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Gene Polymorphisms and Gene Expression Profiles as Potential Predictors of Survival Outcomes in Ovarian Cancer: Systematic Review and Meta-Analysis of Pharmacogenetic/Genomic and Microarray Data

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Abstract

Background: Taxane/platinum chemotherapy has improved ovarian cancer survival, but interindividual variability is a current challenge.

Objectives: To compile published information and online available data regarding the impact of germline polymorphic variants or tumor expression profiles on survival outcomes of ovarian cancer.

Methods: A systematic search was conducted on PubMed, Science Direct, and Scopus to select studies evaluating associations between gene variants and survival outcomes of ovarian cancer patients under taxane/platinum protocols. The genes identified with at least two independent reports regarding their polymorphisms and any survival outcome were also evaluated for the prognostic impact of tumor expression profiles, via online platforms with compiled microarray data (GEO/KM plotter).

Results: The systematic search (CRD42017075105 at PROSPERO) resulted in 82 articles, and meta-analyses were conducted for 13 polymorphisms with at least three independent findings. ERCC1 C8092A (rs3212986) was significantly associated with disease progression (HR=1.32; 95% CI = 1.12-1.55) and death (HR=1.55; 95% CI = 1.23-1.97), whereas ERCC2 C862A (rs1799793) favored progression-free survival (HR=0.81; 95% CI = 0.68-0.97). High ERCC1 mRNA significantly increased the risk of disease progression (HR=1.21; 95% CI = 1.04-1.40) and death (HR=1.21; 95% CI = 1.03-1.41), whereas high GSTP1 mRNA favored better overall survival (HR=0.82; 95% CI = 0.72-0.94).

Conclusion: Variant genotypes of ERCC1 C8092A as well as increased tumor ERCC1 mRNA indicate worse survival outcomes after paclitaxel/carboplatin chemotherapy, and may contribute for prognostic evaluation of ovarian cancer patients.

Keywords: Gene polymorphisms; Tumor expression profile; Prognostic biomarkers; Ovarian cancer; Platinum; Taxanes

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Introduction

Ovarian cancer ranks 7th in incidence (3.6%), mortality (4.3%) and 5-year prevalence (3.4%) among women worldwide [1]. The 5-year survival rates are lower than 30%, mostly because patients are usually diagnosed at advanced stages [2].

Over the past three decades, significant advances have been made in the therapeutic approach of ovarian cancer, and the combination of cytoreductive surgery followed by the doublet of a taxane (paclitaxel 135 mg/m² to 175 mg/m²) and carboplatin (AUC>5), administered every 3 weeks, has been established as the best first-line regimen [3].

Despite the benefits of the taxane/platinum combination therapy to survival rates of ovarian cancer patients [3], response to chemotherapy may be compromised by the development of

tumor resistance to taxanes or to platinum compounds [4]. It has been proposed that sequence variants in the genome, including single nucleotide polymorphisms, might have an impact on clinical outcomes of ovarian cancer either indirectly by altering the systemic disposition of chemotherapeutic agents or by specific changes in the drug concentration or in the cellular sensitivity in target tissues [5].

In addition to sequence variants in the genome, there is also individual variability in the cellular mechanisms of gene transcription, mRNA stability and protein translation, all of which might lead to variations in the final gene expression profile in tumors [4]. Understanding how gene expression profiles might affect tumor sensitivity to chemotherapeutic agents and influence survival outcomes is a challenge towards improving individual prognostic estimates.

In the present review, we aimed to compile all published information and online available data regarding the impact of germline polymorphic variants or tumor expression profiles on survival outcomes of ovarian cancer patients. The main research questions were: a) which gene polymorphisms are reported to affect the progression-free or overall survival of paclitaxel/carboplatin chemotherapy for ovarian cancer? b) Is it possible to establish a consensus for any polymorphism or gene expression profile regarding their association with survival outcomes of ovarian cancer patients?

Material and Methods

Bibliographic review

The present bibliographic review was conducted by following the principles of the Cochrane Handbook for Systematic Reviews of Intervention [6], and the data are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria [7]. The protocol used was prospectively registered with the PROSPERO database (ID: CRD42017075105), and is described below [8].

Search strategy

A systematic review of the literature data was performed *via* electronic search of the following databases: PubMed (using both general and MeSH terms), Science Direct and Scopus. The main search with general terms was as follows: ((((paclitaxel [Title/Abstract/Keywords] OR docetaxel [Title/Abstract/Keywords] OR cisplatin [Title/Abstract] OR carboplatin [Title/Abstract/Keywords])) OR taxane [Title/Abstract/Keywords] OR platinum [Title/Abstract/Keywords]) AND (polymorphism [Title/Abstract/Keywords] OR polymorphisms [Title/Abstract/Keywords] [Title/Abstract/Keywords] OR pharmacogenetics [Title/Abstract/Keywords] OR pharmacogenomics [Title/Abstract/Keywords]) AND (ovarian [Title/Abstract/Keywords] OR gynecological [Title/Abstract/Keywords] OR gynecologic [Title/Abstract/Keywords]))))) NOT Review [ptyp]. Filters: English.

At PubMed/MeSH, the search was as follows: ((((("Paclitaxel"[Mesh] OR "docetaxel" [Supplementary Concept] OR "Carboplatin"[Mesh] OR "Cisplatin"[Mesh]) AND ("Polymorphism, Genetic"[Mesh] OR "Polymorphism, Single Nucleotide"[Mesh]) AND ("Ovarian Neoplasms"[Mesh] OR "Ovarian epithelial cancer" [Supplementary Concept]))))) NOT "Review" [Publication Type]. Filters: English.

There was no time restriction, except for Scopus, which was limited to 2008-2019.

