Moving toward individualized therapy based on NER polymorphisms that predict platinum sensitivity in ovarian cancer patients

J. Salvador Saldivar, a, b, Karen H. Lu, a, Dong Liang, c, Jian Gu, b, Maosheng Huang, b, Anne-Therese Vlastos, d, Michele Follen, e, Xifeng Wu, b

a Department of Gynecology Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
b Department of Epidemiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA
c College of Pharmacy and Health Sciences, Texas Southern University, Houston, TX, USA
d Department of Gynecology and Obstetrics, Geneva University Hospitals, Geneva, Switzerland
e Center for Biomedical Engineering, The University of Texas M. D. Anderson Cancer Center, Houston, TX 77030, USA

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Abstract

Objective. Platinum-based chemotherapy exerts its cytotoxic effect by forming DNA adducts and subsequently inhibiting DNA replication. Removing platinum DNA adducts requires the nucleotide excision repair (NER) pathway. The xeroderma pigmentosum (XP) complementation group of genes plays an essential role in the NER pathway. We hypothesized that genetic polymorphisms in XP genes may predict clinical response to platinum chemotherapeutic treatment and survival in women with gynecological cancers.

Method. We genotyped 146 cases of advanced epithelial ovarian cancer for XP gene polymorphisms using the PCR-RFLP method. Kaplan–Meier plots and the log-rank test were used to assess associations between survival and recurrence-free interval and the XP gene polymorphisms. Hazard ratio of response was estimated from an adjusted multivariate Cox proportional hazard model.

Results. Women with a heterozygous variant XPA allele had shorter median survival (21.5 months, \( P = 0.03 \)) and shorter median time to recurrence (11.3 months, \( P = 0.05 \)) than women with the homozygous wild-type allele (37.9 and 13.9 months, respectively). Women with a homozygous variant XPG allele had significantly shorter median survival (8.3 months, \( P = 0.006 \)) compared with women with the homozygous XPG wild-type allele (24.6 months). Polymorphisms in XPC, XPD exon10, and XPD exon23 were associated with a decreased risk of recurrence and death, but were not statistically significant.

Conclusions. This study suggests that NER gene polymorphisms may correlate with recurrence and patient survival. A larger sample size is needed to assess platinum chemotherapy response with these polymorphisms. These findings may help identify subgroups of cancer patients likely to benefit from individualized treatment strategies. Our next study will examine NER gene polymorphisms in cervical cancer patients.

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Keywords: Ovarian cancer; NER polymorphisms; XP genes; XPA; XPC; XPD exon10; XPD exon23; XPG; Platinum sensitivity; Platinum resistance

Introduction

Ovarian cancer is the leading cause of death from gynecologic malignancies and the fifth most common cancer diagnosed in women in the United States. In 2005, an estimated 22,220 new cases were diagnosed and 16,210 deaths resulted from ovarian cancer [1]. Of all the gynecologic cancers, ovarian cancer has the largest case fatality ratio. The overall 5-year survival rate for women with advanced staged ovarian cancer is approximately 20–25%. Despite advances in ovarian cancer biology, imaging, surgical support, surgical technique, and chemotherapy, the survival rate has not changed significantly in the past 30 years [2]. The high mortality rate from ovarian cancer is attributable to the advanced stage of disease at the time of diagnosis. Despite the discovery of tumor markers such as CA-125, refinements in ultrasonography, and the introduction of novel optical technologies, there is no cost-effective
screening strategy for early-stage disease. Better definition of both patients at risk and the response to therapy could affect survival.

Platinum-based chemotherapy has been the mainstay of treatment for advanced epithelial ovarian cancer following aggressive cytoreductive surgery [3]. In fact, it was hoped that taxanes would significantly improve ovarian cancer survival. However, taxanes alone have not significantly improved survival and are now used in conjunction with platinum. Although response rates to platinum-based regimens are greater than 70%, a relevant clinical problem in the treatment of ovarian cancer is the development of tumor resistance to platinum compounds [4,5]. In advanced ovarian cancer cases, tumors recur within 2 years of initial treatment, with only 20–25% of patients surviving 5 years from diagnosis. Ideally, identification of patients who are platinum resistant before therapy could lead to better selection of therapy and could improve survival.

