, 2.29]	0.26	0.25
Sample size												
≥200	0.97 [0.42, 2.24]	0.93	NA	1.21 [0.65, 2.26]	0.55	NA	1.13 [0.64, 2.00]	0.66	NA	0.89 [0.40, 1.99]	0.78	NA
<200	2.01 [0.96, 4.20]	0.06	0.53	1.23 [0.86, 1.76]	0.25	0.44	1.32 [0.94, 1.86]	0.11	0.56	1.85 [0.92, 3.71]	0.08	0.34
Criteria												
WHO/ RECIST	2.01 [0.96, 4.20]	0.06	0.53	1.23 [0.86, 1.76]	0.25	0.44	1.32 [0.94, 1.86]	0.11	0.56	1.85 [0.92, 3.71]	0.08	0.34
Others	0.97 [0.42, 2.24]	0.93	NA	1.21[0.65, 2.26]	0.55	NA	1.13 [0.64, 2.00]	0.66	NA	0.89 [0.40, 1.99]	0.78	NA
Cancer type												
Lung cancer	1.38 [0.54, 3.54]	0.50	0.53	1.23 [0.83, 1.84]	0.30	0.29	1.25 [0.85, 1.85]	0.26	0.45	1.29 [0.53, 3.11]	0.57	0.28
Others	1.50 [0.75, 2.99]	0.25	0.10	1.22 [0.75, 1.98]	0.43	0.98	1.29 [0.83, 2.02]	0.26	0.46	1.57 [0.43, 5.71]	0.50	0.09
Country												
China	1.52 [0.84, 2.77]	0.16	0.21	1.34 [0.92, 1.95]	0.12	0.40	1.40 [0.99, 1.99]	0.06	0.55	1.40 [0.79, 2.46]	0.25	0.10
Others	1.08 [0.23, 5.14]	0.93	0.62	1.00 [0.58, 1.75]	0.99	0.70	1.00 [0.58, 1.72]	0.99	0.82	1.05 [0.23, 4.86]	0.95	0.58

Abbreviations: OR, odds ratio; CI, confidence interval; RECIST, Response Evaluation Criteria In Solid Tumors; WHO response evaluation criteria introduced by the World Health Organization; P_h, *P*-value for heterogeneity test; NA, not applicable.

Results

Literature search and data extraction

After removing duplicates, our initial literature screening yielded 282 manuscripts and theses. Among them, 76 were in English and 206 were in Chinese. The number of relevant studies was narrowed down through the implementation of the predefined inclusion and exclusion criteria. A total of ten articles with relevant datasets were identified.[15–24] Of the ten included datasets, there were four studies for lung cancer,[15,16,19,23] three for ovarian cancer,[20,22,24] one for cervical cancer,[21] one for gastric cancer,[18] and one for bone malignant tumor.[17] For the *XPC* rs2228000 polymorphism, six studies with 409 good responders and 449 poor responders to chemotherapy were included.[15,16,19,20,22,23] For the *XPC* rs2228001 polymorphism, the corresponding numbers collected from 10 datasets were 892 and 723, respectively.[15–24] The workflow of the literature selection process is demonstrated in Figure 1. The characteristics of the involved studies are summarized in Table 1. All included studies for both polymorphisms were considered good or moderate quality according to the NOS scores. Specifically, one cervical cancer study for the rs2228001 polymorphism only presented the genotype data for the major allele homozygote (AA) and the minor allele carriers (Aa+aa), which could only be integrated in the dominant model.[21] Two case–control studies were not integrated into our meta-analysis for the rs2228001 polymorphism. One osteosarcoma study was excluded because of the discrepancy between the number of poor responders and the sum of homozygote wild-type, heterozygote mutant, and homozygote mutant of these samples.[25] One study for cisplatin-based chemotherapy on esophageal squamous cell carcinoma was not included due to the lack of details of the definitions of good and poor responders.[26]

Meta-analysis and subgroup analysis

In the overall population, there was no statistical significance for the association between the *XPC* rs2228000 polymorphism and the response to platinum-based

chemotherapy (homozygote model: OR=1.46, 95% CI 0.84–2.54; heterozygote model: OR=1.23, 95% CI 0.90–1.67; dominant model: OR=1.27, 95% CI 0.95–1.70, Figure 2; recessive model: OR=1.35, 95% CI 0.80–2.29). Stratified analysis by sample size did not reveal a material difference between the large sample size subgroup and the small sample size subgroup. Studies were also classified according to geographical region. The pooled estimates suggested that this polymorphism could not influence the platinum-based chemotherapy response in the Chinese population and in populations from other countries. No statistical significance for pooled estimates could be observed in all subgroups divided according to chemotherapy response evaluation criteria. Stratification by cancer type also showed no substantial differences for the subgroups of lung cancer and other cancers (Table 2).