Study selection

After removal of duplicates, abstracts were retrieved and used for selection of articles to be used in the review (authors CLC, DRF-A, JBP). The predefined inclusion criteria were: Original articles (clinical trials or epidemiological studies), involving ovarian cancer patients treated with taxanes or platinum drugs, and evaluating associations between germline polymorphic variants and any clinical response or survival outcome. Abstracts identified as "non-original study" (letters, commentaries, editorials or reviews), "case report", "non-ovarian cancer" or "non-available article" were excluded. Full-text articles were obtained for the remainder.

Available articles of selected abstracts were screened in full for exclusion criteria by three independent reviewers (CLC, DRF-A, JBP), as follows: *in vitro* studies or reports of somatic mutations only; lack of treatment description and articles with data on the prevalence of polymorphisms, pharmacokinetics, gene expression or histopathological features, but no evaluation of clinical outcomes (either efficacy or survival). Doubts and discrepancies were resolved through discussion and further checked with a fourth author (RV-J). The process of study selection is demonstrated by the flow chart in Figure 1.

Data extraction and management

Selected articles were read to extract information regarding study design (including recruitment strategies, eligibility criteria, chemotherapy protocols, treatment details and study completion rates), characterization of the study population (size, demographics and baseline characteristics); genotyping methodology; outcomes analyzed and analytical strategies (including whether multivariate analyses were performed). Three review authors extracted data independently (CLC, DRF-A, JBP). Discrepancies were double-checked and resolved through discussion with a fourth author when necessary (RV-J).

Assessment of risk of bias in included studies

The risk of bias in each included study was evaluated using the Cochrane Collaboration's tool and criteria [6]. In brief, the following aspects were considered: (i) study design; (ii) criteria for patients enrollment and treatment selection; (iii) source of DNA (tumoral or non-tumoral), genotyping method, prevalence of polymorphisms and adherence or not to Hardy-Weinberg Equilibrium; iv) whether or not patients included in analyses of each study are representative of the larger population who would be treated for this condition (external validity); iv) whether or not internal variations (for example: Histological types of ovarian cancer, clinical staging, ethnicities, various treatments) were appropriately considered for analyses (i.e. internal validity). Three authors reviewed the articles independently (CLC, DRF-A, JBP); differences were resolved by consensus or discussion with a fourth author when necessary (RV-J).

Meta-analyses

Statistical analyses were conducted with Stata 13.0 (College Station, TX). The association between polymorphisms and Progression-Free Survival (PFS) or Overall Survival (OS) in ovarian cancer patients was based on the Hazard Ratios (HR) and corresponding 95% Confidence Intervals (CIs). The between-study heterogeneity was tested using Q test and I2 test, and was considered significant if P-value was less than 0.05. Summary statistics were obtained using a fixed-effects model if the P-value was more than 0.05; otherwise, random effects model was used [9]. Inverted funnel plots and Egger's test were used to evaluate

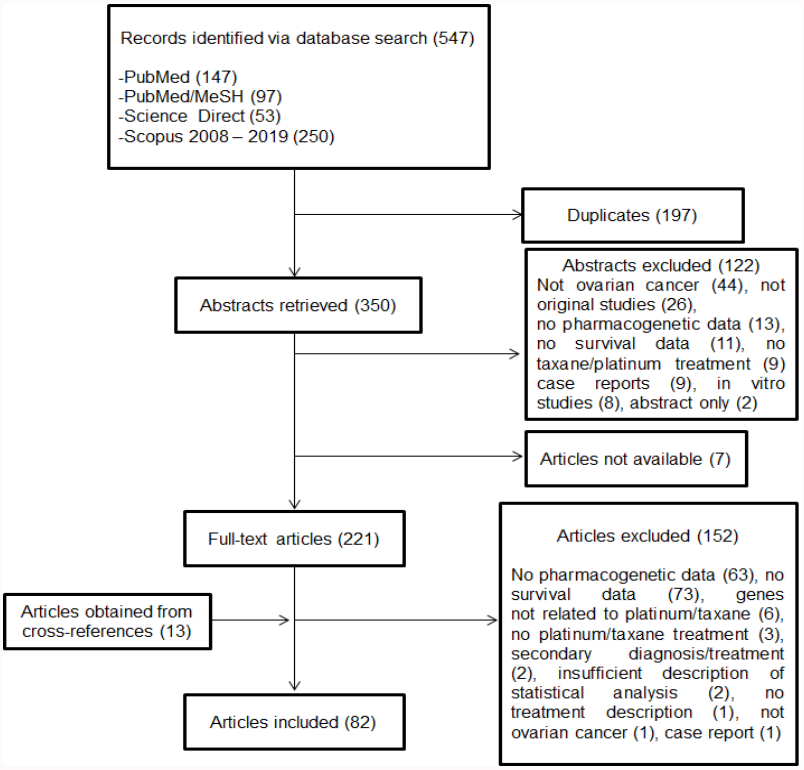

Figure 1: Flow chart showing the process of study selection.

the effect of publication bias (by linear regression analysis).

Impact of tumor expression profiles on survival outcomes

Progression-free and overall survival analyses were analyzed according to tumor mRNA levels, using data obtained from publically available gene expression array databases. The analyses were conducted using data compiled in the GEO platform *via* the online software KM plotter (www.kmplot.com) [10], with evaluation of all available probes for each gene, and setting the automatic selection of best cutoff value of mRNA expression to categorize tumor expression as "low" or "high". PFS and OS were estimated at 60 months of follow-up. No additional filters were used.