The antitumor effect of platinum compounds such as carboplatin or cisplatin has been correlated with binding to DNA and the production of intra- and inter-structural cross-links and the formation of DNA adducts [6]. Bulky DNA adducts cause changes in DNA conformation that may affect DNA replication and inhibition of DNA synthesis [7]. These adducts are responsible for the cytotoxicity of this drug, and clinical response correlates with the level of platinum-DNA adducts in the circulation [8]. One of the mechanisms by which tumor cells develop resistance to platinum agents is enhanced repair of bulky DNA adducts [9]. Thus, suboptimal DNA repair may predict a better response to platinum-based chemotherapy and may be a prognostic factor for improved survival in advanced ovarian cancer.

A complex system of DNA repair enzymes plays a central role in maintaining genomic integrity by counteracting insults from endogenous and exogenous damaging agents, including platinum compounds. There are at least four DNA repair pathways that operate on specific types of DNA damage: base excision repair, mismatch repair, double-strand break repair, and nucleotide excision repair (NER) [10]. In vitro and in vivo studies have shown definitively that the NER is the principal pathway involved with removal of platinum adducts and with platinum resistance [9]. The coordinated action of the xeroderma pigmentosum (XP) complementation family group of proteins (XPA through XPG) in the NER pathway is critical in the recognition and removal of bulky adducts [10]. These core factors account for the majority of platinum-DNA adduct repair, and any functional mutations in these genes will lead to NER abnormalities associated with increased susceptibility to cancer and decreased patient survival [11–14].

Recently, several studies have examined the role of NER pathway single nucleotide polymorphisms (SNPs) in clinical cancer outcomes and response to cisplatin-based chemotherapy [15–18]. However, reports in the literature of DNA repair polymorphisms and ovarian cancer are limited. In this study, we hypothesized that the SNPs in the XP group genes XPA, XPC, XPD10, XPD23, and XPG may predict clinical response to platinum agents and patient survival. To our knowledge, this is the first study to assess DNA repair genetic polymorphisms as predictive biomarkers of disease outcome and response to chemotherapy in ovarian cancer patients.

Methods

Study subjects

This study included 183 patients who had presented for treatment of ovarian neoplasms to The University of Texas M. D. Anderson Cancer Center between 1995 and 2003. Whole blood (10 ml) in heparinized tubes was collected at the time of initial surgery. Lymphocytes were extracted immediately and stored at −80 °C in the multidisciplinary gynecologic cancer translational research tumor bank until the analysis for this study. Blood samples were obtained after informed consent of the participants prior to their inclusion in the study.

Eligibility criteria for this cohort included newly diagnosed, histologically confirmed primary epithelial ovarian cancer in women of any age and race/ethnicity. The patients had been evaluated according to the FIGO surgical staging system. Subsequently, patients had undergone platinum-based combination or platinum-alone chemotherapy after cytoreductive surgery. The current standard chemotherapy protocol included carboplatin at a dose yielding an area under the curve of 5–6 and paclitaxel at 175 mg/m² at 3 week intervals for six cycles. Women were excluded from this study if they had neoadjuvant chemotherapy, any chemotherapy in the 6 months prior to surgical staging, concurrent primary neoplasms, benign ovarian disease, and/or insufficient referral history. After exclusions, the final number of cases analyzed was 146.

Data collection

Institutional Review Board approval was obtained and guidelines for the protection of human subjects were followed. Demographic data were collected from the medical record. Data were collected on characteristics such as age, ethnicity, alcohol and smoking history, age of menarche and menopause, parity, hormonal use, and past and current personal and family history. Similarly, clinical data regarding initial and previous surgery, stage and histologic diagnosis, post-operative therapy, and response to treatment, as well as management of persistent and recurrent disease were also abstracted from the medical record.

The M. D. Anderson Tumor Registry and Social Security Death Index were used to assess patient outcome such as the date of last contact and status of last contact when this information was missing from the medical record.