As for the *XPC* rs2228001 polymorphism, the quantitative synthesis of the included studies revealed no statistical significance for its association with response to platinum-based chemotherapy (homozygote model: OR=0.84, 95% CI 0.53–1.32; heterozygote model: OR=0.83, 95% CI 0.54–1.27; dominant model: OR=0.87, 95% CI 0.60–1.27, Figure 3; recessive model: OR=0.99, 95% CI 0.75–1.32). When subdivided by sample size, neither the subgroup with ≥200 samples nor the subgroup with <200 samples showed a statistically significant change. Regarding the geographical region of the involved studies, the pooled estimates indicated no conflict between patients from China and from other nations. Stratified analysis according to chemotherapy response evaluation criteria indicated that the null hypothesis could not be rejected in any subgroups. When restricting the analysis to lung cancer or other cancers, no significance was evident in either subgroup under all genetic models (Table 3).

Publication bias and sensitivity analysis

Publication bias was interpreted by visual inspection of the degree of asymmetry in the Begg's funnel plots. For both polymorphisms studied in this meta-analysis (Figures 4 and 5), no evidence of obvious asymmetry could be drawn from the funnel plots, which indicated only a tiny likelihood of publication bias. By omitting individual datasets, their influence on the pooled estimates was evaluated. The results suggested no material change of statistical significance (data not shown).

Heterogeneity analysis

For the *XPC* rs2228001 polymorphism, significant between-study heterogeneity was detected in the homozygote, heterozygote, and dominant models. Galbraith plot analysis (data not