Results

Bibliographic search, study selection and data extraction

The bibliographic search, whose steps are described in a flowchart (Figure 1), resulted in 82 original studies that were identified as evaluating the association between gene polymorphisms and clinical response or survival outcomes of ovarian cancer, either overall or progression-free survival. The main characteristics of these studies are depicted in Supplementary Table S1. Most articles were observational studies of case series (n=52; 63.4%). Other study designs included case-control studies (n=14; 17.1%), secondary analyses of randomized clinical trials (n=7; 8.5%), cohorts (n=4; 4.9%) or consortia of independent cohorts (n=5; 6.1%). Study size, based on the number of individuals who had genotyping data, ranged from 24 to 5248 patients, with a median of 205.5 and a mean of 373.6. Origin of participants was referred mainly as their geographical origin (N=75; 91.5%), with a predominance of countries or regions in Europe (N=40; 48.8%), followed by Asia (N=17; 20.7%) and America (N=16; 19.5%). Ethnicity was explicitly stated in 14 articles (17.1%), with Caucasian being the predominant description (N=10; 12.2%), followed by Chinese Han (N=4; 4.9%).

Additional information regarding specific aspects of the study design was also collected in order to evaluate possible causes of bias. In brief, most studies included all histological types and all stages of epithelial ovarian cancer; only seven reports (8.5%) restricted their analysis to serous tumors [11-17], and other seven studies (8.5%) evaluated only late stage tumors [13,18-23]. Staging or other parameters of internal validity were not reported by only five studies (6.1%) [12,17,24-26]. Chemotherapeutic protocols were mostly referred as platinum-based (n=38; 46.3%) [4,11-13,15,16,18,20-22,24,25,27-52], or platinum/taxane combinations (n=33; 40.2%) [5,14,19,23,53-81], with the specific association of carboplatin/paclitaxel being reported in 18 studies (21.9%) [5,14,53,55,57,58,61-65,67-69,73,74,76,78], followed by cisplatin/paclitaxel (n=5; 6.1) [23,70,72,75,77]. Only one study described treatment as taxane-based [82]. Regarding genotyping analysis, most studies (n=62; 75.6%) used blood-derived specimens [4,11,13,15,16,18,22-26,29-32,35-37,39-45,48,54,56,60-70,72,74-95], nineteen studies (23.17%) used frozen tumor tissue [16,17,19,21,28,33,34,47,49,52,66,71,83,87,89,96-99], four studies (4.9%) performed genotyping on formalin-fixed paraffin-embedded material [5,12,20,27], and in three studies (3.7%) the source for genotyping was not clearly stated [14,50,59]. Fourteen studies (17.1%) did not report multivariate analysis of their results [15,21,24,26,30,34,36,58,69,74,81,89,92,95].

Impact of polymorphisms on survival outcomes of ovarian cancer patients treated with platinum/taxane chemotherapy

All significant associations that were reported by single studies are presented in Supplementary Table S2. In addition, Table 1 summarizes the findings for 31 polymorphisms that were evaluated by at least two independent studies [4,5,11-13,15,16,18,20,21,23,24,27-

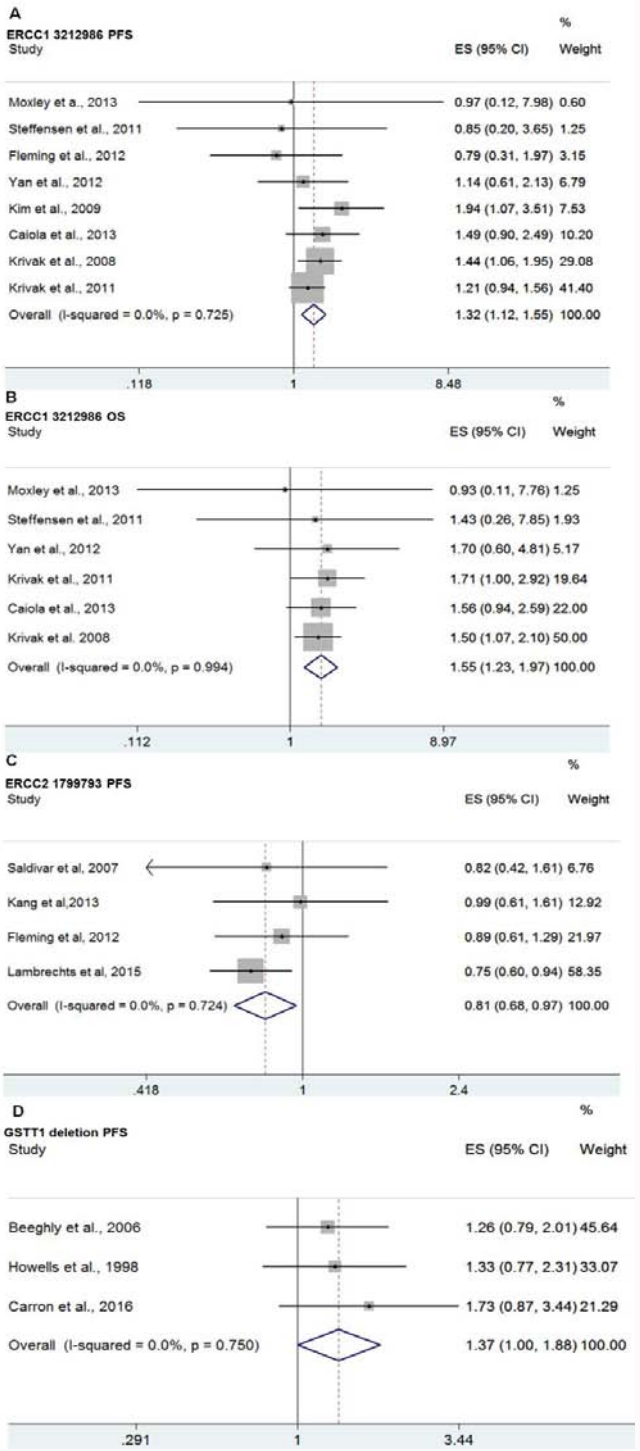

Figure 2: Forest plots for the meta-analyses of the impacts of the polymorphism ERCC1 rs3212986 on PFS (A) and OS (B) and of the polymorphism ERCC2 rs1799793 on OS (C) of ovarian cancer patients treated with taxane/platinum chemotherapy.