Genotyping methods

DNA was isolated from a 200-μl peripheral blood lymphocyte sample using the Qiagen DNA Blood Mini Kit (Qiagen Inc., Valencia, CA) according to the manufacturer’s protocol. Genotyping of the panel of polymorphisms of the NER pathway XPA (5′-UTR), XPC (poly-T), XPD exon10 (Asp312Asn), XPD exon23 (Lys751Gln), and XPG (Asp1104His) was performed by using a polymerase chain reaction (PCR) restriction fragment length polymorphism-based assay. The following PCR primers (5′→3′) were used for each SNP: XPA (forward) 5′-CTA GGT CCT CGG AGT GGT CC-3′, (reverse) 5′-GCC CAA ACC TCC AGT AGC C-3′; XPC (forward) 5′-TAG CAC CCA GCA GTC AAA-3′, (reverse) 5′-TGC GAA TGT GCC TAA GTC TG-3′; XPD 10 (forward) 5′-CTG TTG GTG GTG GCC GCC ATC TGT TGG TCT-3′, (reverse) 5′-AAT TAG CGG GCC TCA CCC TG CAG ACT TCC TCT-3′; XPD 23 (forward) 5′-GCC CGC TCT GGA TTA TAC G-3′, (reverse) 5′-CTA TAC TCT CTC GTG CCC CC-3′; XPG (forward) 5′-GGA GAC CGT CCT CTC AGA ATC-3′, (reverse) 5′-TCT TCC CCT CCA TCG TCA TCT-3′.

PCR products were generated using 100 ng of genomic DNA as a template in a Perkin-Elmer Corp. 9600 thermocycler (Applied Biosystems, Foster City, CA). The PCR was performed using a 25-μl total reaction volume with a final concentration of 0.2 mM of dNTPs, 2.5 mM MgCl₂, 1.5 units of Taq polymerase (Promega, Madison, WI), and 0.2 μM of each primer. Thermal cycling conditions were as follows: initial denaturation at 94 °C for 5 min, then 35 cycles of denaturation at 94 °C for 30 s; annealing at 55 °C (XPA), 57 °C (XPC), 60 °C (XPD10), 61 °C (XPD23), and 60.5 °C (XPG) for 30 s; extension at 72 °C for 30 s (XPC, XPG), 50 s (XPD10, XPD23), and 60 s (XPA); and a final extension at 72 °C for 5 min.
Variable definitions

Independent variables

Independent variables considered in this analysis were defined as follows:
Age was patient age at diagnosis (analyzed as a continuous variable). Race/ethnicity was categorized into three groups: Caucasian, African-American, and Hispanic. Smoking status was defined by four groups: never smoker, a woman who had never smoked less than 100 cigarettes in her lifetime; former smoker, a woman who had quit smoking for at least 1 year prior to the diagnosis date; current smoker, and ever smoker, the sum of former and current smokers. Alcohol status was defined by four groups: never user, a woman who never used alcohol or consumed no more than one drink per week; former user, a woman who had quit drinking for at least 1 year prior to the diagnosis date; current user, a woman consuming at least one drink per day; and ever users, the sum of former and current users. Histological types were dichotomized into papillary serous and “others” (mucinous, endometrioid, clear cell, undifferentiated and mixed epithelial) based on the classification scheme of the World Health Organization [19]. Grade was defined pathologically by the extent of cellular anaplasia into four groups: grade 1, grade 2, grade 3a, and grade 3b. FIGO stage was divided into four groups: stages I and II and advanced disease (stages III to IV) according to the International Federation of Gynecology and Obstetrics (FIGO) staging system [20]. Platinum-based therapy was divided into a “yes” group if the patient received platinum-based chemotherapy and a “no” group if the patient received chemotherapy other than platinum agent(s). Therapy cycles were also divided into two groups: <6 if the patient received fewer than six cycles of single-agent or combination chemotherapy and ≥6 if the patient received six or more cycles of single-agent or combination chemotherapy.