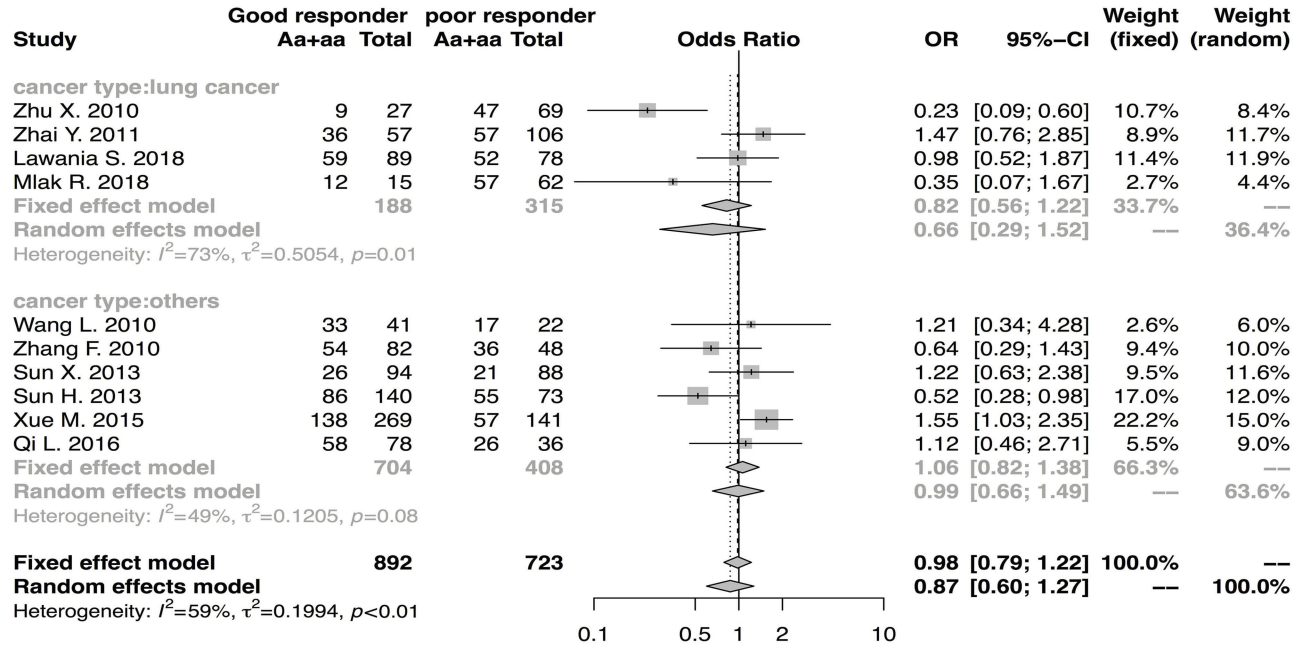

Figure 3 Forest plot showing the association between the *XPC* rs2228001 polymorphism and the response to platinum-based chemotherapy. The odds ratio (OR) and corresponding 95% confidence interval (95% CI) were calculated under the dominant model. Involved studies were stratified according to cancer type. Each study was labeled with the name of the author and the year of publication. The area of the gray box represents the weight of the sample size assigned under the fixed effect model. The lateral points of the gray diamond icon represent the upper and lower bounds of a 95% CI, while the vertical points indicate the point estimate. The solid vertical line represents the null effect (OR=1). A represents the major allele, and a represents the minor allele.

Table 3 Association between the *XPC* rs2228001 polymorphism and the response to platinum-based chemotherapy

	Homozygote model			Heterozygote model			Dominant model			Recessive model		
	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h	OR (95% CI)	*P*	P_h
Overall	0.84 [0.53, 1.32]	0.44	0.07	0.83 [0.54, 1.27]	0.39	0.01	0.87 [0.60, 1.27]	0.47	<0.01	0.99[0.75, 1.32]	0.95	0.21
Sample size												
≥200	0.90 [0.27, 3.05]	0.87	0.02	0.93 [0.34, 2.56]	0.89	0.01	0.92 [0.32, 2.69]	0.88	<0.01	1.07 [0.69, 1.68]	0.75	0.13
<200	0.79 [0.52, 1.20]	0.28	0.23	0.78 [0.46, 1.31]	0.34	0.04	0.85 [0.56, 1.29]	0.44	0.06	0.94 [0.65, 1.36]	0.73	0.21
Criteria												
WHO/ RECIST	0.85 [0.49, 1.48]	0.57	0.08	0.83 [0.49, 1.42]	0.50	0.01	0.89 [0.57, 1.39]	0.61	0.01	1.03 [0.74, 1.43]	0.86	0.15
Others	0.75 [0.40, 1.41]	0.37	0.11	0.72 [0.44, 1.20]	0.21	0.17	0.79 [0.34, 1.82]	0.58	0.07	0.88 [0.49, 1.57]	0.66	0.28
Cancer type												
Lung cancer	0.77 [0.43, 1.36]	0.37	0.44	0.59 [0.22, 1.55]	0.28	<0.01	0.66 [0.29, 1.52]	0.33	0.01	1.00 [0.60, 1.66]	1.00	0.70
Others	0.88 [0.44, 1.76]	0.72	0.02	1.04[0.76, 1.41]	0.82	0.16	0.99 [0.66, 1.49]	0.96	0.08	0.95 [0.54, 1.66]	0.85	0.05
Country												
China	0.85 [0.48, 1.51]	0.58	0.03	0.86 [0.53, 1.40]	0.54	0.01	0.89 [0.58, 1.38]	0.61	<0.01	0.97 [0.71, 1.34]	0.87	0.13
Others	0.78 [0.36, 1.67]	0.52	0.58	0.54 [0.10, 2.84]	0.46	0.08	0.86 [0.47, 1.57]	0.62	0.23	1.06 [0.56, 2.00]	0.86	0.32

Note: OR, odds ratio; CI, confidence interval; RECIST, Response Evaluation Criteria In Solid Tumors; WHO response evaluation criteria introduced by the World Health Organization; P_h, *P*-value for heterogeneity test.

shown) identified two outliers in the homozygote model,[18,22] two in the heterozygote model,[18,19] and three in the dominant model[18-20] as the potential sources of heterogeneity. The removal of these outliers significantly reduced the between-study heterogeneity (homozygote model: heterogeneity test *P*-value=0.38; heterozygote model: heterogeneity test *P*-value=0.26; dominant model: heterogeneity test *P*-value=0.59) but did not materially influence the significance of the pooled estimates (homozygote model: OR=0.81, 95% CI 0.54–1.22, *P*-value=0.31; heterozygote model: OR=0.90, 95% CI 0.66–1.23, *P*-value=0.50; dominant model: OR=1.04, 95% CI 0.77–1.41, *P*-value =0.78).