32,35,41,42,44,46-48,50,58,62,63,65,67-70,72,74,76,77,82-84,98,100].

Significant associations were found for 21 polymorphisms, 14 of which had at least one report of increased risk of disease progression or cancer-related death (ABCB1 G2677T/A, ABCB1 C3435T, ABCB1 G1199A, ABCC2 G1249, CYP3A4 A392G, GSTM1 gene deletion, GSTP1 A313G, GSTT1 gene deletion, ERCC1 C118T, ERCC1 C8092A, XPG rs17655, XRCC1 C580T, XRCC1 A1196G, TP53 C215G). Such findings, however, were not consistent among different studies.

In order to have a combined evaluation of the multiple available results regarding the impact of gene polymorphisms on survival outcomes of ovarian cancer patients, we conducted separate meta-analyses for each polymorphism with at least three independent reports. The meta-analyses were performed including all individual studies with available HR data, and considering all variant genotypes for pooled statistics. The results are presented in Table 2 [5,12,13,16,18,20,23,24,28-30,35,44,46,50,63,65,67,68,70,76,77,82,84].

Figure 2 shows the forest plots for the meta-analyses with significant results: ERCC1 C8092A (rs3212986) showed an increased risk of disease progression (HR=1.32; 95% CI = 1.12-1.55) or death (HR=1.55; 95% CI = 1.23-1.97), whereas ERCC2 C862A (rs1799793) favored PFS (HR=0.81; 95% CI = 0.68-0.97). GSTT1 null genotypes also showed a borderline increase in the risk of disease progression (HR=1.32; 95% CI = 1.00-1.88). No publication bias was detected using either the funnel plot or Egger's test (data not shown).

Impact of tumor expression profiles on survival outcomes of ovarian cancer

The impact of tumor expression profile on survival outcomes of ovarian cancer patients was analyzed for all genes identified at the bibliographic search with at least two independent reports regarding possible associations between polymorphisms and survival (Table 1). Table 3 presents the findings obtained for all genes with available data in the online platform [101]. The results indicate significant associations between tumor expression and PFS for all genes except GSTT1. In contrast, only ERCC1 and GSTP1were significantly associated with OS, high tumor expression of ERCC1 presenting an increased risk of death (HR=1.21; 95% CI = 1.03 - 1.41), whereas high GSTP1expression had a protective effect (HR=0.82; 95% CI = 0.72-0.94).

Discussion

Ovarian cancer mortality is still a major concern worldwide. Despite the improvements on treatment outcomes with aggressive surgical cytoreduction and platinum/paclitaxel combination chemotherapy, long-term survival has not been uniformly increased [3]. Many studies have demonstrated that drug response to antineoplastic chemotherapy may be influenced by genetic variation affecting pharmacokinetic pathways or tumor cell targets. Nevertheless, literature information on potential new biomarkers is quite scarce, and no consensus has emerged yet. In this regard, the present systematic review aimed to compile all available published data on the effects of gene polymorphisms on survival outcomes of platinum/taxane-based chemotherapy for ovarian cancer. To the best of our knowledge, this is the most extensive literature search conducted so far, with 82 reports involving 132 genes and 228 polymorphisms with significant associations on survival outcomes of ovarian cancer patients.

Most polymorphisms (N=126) were evaluated in single studies or had not enough quantitative data for compiled analysis. For example, the only ABCB1 polymorphism with at least three independent articles presenting quantitative data of its impact on ovarian cancer outcomes was G2677T/A [5,62,63,76,77]. However, the meta-analysis of such data suggested no significant impact either on PFS or OS.

Regarding GST genes, the current meta-analysis showed no

Table 1: Reported associations between gene polymorphisms and ovarian cancer survival outcomes (results from multiple studies).