Outcome variables

Recurrence-free interval was defined as the time interval between date of diagnosis and date of first recurrence. Disease recurrence was defined as a biopsy-verified appearance of a new lesion, reappearance of any lesion that had disappeared, or development of tumor-related symptoms. Survival time was defined as the time interval between date of diagnosis and date of death or date of last contact [21]. Patients lost to follow-up or alive at the end of follow-up were censored.

Response to chemotherapy was defined as responders (platinum-sensitive) and non-responders (platinum-resistant) based on the treatment-free interval after initial chemotherapy [22]. A responder was defined as an ovarian cancer patient who had a treatment-free interval greater than 6 months from the last date of the initial six cycles of platinum-based single-agent or combination chemotherapy. A non-responder was defined as an ovarian cancer patient who had a treatment-free interval less than 6 months from the last date of the initial six cycles of platinum-based single-agent or combination chemotherapy. This group included patients who progressed during chemotherapy or had persistent disease at completion of chemotherapy. Finally, residual disease after primary cytoreductive surgery was defined as optimal if cytoreduction of all visible tumor down to ≤2 cm maximum diameter was performed and as suboptimal if residual disease was >2 cm after surgery.

Statistical analysis

The distributions of the demographic variables by outcomes of interest among patients were compared using the χ² test for categorical variables and the two-sample Student’s t-test for continuous variables. The association of each SNP with the risk of recurrence and death was analyzed by the Cox proportional hazard model adjusting for age, histology, and stage. The probabilities of survival and recurrence-free interval were calculated using the product-limit estimate of Kaplan and Meier. The curves were examined for equality of survival distributions by the log-rank test. P values for the log-rank test were adjusted for smoking, alcohol consumption, ethnicity, history type, stage, platinum-based treatment, and treatment cycles. P < 0.05 was considered statistically significant. All statistical analyses were performed using STATA statistical software (STATA, College Station, TX) [23].

Results

We analyzed 146 ovarian cancer patient samples for the panel of XP genotypes. The mean age was 57.1 (±13.8) years for all patients. The median follow-up time was 22.1 months (range 3–60 months). Table 1 summarizes the distribution of demographic, risk factor, and clinical characteristics among ovarian cancer patients with or without recurrent disease and survival. There were 83 (56.9%) recurrences and 46 (31.5%)...
deaths during the follow-up period. Clinical factors associated
with both increased recurrence and decreased survival included
high-tumor grade (P < 0.0001 and P = 0.002, respectively) and
advanced stage (P < 0.0001 and P = 0.013, respectively). Of the
146 patients analyzed, 125 (85.6%) were Caucasian. In addi-
tion, papillary serous histology was over-represented in patients
with recurrence (P = 0.012). Most patients (59%) had a dia-
gnosis of stage IIIIC high-grade papillary serous histology, and
most (76%) received platinum combination chemotherapy for
≥ 6 cycles as first-line treatment. Platinum-based chemotherapy
was used most often in patients with increased recurrences and
decreased survival (P < 0.0001 and P = 0.02, respectively).
Smoking, alcohol consumption, age, and ethnicity were not
significantly associated with the outcome variables in this study.
The study sample was representative of patients with ovarian
cancer followed for approximately 2 years, accounting for the
increased survival in advanced stage disease (65%).

Table 2 shows the association of each individual SNP with
risk of recurrence and death from ovarian cancer analyzed by a
multivariate Cox proportional hazard model adjusted for age,
stage, and histology in Caucasians. There were insufficient
Hispanic and African-American patients for subgroup analysis.
Carriers of at least one variant allele of the XPA SNP had a
significant risk of recurrence compared with carriers of the wild-type allele (HR 9.11, 95% CI 1.12–73.90). The XPD
polymorphisms were also significantly associated with overall survival: carriers of at least one variant allele of the XPD
exon10 SNP had a significantly reduced risk of death compared with carriers of the wild-type allele (HR 0.19, 95% CI 0.05–
0.68); the association was similar for XPD exon23 SNP (HR
0.17, 95% CI 0.01–0.96). For XPG, carriers of at least one
variant allele had a significantly increased risk of death com-
pared with carriers of the wild-type allele (HR 8.90, 95% CI
1.25–63.57).