Discussion

Based on the published datasets, we intended to quantitatively elucidate the possible genetic impact of the *XPC* rs2228000 and rs2228001 polymorphisms on the response to platinum-based chemotherapy. The lack of a significant effect on the response to chemotherapy might reflect the unlikelihood of these two *XPC* polymorphisms as causative factors for altered sensitivity to platinum-based regimens, masking the potential involvement of other genetic or clinical factors. However, these conclusions did not differ from the findings in the stratified analysis according to cancer type, sample size, and country. Other confounding factors not discussed in this study, such as cancer stage, patient age, and accumulative effect of genetic variances, should be included in further research when data are available.

In this meta-analysis, we only selected studies with explicit criteria for chemotherapy response evaluation and details of the definition process. This selection was done to avoid the impact on the accuracy of pooled estimates led by inconsistency, which could result from the simultaneous inclusion of heterogeneous case and control groups. The details for using the same response evaluation criteria could be quite different between studies. For example, several studies using the RECIST criteria defined complete response (CR), partial response (PR), and stable disease (SD) as good responders,[27,28] while some studies grouped CR and PR as good responders[15,21] We did not include the data set for esophageal squamous cell carcinoma[26] in our meta-analysis for rs2228001 due to its lack of details in responder definition.

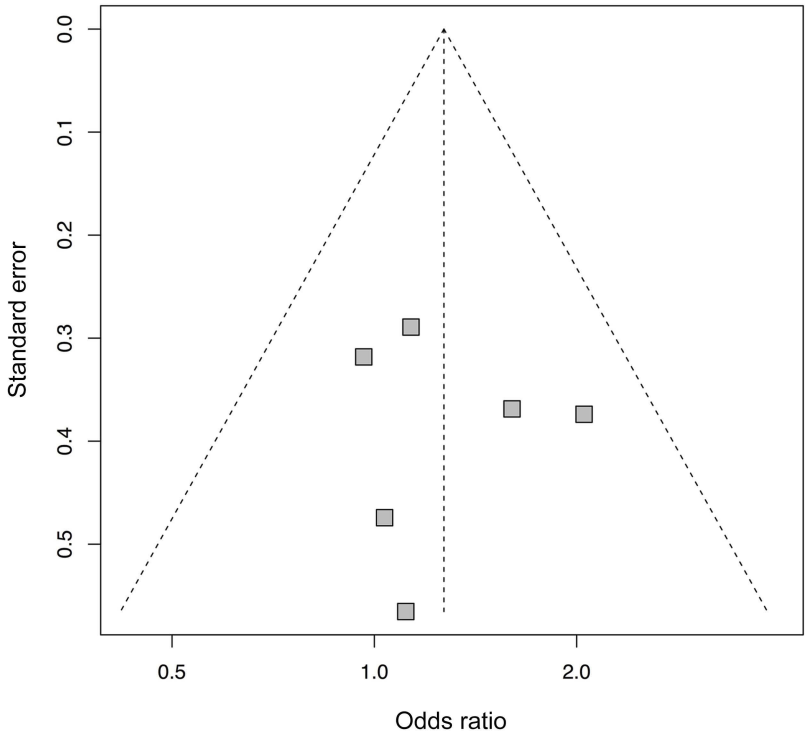

Figure 4 Funnel plot of the meta-analysis for the *XPC* rs2228000 polymorphism under the dominant model. Each gray square represents an included dataset. The vertical dashed line indicates the pooled odds ratio. The funnel defined by the two crossed dashed lines represents the pseudo 95% confidence interval.