Cellfunction	Gene	rs	Polymorphism	Phenotype	Affected	Outcome	HR	95% CI	P	N	Author	Protocol
Transmembrane transport	*ABCB1*	1128503	C1236T	Synonymous	wt/var	PFS	**0.7**	**0.48-0.91**	**0.012**[a]	**309**	Johnatty et al. [62]	Carbo/PXT
					var/var	PFS	**0.6**	**0.40-0.89**	**0.012**[a]			
					wt/var	PFS	-	-	NS	51	Gréen et al. [58]	PXT/Carbo
					anyvariant	PFS	1.02	0.94-1.11	0.57	1873	Johnatty et al. [63]	Carbo/PXT
					anyvariant	PFS	-	-	0.719[b]	454	Marsh et al. [4]	Carbo/Tax
					var/var	PFS	-	-	NS	60	Obata et al. [21]	Plat-based
					wt/var	PFS	**0.7**	**0.46-0.90**	**0.011**	265	Björn et al. [26]	Carbo/Tax
					var/var	PFS	0.69	0.46-1.04	0.079	265		
					var/var	OS	1.18	0.84-1.66	NS	119	Bergmann et al. [5]	Carbo/PXT
					var/var	OS	0.75	0.38-1.46	0.4	309	Johnatty et al. [62]	Carbo/PXT
					anyvariant	OS	0.98	0.89-1.08	0.75	1873	Johnatty et al. [63]	Carbo/PXT
					vt/var	OS	0.87	0.46-1.66	0.68	265	Björn et al. [26]	Carbo/Tax
					var/var	OS	0.59	0.26-1.30	0.19	265		
					var/var	OS	-	-	**0.025**	**276**	Maliszewska et al. [91]	Plat-based
		2032582	G2677T/A	Ala893Thr	anyvariant	PFS	**0.6**	**0.45-0.83**	**0.002**[a]	**309**	Johnatty et al. [62]	Carbo/PXT
					anyvariant	PFS	**0.7**	**0.61-0.88**	**0.001**	**433**[c]	Johnatty et al. [63]	Carbo/PXT
					anyvariant	PFS	**2.1**	**1.07-4.28**	**0.031**	**126**	Teczaet al. [76]	CDDP/PXT
					NI	PFS	-	-	0.7[b]	106	Grimm et al. [31]	Plat-based
					anyvariant	PFS	0.99	0.91-1.08	0.83	1882	Johnatty et al. [63]	Carbo/PXT
					anyvariant	PFS	-	-	0.023[b]	454	Marsh et al. [4]	Carbo/Tax
					anyvariant	PFS	0.99	0.81-1.22	0.92	511	Tian et al. [77]	Plat/Tax
					anyvariant	OS	**0.7**	**0.62-0.89**	**0.001**	**433**[c]	Johnatty et al. [63]	Carbo/PXT
					anyvariant	OS	1.16	0.84-3.5	NS	119	Bergmann et al. [5]	Carbo/PXT
					anyvariant	OS	-	-	0.8[b]	106	Grimm et al. [31]	Plat-based
					anyvariant	OS	0.93	0.56-1.58	0.8	309	Johnatty et al. [62]	Carbo/PXT
					anyvariant	OS	1	0.9-1.1	0.92	1882	Johnatty et al. [63]	Carbo/PXT
					anyvariant	OS	0.89	0.71-1.11	0.29	511	Tian et al. [77]	Plat/Tax
					wt/var	OS	1.09	0.55-2.17	0.801	265	Björn et al. [26]	Carbo/Tax
					var/var	OS	0.64	0.28-1.47	0.29	265		
					NI	PFS/OS	-	-	NS	118	Kim et al. [16]	Plat/Tax
	ABCB1	1045642	C3435T	Synonymous	var/var	PFS	**1.6**	**1.07-2.40**	**0.02**[a]	**309**	Johnatty et al. [62]	Carbo/PXT
					anyvariant	PFS	-	-	0.7*	106	Grimm et al. [31]	Plat-based
					anyvariant	PFS	0.99	0.91-1.07	0.81	1873	Johnatty et al. [63]	Carbo/PXT
					anyvariant	PFS	-	-	0.614[b]	454	Marsh et al. [4]	Carbo/Tax
					var/var	PFS	-	-	NS	60	Obata et al. [21]	Plat-based
					anyvariant	PFS	1.07	0.86-1.34	0.55	512	Tian et al. [77]	Plat/Tax
					wt/var	PFS	**0.6**	**0.41-0.88**	**0.009**	**265**	Björn et al. [26]	Carbo/Tax
					var/var	PFS	**0.6**	**0.41-0.96**	**0.032**	**265**		
					var/var	OS	-	-	NS	119	Bergmann et al. [5]	Carbo/PXT
					anyvariant	OS	-	-	0.5[b]	106	Grimm et al. [31]	Plat-based
					var/var	OS	1.4	0.74-2.63	0.3	309	Johnatty et al. [62]	Carbo/PXT
					anyvariant	OS	0.97	0.88-1.06	0.51	1873	Johnattyet al. [63]	Carbo/PXT
					anyvariant	OS	0.97	0.76-1.24	0.8	512	Tian et al. [77]	Plat/Tax
					wt/var	OS	0.93	0.41-2.1	0.87	265	Björn et al. [26]	Carbo/Tax
					var/var	OS	0.67	0.27-1.68	0.4	265		
					NI	PFS/OS	-	-	NS	118	Kim et al. [16]	Plat/Tax