Table 2
<table>
<thead>
<tr>
<th>Gene Genotype</th>
<th>Non-responders</th>
<th>Responders</th>
<th>Adjusted HR (95% CI)</th>
</tr>
</thead>
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<tr>
<td>XPA AA</td>
<td>3 (7.5)</td>
<td>5 (7.6)</td>
<td>Ref.</td>
</tr>
<tr>
<td>AG</td>
<td>13 (32.5)</td>
<td>31 (46.9)</td>
<td>2.35 (0.38–14.51)</td>
</tr>
<tr>
<td>GG</td>
<td>24 (60.0)</td>
<td>30 (45.5)</td>
<td>1.09 (0.18–6.65)</td>
</tr>
<tr>
<td>AG+GG</td>
<td></td>
<td></td>
<td>1.54 (0.27–8.56)</td>
</tr>
<tr>
<td>XPC −/−</td>
<td>14 (35.0)</td>
<td>26 (39.4)</td>
<td>Ref.</td>
</tr>
<tr>
<td>−/+</td>
<td>18 (45.0)</td>
<td>29 (43.9)</td>
<td>0.61 (0.22–1.69)</td>
</tr>
<tr>
<td>+/+</td>
<td>8 (20.0)</td>
<td>11 (16.7)</td>
<td>0.35 (0.09–1.35)</td>
</tr>
<tr>
<td>−/+ and +/+</td>
<td></td>
<td></td>
<td>0.48 (0.18–1.23)</td>
</tr>
<tr>
<td>XPD10 GG</td>
<td>16 (41.0)</td>
<td>31 (46.3)</td>
<td>Ref.</td>
</tr>
<tr>
<td>GA</td>
<td>15 (38.5)</td>
<td>30 (44.8)</td>
<td>0.82 (0.30–2.21)</td>
</tr>
<tr>
<td>AA</td>
<td>8 (20.5)</td>
<td>6 (8.9)</td>
<td>0.55 (0.14–2.16)</td>
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<tr>
<td>GA + AA</td>
<td></td>
<td></td>
<td>0.72 (0.29–1.80)</td>
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<tr>
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<td>14 (35.0)</td>
<td>25 (37.3)</td>
<td>Ref.</td>
</tr>
<tr>
<td>AC</td>
<td>19 (47.5)</td>
<td>27 (40.3)</td>
<td>0.61 (0.23–1.64)</td>
</tr>
<tr>
<td>CC</td>
<td>7 (17.5)</td>
<td>15 (22.4)</td>
<td>1.21 (0.35–4.19)</td>
</tr>
<tr>
<td>AC + CC</td>
<td></td>
<td></td>
<td>0.75 (0.30–1.84)</td>
</tr>
<tr>
<td>XPG GG</td>
<td>25 (62.5)</td>
<td>45 (67.2)</td>
<td>Ref.</td>
</tr>
<tr>
<td>GC</td>
<td>12 (30.0)</td>
<td>20 (29.8)</td>
<td>1.05 (0.40–2.76)</td>
</tr>
<tr>
<td>CC</td>
<td>3 (7.5)</td>
<td>2 (3.0)</td>
<td>0.48 (0.07–3.37)</td>
</tr>
<tr>
<td>GC + CC</td>
<td></td>
<td></td>
<td>0.92 (0.37–2.28)</td>
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</table>

* Adjusted for age, stage, and histology.