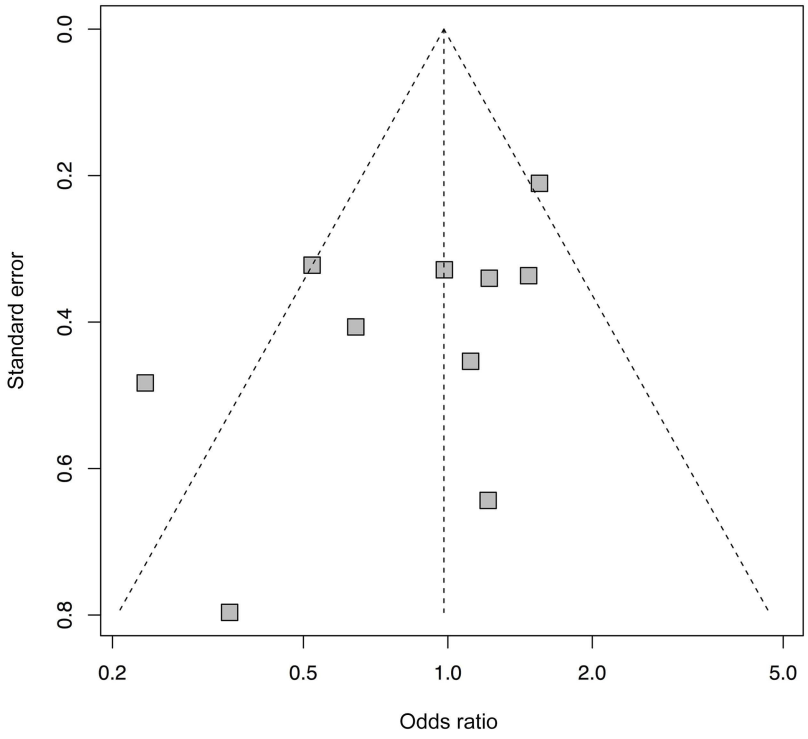

Figure 5 Funnel plot of the meta-analysis for the *XPC* rs2228001 polymorphism under the dominant model. Each gray square represents an included dataset. The vertical dashed line indicates the pooled odds ratio. The funnel defined by the two crossed dashed lines represents the pseudo 95% confidence interval.

However, we still calculated the pooled estimates after adding this dataset. No material change for statistical significance could be observed (homozygote model: OR=0.75, 95% CI 0.48–1.18; heterozygote model: OR=0.87, 95% CI 0.60–1.25; dominant model: OR=0.87, 95% CI 0.63–1.21; recessive model: OR=0.86, 95% CI 0.59–1.27), which indicated the stability of our results.

For the *XPC* rs2228001 polymorphism, significant between-study heterogeneity was detected in the homozygote, heterozygote and dominant models. However, the removal of the identified outliers[18-20,22] in the Galbraith plots not only led to significant relief of heterogeneity but also indicated the stability of the pooled estimates. However, the hidden confounding factors introduced by these outliers could not be explored in the present study due to the lack of detailed clinical information for the samples involved in the included studies. For this reason, further large-scale multicenter-clinical studies with elaborate, relevant data should be performed to address the impact of these factors. For the two polymorphisms, sensitivity analysis further strengthened stability, and the inference of publication bias also revealed unbiasedness. Because of the advantages listed earlier, we are greatly confident in the robustness of the results.

The accuracy of genotyping experiments and chemotherapy response measurements in the genetic association studies involved in this meta-analysis could vary according to the personal experience of the genotype researchers and clinical investigators. Furthermore, the differences inherent in both the variance of chemotherapy regimens and the different chemotherapy response evaluation criteria should not be ignored. These subjective factors were out of the scope of this study but are important areas that need to be taken into account in prospective settings for future research.

Although this meta-analysis strictly followed the principles suggested by the PRISMA guidelines for meta-analysis,[14] a number of inherent limitations should be noted when interpreting the results. First, the number of involved studies was relatively small, and the sample size was comparatively limited, especially for the *XPC* rs2228000 polymorphism, calling for updated analyses when more datasets are available. Moreover, the influence of other *XPC* polymorphisms in the response to platinum-based chemotherapy was not evaluated in this meta-analysis because of limited sample sizes. Furthermore, several cancer types receiving platinum-based chemotherapy were not covered in this meta-analysis also due to the lack of data. Last but not least, most of the involved studies originated from Asia, especially China, which significantly impacted ethnic variety and could subsequently lead to sampling bias. However, the superiority of this meta-analysis should be worth noting. Compared with every single study included, the conclusions drawn from this meta-analysis showed higher authenticity based on a substantially enlarged sample size and consequently increased statistical power and a greatly minified risk of random errors. On the other hand, the results of the NOS quality assessment, sensitivity evaluation, and publication bias analysis further ensured robustness.

Conclusions

In conclusion, our pooled estimates of meta-analysis based on a systematic literature review revealed no statistically significant association between the *XPC* rs2228000 and rs2228001 polymorphisms and the response to platinum-based chemotherapy. However, further statistical investigation will be merited with the synthesis of more multicentric datasets with a large sample size to elucidate the impact of the *XPC* polymorphisms on the response to platinum-based chemotherapy.

Acknowledgments

This study was funded by the research start-up fund of Soochow University (Q413400116), the natural Science Foundation of Jiangsu Province (No. BK20170334), the Priority Academic Program Development of Jiangsu Higher Education Institutions, and the National Undergraduate Training Program for Innovation and Entrepreneurship (201810285050Z).

Disclosure

The authors declare no conflicts of interest in this work.

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