Transmembrane transport	*ABCB1*	2229109	G1199T/A	Ser400Asn	wt/var	PFS	-	-	NS	51	Gréen et al. [58]	Carbo/PXT
					anyvariant	PFS	**2.4**	**1.15-4.98**	**0.02**	**265**	Björn et al. [26]	Carbo/Tax
					wt/var	OS	**2**	**1.08-3.83**	**0.03**	**119**	Bergmann et al. [5]	PXT /Carbo
					wt/var	OS	-	-	0.89	**276**	Maliszewska et al. [91]	Plat-based
					var/var	OS	-	-	0.54	**276**	Maliszewska et al. [91]	Plat-based
		12334183	C/T	Intronvariant	per allele	PFS	**0.7**	**0.52-0.88**	**0.004**	**367**	Peethambaram et al. [42]	Tax-based
					anyvariant	OS	0.98	0.93-1.03	0.37	5248	White et al. [50]	Plat-based
		10264990	T/C	Intron variant	per allele	PFS	1.2	1.00-1.44	0.05	368	Peethambaram et al. [42]	Tax-based
					anyvariant	OS	1	0.96-1.05	0.84	5248	White et al. [50]	Plat-based
	ABCC2	2273697	G1249A	Ile417Val	var/var	PFS	**1.6**	**1.06-2.48**	**0.025**	**511**	Tian et al. [77]	Plat/Tax
					anyvariant	PFS	-	-	0.278[b]	454	Marsh et al. [4]	Carbo/Tax
					var/var	PFS	-	-	NS	60	Obata et al. [21]	Plat-based
					anyvariant	OS	1.04	0.86-1.27	0.692	511	Tian et al. [77]	Plat/Tax
		717620	C24T	non-coding	anyvariant	PFS	-	-	0.619[b]	454	Marsh et al. [4]	Carbo/Tax
					var/var	PFS	-	-	NS	60	Obata et al. [21]	Plat-based
	ABCG2	2231142	C421A	Gln141Lys	anyvariant	PFS	**0.8**	**0.59-0.96**	**0.022**	511	Tian et al. [77]	Plat/Tax
					anyvariant	PFS	-	-	0.427[b]	454	Marsh et al. [4]	Carbo/Tax
					anyvariant	OS	0.88	0.67-1.15	0.356	511	Tian et al. [77]	Plat/Tax
Conjugation/oxidative metabolism	*CYP2C8*	11572080/ 10509681	G416A/ A1196G (*3)	Arg139Lys/ Lys399Arg	anyvariant	PFS	-	-	0.617[b]	454	Marsh et al. [4]	Carbo/Tax
					var/var	OS	-	-	NS	119	Bergmann et al. [5]	PXT /Carbo
	CYP3A4	2740574	A392G (*1)	non-coding	anyvariant	PFS	-	-	0.687[b]	454	Marsh et al. [4]	Carbo/Tax
					anyvariant	OS	**2.2**	**1.03-4.52**	**0.043**	**261**	Assis et al. [11]	Plat-based
	GSTM1	____	Gene deletion	null/non-null	null	PFS	**0.7**	**0.43-0.99**	–	**215**	Beeghlyet al. [28]	Plat-based
						PFS	**increased PFS**		**0.024**[b]	**24**	Medeiros et al.[69]	CDDP/PXT
						PFS	**increased PFS**		**0.013**[b]	**261**	Pereira et al.[82]	Plat/Tax
						PFS	1.26	0.63-2.50	0.50[a]	84	Carron et al. [86]	Plat-based
						PFI	1.42	0.88-2.78	0.15	148	Howells et al. [87]	Plat-based
						OS	**2.3**	**1.04-5.03**	**0.039**	**261**	Pereira et al. [82]	Plat/Tax
						OS	**increased OS**		**0.006**[b]	**24**	Medeiros et al.[69]	CDDP/PXT
						OS	0.68	0.45-1.03	NS	215	Beeghlyet al. [28]	Plat-based
						OS	0.71	0.22-2.28	0.56	95	Cong et al. [12]	Plat-based
						OS	0.82	0.59-1.14	0.25	239	Nagle et al. [18]	Plat-based
						OS	-	-	NS	29	Morari et al. [41]	Plat-based
						OS	1.22	0.58-2.59	0.59[a]	84	Carron et al. [86]	Plat-based
						OS	1.65	0.98-2.79	0.06	148	Howells et al. [87]	Plat-based
						OS	-	-	NS	33	Lallas et al. [89]	Platinum/CTX/ PXT
						OS	3.78	0.46-31.4	0.22	64	Zhai et al. [17]	PXT+Carbo
						PFS/OS	-	-	NS	118	Kim et al. [16]	Plat/Tax
	GSTP1	1695	A313G	Ile105Val	wt/wt	PFS	**decreased PFS**		**<0.001**[b]	**100**	Khrunin et al.[24]	CDDP/CTX
					var/var	PFS	1.03	0.69-1.56	NS	215	Beeghlyet al. [28]	Plat-based
					anyvariant	PFS	-	-	NS	454	Marsh et al. [4]	Carbo/Tax
					anyvariant	PFS	**decreased**		0.0007	56	Yoshihama et al.[95]	PXT/carbo
					anyvariant	PFS	**1.2**	**0.65-2.33**	0.51[a]	84	Carron et al. [86]	Plat-based
					anyvariant	OS	**0.8**	**0.61-0.99**	**0.04**	**448**	Nagle et al. [18]	Plat-based
					wt/var	OS	1.78	0.77-4.12	0.18	95	Cong et al. [12]	Plat-based
					var/var	OS	0.93	0.61-1.42	NS	215	Beeghly et al. [28]	Plat-based
					NI	OS	-	-	NS	100	Khrunin et al. [24]	CDDP/CTX
					NI	OS	-	-	NS	29	Morari et al. [41]	Plat-based
					anyvariant	OS	**decreased**		0.0012	56	Yoshihama et al.[95]	PXT/carbo