Table 3
<table>
<thead>
<tr>
<th>NER gene polymorphisms and chemotherapy response in ovarian cancer patients treated with platinum-based chemotherapy (≥ 6 cycles)</th>
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<tbody>
<tr>
<td>Gene</td>
</tr>
<tr>
<td>------</td>
</tr>
<tr>
<td>XPA</td>
</tr>
<tr>
<td>AG</td>
</tr>
<tr>
<td>GG</td>
</tr>
<tr>
<td>AG+GG</td>
</tr>
<tr>
<td>XPC</td>
</tr>
<tr>
<td>−/+</td>
</tr>
<tr>
<td>+/+</td>
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<tr>
<td>−/+ and +/+</td>
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<td>XPD10</td>
</tr>
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<td>GA</td>
</tr>
<tr>
<td>AA</td>
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<tr>
<td>GA + AA</td>
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<td>XPD23</td>
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<tr>
<td>AC</td>
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<td>CC</td>
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<td>AC + CC</td>
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<tr>
<td>XPG</td>
</tr>
<tr>
<td>GC</td>
</tr>
<tr>
<td>CC</td>
</tr>
<tr>
<td>GC + CC</td>
</tr>
</tbody>
</table>

* Adjusted for age, stage, and histology.
NER gene polymorphisms and chemotherapy response in ovarian cancer patients treated with first-line platinum-based single-agent or combination chemotherapy for \( \geq 6 \) cycles are shown in Table 3. The association between responders (platinum-sensitive) and non-responders (platinum-resistant) and the panel of XP polymorphisms was assessed by a multivariable logistic regression model adjusted for age, stage, and histology. Each gene was compared with the wild genotypes. There was no statistical significant difference between responders and non-responders and the XP genotypes. The lack of statistical significance can be accounted for by the low sample size.

We further analyzed the associations of these polymorphisms with recurrence-free interval and overall survival using the Kaplan–Meier survival functions (see Fig. 1A–C). The median recurrence-free survival time for patients with the XPA heterozygous variant genotype (AG) (11.3 months) was significantly shorter than that for women with the wild-type genotype (AA) (13.9 months, \( P = 0.05 \), Fig. 1A). The median survival time for patients with the XPA heterozygous variant genotype (21.5 months) was significantly shorter than that for women with the wild-type genotype (37.9 months, \( P = 0.03 \), Fig. 1B). Finally, the median survival time for patients with the XPG homozygous variant genotype (CC) (8.3 months) was significantly shorter than the median for patients with the wild-type genotype (GG) (24.6 months, \( P = 0.006 \), Fig. 1C).

**Discussion**

Platinum-based therapy is a cornerstone of advanced ovarian cancer treatment and radiosensitization in cervical cancer treatment. Cisplatin forms many di-adducts in DNA, reacting mostly with guanines [24]. The NER pathway is the major repair system for removing bulky DNA lesions, including cisplatin-induced DNA intrastrand links. Genetic variation in the form of SNPs in coding and regulatory sequences of the NER pathway may result in subtle structural alterations in DNA repair enzymes and subsequent modulation of NER capacity. Several studies have reported conflicting findings regarding the association of DNA repair gene polymorphisms with clinical outcomes in other cancers [15–18]. For example, a study by Park et al. [15] of patients with advanced colorectal cancer suggested that the XPD exon23 wild-type variant polymorphism was associated with a better response to chemotherapy (\( P = 0.015 \)) and a longer median survival (\( P = 0.002 \)) compared with the heterozygous and homozygous variants. However, a study in patients with non-small-cell lung cancer treated with platinum chemotherapy reported a shorter overall survival (\( P = 0.003 \)) with the variant alleles in the XPD exon10 gene polymorphism [17]. A similar study in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy did not find an association between either XPD10 or XPD23 and survival [18].

Our study assessed the association between a panel of DNA repair polymorphisms of the NER pathway and clinical outcome in a cohort of ovarian cancer patients. Results of our analysis of the XPD polymorphisms show that they were significantly associated with overall survival. For example, carriers of at least one variant allele of the XPD exon10 SNP had a significant 81% reduced risk of death; the association was similar for XPD exon23 SNP, with an 83% reduced risk of death. These results are in agreement with the findings of Park et al. [15]. For XPG SNP, carriers of at least one variant allele had approximately 9-fold increased risk of death. Furthermore, individuals with a homozygous variant XPG allele had a significantly shorter median survival compared with individuals with the homozygous XPG wild-type allele.