Conjugation/oxidative metabolism					anyvariant	OS	**1.1**	**0.53-2.19**	0.81[a]	84	Carron et al. [86]	Plat-based
					wt/var	OS	1.45	0.32-6.54	0.63	64	Zhai et al. [17]	PXT+Carbo
					NI	PFS/OS	-	-	NS	118	Kim et al. [16]	Plat/Tax
	GSTT1	____	Gene deletion	null/non-null	non null	PFS	**decreased PFS**		**0.013**[b]	**118**	Kim et al.[16]	Plat/Tax
					null	PFS	1.26	0.79-2.02	NS	215	Beeghly et al. [28]	Plat-based
	GSTT1	____	Gene deletion	null/non-null	null	PFS	-	-	0.853[b]	24	Medeiros et al. [69]	CDDP/PXT
					null	PFS	1.73	0.87-3.44	0.11[a]	84	Carron et al. [86]	Plat-based
					null	PFI	1.33	0.77-2.32	0.31	148	Howells et al. [87]	Plat-based
					non null	OS	**1.7**	**1.79-3.42**	**0.038**	**118**	Kim et al. [16]	Plat/Tax
					null	OS	1.2	0.75-1.91	NS	215	Beeghlyet al. [28]	Plat-based
					null	OS	0.82	0.54-1.23	0.34	239	Nagle et al. [18]	Plat-based
					non null	OS	-	-	0.525[b]	24	Medeiros et al. [69]	CDDP/PXT
					NI	OS	-	-	NS	29	Morari et al. [41]	Plat-based
					null	OS	**2.1**	**1.02-4.36**	**0.04**	**84**	Carron et al. [86]	Plat-based
					null	OS	1.28	0.7-2.35	0.43	148	Howells et al. [87]	Plat-based
					non null	PFS/OS	-	-	NS	261	Pereira et al. [82]	Plat/Tax
	GSTM1/ GSTT1	____/___	Gene deletion/ Gene deletion	null/non-null	null	PFS	1.07	0.61-1.87	NS	215	Beeghlyet al. [28]	Plat-based
					non null	PFS	-	-	NS	24	Medeiros et al. [69]	CDDP/PXT
					null/null	PFI	**2.9**	**1.43-5.97**	**0.003**	**148**	Howells et al. [87]	Plat-based
					anynull	OS	**increased OS**		**0.009**[b]	**24**	Medeiros et al. [69]	CDDP/PXT
					null	OS	0.97	0.54-1.71	NS	215	Beeghly et al. [28]	Plat-based
					null/null	OS	**3.4**	**1.67-7.09**	**0.001**	**148**	Howells et al. [87]	Plat-based
DNA repair	*ERCC1*	11615	C118T	Asn118Asn	TT (ref.CC)	PFS	**3.3**	**1.77-6.29**	**-**	209	Yan et al. [84]	Plat-based
					CC+CT (ref.TT)	PFS	1.05	0.77-1.44	0.744	235	Caiola et al. [29]	Plat-based
					CT (ref.TT)	PFS	1.16	0.73-1.85	NS	99	Fleming et al. [13]	Plat-based
					TT (ref.CC)	PFS	0.79	0.51-1.22	NS	233	Krivak et al. [23]	CDDP/PXT
					CT+TT (ref.CC)	PFS	0.85	0.63-1.15	0.288	280	Krivak et al. [35]	CDDP/PXT
					CC (ref.TT)	PFS	1.07	0.61-1.86	0.812	176	Smith et al. [46]	Plat-based
					TT (ref.CC)	PFS	0.6	0.25-1.48	0.271	183	Steffensen et al. [100]	Carbo/PXT
					CT+TT(ref.CC)	PFS	-	-	0.268[b]	60	Kang et al. [15]	Plat-based
					anyvariant	PFS	-	-	0.851[b]	454	Marsh et al. [4]	Carbo/Tax
					per- gen(ref.TT)	PFS	-	-	0.85[b]	98	Moxley et al. [20]	Plat-based
					CT+TT (ref.CC)	OS	**0.7**	**0.49-0.95**	**0.025**	**280**	Krivak et al. [35]	(Carbo/PXT)-based
					TT (ref.CC)	OS	**2.9**	**1.38-5.96**	**-**	**209**	Yan et al. [84]	Plat-based
					CC+CT (ref.TT)	OS	0.93	0.67-1.29	0.667	235	Caiola et al. [29]	Plat-based
					TT (ref.CC)	OS	0.72	0.45-1.16	-	233	Krivak et al. [23]	CDDP/PXT
					CC (ref.TT)	OS	1.55	0.90-2.65	0.113	176	Smith et al. [46]	Plat-based
					TT (ref.CC)	OS	1.61	0.83-3.13	0.16	159	Steffensen et al. [47]	Carbo/CTX
					TT (ref.CC)	OS	0.87	0.26-2.89	0.826	183	Steffensen et al. [100]	Carbo/PXT
					CT+TT(ref.CC	OS	-	-	0.622[b]	60	Kang et al. [15]	Plat-based
					per- gen(ref.TT)	OS	-	-	0.58[b]	98	Moxley et al. [20]	Plat-based
					NI	PFS/OS	-	-	NS	118	Kim et al. [16]	Plat/Tax
	ERCC1	3212986	C8092A	Gln504Lys	any variant (ref CC)	PFS	**1.9**	**1.07-3.51**	**0.03**	**118**	Kim et al. [16]	Plat/Tax
					anyvariant (ref CC)	PFS	**1.4**	**1.06-1.94**	**0.018**	**233**	Krivak et al. [23]	CDDP/PXT
					AA (ref CC)	PFS	0.97	0.11-8.11	0.978	106	Moxley et al. [20]	Plat-based
					CA + CC (ref AA)	PFS	0.67	0.4-1.11	0.118	235	Caiola et al. [29]	Plat-based
					CC (ref AA)	PFS	1.27	0.51-3.2	NS	99	Fleming et al. [13]	Plat-based
					any variant (ref CC)	PFS	1.21	0.94-1.56	0.132	280	Krivak et al. [35]	(Carbo/PXT)-based