Among the NER genes in our study, XPA is an essential DNA-binding protein in the NER pathway [25]. We have previously reported that the G variant allele seems to have a protective effect in lung cancer subjects with at least one copy of the G allele; those individuals had a more efficient DNA repair capacity than individuals with the homozygous A allele [26]. In this study, we found that individuals with a heterozygous...
variant XPA allele had a shorter median survival and shorter median time to recurrence than individuals with the homozygous wild-type allele. This finding is consistent with our hypothesis that efficient DNA repair genotype is associated with a reduced cancer risk but poorer clinical outcome.

The two most frequently studied XPD polymorphisms have been exon 10 Asp312Asn (G/A transition) and exon 23 Lys751Gln (C/A transversion) [27–29]. We have previously reported a suboptimal DNA repair capacity in head and neck cancer patients with the variant A allele of exon10 SNP (Asp312Asn) [30]. Results of our analysis of the XPD polymorphisms show that carriers of at least one variant allele of the exon10 (Asp312Asn) SNP had a significantly reduced risk of death and the association was similar for XPD exon23 (Lys751Gln) SNP. This finding again supports our hypothesis that DNA repair genotypes play an opposing role in cancer risk as well as clinical outcome.

The role of XPG in predicting ovarian cancer outcome is also interesting [31,32]. Carriers of at least one variant allele of Asp1104His SNP had a significantly increased risk of death compared with carriers of the wild-type allele. Furthermore, individuals with a homozygous variant XPG allele had a significantly shorter median survival (8.3 months, \( P=0.006 \)) compared with individuals with the homozygous XPG wild-type allele (24.6 months). The functional impact of this XPG SNP however, is unclear.

To evaluate platinum sensitivity, the panel of XP polymorphisms and the chemotherapy response were also assessed in this study. Patients were classified as “responders” and “non-responders” based on treatment response. No statistically significant difference was seen in response to chemotherapy and the XP genotypes probably due to the limited sample size. In a study by Ryu et al. [18], the association between polymorphisms of ERCC1 (excision repair cross-complementing group 1) and chemotherapy response in non-small-cell lung cancer patients treated with cisplatin combination chemotherapy was similarly evaluated. They found that the presence of the C/C genotype of ERCC1 suggested a trend of greater response (platinum sensitivity) than that of C/T or T/T genotypes compared with non-responders. No other study in ovarian cancer and DNA repair polymorphisms has evaluated the data in this manner.

To our knowledge, this is the first study to study the use of DNA repair genetic polymorphisms as predictive biomarkers of disease outcome and response to chemotherapy. However, there were limitations in this study. The sample size was inadequate to draw any definitive conclusions or perform any subgroup analyses with respect to associations between the NER genotypes and platinum response. As with other retrospective study designs, information bias is present. For example, evaluation of clinical response and ascertainment of time progression, as well as certain clinical information, were difficult to obtain from the medical record. Such cases were excluded, further limiting our sample size. Every effort was made to gather missing information, including use of the Tumor Registry and Social Security Death Index. Furthermore, an element of selection bias may have been introduced in our cohort population by the fact that M. D. Anderson Cancer Center is a large referral center and may not be reflective of the population of typical ovarian cancer patients. However, the prevalence of the polymorphisms in these patients did not differ from that in the general population.

Evaluations of clinical response and time to progression are often imprecise but nonetheless critical to further elucidating the mechanism by which DNA repair affects outcome. The predictive and prognostic role of DNA repair gene polymorphisms in clinical outcomes is the subject of a growing body of literature in pharmacogenomics [33,34]. These parameters can determine whether these polymorphisms are predictive of treatment response or prognostic by determining outcome. On the basis of the expected outcome of the patient, both factors may be important in the choice of chemotherapy agents. Evaluation of genetic polymorphisms in cancer susceptibility may help us to understand the significance of these polymorphisms in the identification of individuals at higher risk of developing resistance to anticancer drug therapies. This study suggests that NER gene polymorphisms may modulate platinum chemotherapy response and patient survival. In the future, larger studies may provide a more complete understanding of relevant genetic factors and environmental exposures that could result in improved strategies for determining both chemotherapy choice and efficacy in clinical trials.

Conflict of interest statement
We declare that we have no conflict of interest.

References