DNA repair	*ERCC1*	3212986	C8092A	Gln504Lys	AA (ref CC)	PFS	0.85	0.2-3.67	0.825	183	Steffensen et al. [100]	Carbo/PXT
					AA (ref CC)	PFS	1.14	0.61-2.13	NS	209	Yan et al. [84]	Plat-based
					anyvariant (ref CC)	PFS	-	-	0.677[b]	454	Marsh et al. [4]	Carbo/Tax
					anyvariant (ref CC)	OS	**decreased OS**		**0.042**[b]	**118**	Kim et al.[16]	Plat/Tax
					anyvariant (ref CC)	OS	**1.5**	**1.07-2.09**	**0.018**	**233**	Krivak et al. [23]	CDDP/PXT
					var/var	OS	**1.7**	**1.00-2.91**	**0.049**	**280**	Krivak et al. [35]	(Carbo/PXT)-based
					CA + CC (ref AA)	OS	0.64	0.39-1.07	0.088	235	Caiola et al. [29]	Plat-based
					AA (ref CC)	OS	0.93	0 0.11-7.65	0.946	106	Moxley et al. [20]	Plat-based
					AA (ref CC)	OS	1.43	0.26-7.81	0.677	183	Steffensen et al. [100]	Carbo/PXT
					AA (ref CC)	OS	1.7	0.6-4.81	NS	209	Yan et al. [84]	Plat-based
	ERCC2	1799793	G862A	Asp312Asn	anyvariant	PFS	**increased PFS**		**0.027**[a]	**100**	Khrunin et al. [24]	CDDP/CTX
					anyvariant	PFS	**0.8**	**0.60-0.95**	**0.016**	**241**	Lambrechts et al. [67]	Carbo/PXT
					anyvariant	PFS	**0.8**	**0.42-1.62**	**-**	**183**	Saldivar et al. [44]	Carbo/PXT
					anyvariant	PFS	0.89	0.61-1.29	NS	126	Fleming et al. [13]	Plat-based
					var/var	PFS	0.99	0.61-1.62	NS	213	Kang et al. [65]	Plat-based
					var/var	OS	1.07	0.62-1.87	NS	213	Kang et al. [65]	Plat-based
					anyvariant	OS	**0.2**	**0.05-0.68**	-	183	Saldivar et al. [44]	Carbo/PXT
					NI	OS	-	-	NS	100	Khrunin et al. [24]	CDDP/CTX
		13181	A2251C	Lys751Gln	anyvariant	PFS	**increased PFS**		**0.017**[a]	**100**	Khrunin et al. [24]	CDDP/CTX
					anyvariant	PFS	1	0.68-1.48	NS	134	Fleming et al. [13]	Plat-based
					any variant	PFS	1.25	0.76-2.05	NS	213	Kang et al. [65]	Plat-based
					any variant	PFS	0.6	0.28-1.29	-	183	Saldivar et al. [44]	Carbo/PXT
					anyvariant	PFS	-	-	0.562[b]	454	Marsh et al. [4]	Carbo/Tax
					anyvariant	OS	**0.2**	**0.01-0.96**	**-**	**183**	Saldivar et al. [44]	Carbo/PXT
					anyvariant	OS	1.41	0.80-2.50	NS	213	Kang et al. [65]	Plat-based
					anyvariant	OS	0.99	0.95-1.04	0.71	5248	White et al. [50]	Plat-based
					NI	OS	-	-	NS	100	Khrunin et al. [24]	CDDP/CTX
					NI	PFS/OS	-	-	NS	118	Kim et al. [16]	Plat/Tax
	ERCC2	238417	C/G	Intronvariant	per-allele	PFS	**0.8**	**0.60-0.94**	**0.01**	**365**	Peethambaram et al. [42]	Plat-based
					anyvariant	OS	1.01	0.97-1.06	0.49	5248	White et al. [50]	Plat-based
		238415	C/G	Intron variant	per-allele	PFS	**0.8**	**0.60-0.95**	**0.02**	**365**	Peethambaram et al. [42]	Plat-based
					anyvariant	OS	1.02	0.97-1.06	0.46	5248	White et al. [50]	Plat-based
	XPG	17655	C/G	Intron variant	any variant (ref CC)	PFS	**2.1**	**1.1-4.12**	**0.026**	**235**	Caiola et al. [29]	Plat-based
					GC+CC (ref GG)	PFS	1.16	0.56-2.4	-	183	Saldivar et al. [44]	Carbo/PXT
					GC+CC (ref GG)	OS	**8.9**	**1.25-63.6**	**-**	**183**	Saldivar et al. [44]	Carbo/PXT
					anyvariant (ref CC)	OS	1.5	0.77-2.91	0.229	235	Caiola et al. [29]	Plat-based
	XRCC1	1799782	C580T	Arg194Trp	var/var	OS	**0.6**	**0.34-0.96**	**<0.05**	**335**	Li & Li [68]	Plat-based
					var/var	OS	**1.6**	**1.04-3.15**	**<0.05**	**195**	Miao et al. [70]	BLM/VP/CDDP
					var/var	OS	1.11	0.55-2.18	0.76	310	Cheng C-X [30]	Plat-based
					wt/var	OS	0.57	0.10-3.15	0.52	64	Zhai et al. [7]	PXT+Carbo
					var/var	OS	0.46	0.08-2.63	0.38	64	Zhai et al. [17]	PXT+Carbo
					per-genotype	PFS/OS	-	-	NS	213	Kang et al. [65]	Plat-based
					NI	PFS/OS	-	-	NS	118	Kim et al. [16]	Plat/Tax
		25487	A1196G	Arg399Gln	anyvariant	PFS	1.12	0.76-1.65	NS	213	Kang et al. [65]	Plat-based
					anyvariant	PFS	-	-	0.254[b]	454	Marsh et al. [4]	Carbo/Tax
					var/var	OS	**1.7**	**1.07-2.78**	**<0.05**	**309**	Cheng et al. [30]	Plat-based
					var/var	OS	**0.4**	**0.28-0.91**	**<0.05**	**335**	Li & Li [68]	Plat-based
					var/var	OS	**2**	**1.09-3.93**	**<0.05**	**195**	Miao et al. [70]	BLM/VP/CDDP

DNA repair	*XRCC1*	25487	A1196G	Arg399Gln	anyvariant	OS	1	0.63-1.58	NS	213	Kang et al. [65]	Plat-based
					wt/var	OS	1.43	0.33-6.10	0.63	64	Zhai et al. [17]	PXT+Carbo
					NI	PFS/OS	-	-	NS	118	Kim et al. [16]	Plat/Tax
		25489	G839A	Arg280His	anyvariant	PFS	1.13	0.73-1.74	NS	213	Kang et al. [65]	Plat-based
					var/var	OS	1.16	0.37-3.46	0.77	310	Cheng et al. [30]	Plat-based
					anyvariant	OS	0.96	0.56-1.63	NS	213	Kang et al. [65]	Plat-based
					var/var	OS	1.06	0.31-3.68	0.81	335	Li & Li [68]	Plat-based
					var/var	OS	1.46	0.72-3.01	0.37	195	Miao et al. [70]	BLM/VP/CDDP
Signaltransduction	*VEGFA*	2010963	G405C	non-coding	anyvariant	PFS	0.9	0.7-1.3	0.7	553	Polterauer et al. [72]	Plat-based
					wt/var	PFS	-	-	0.33[b]	143	Steffensen et al. [48]	Carbo/PXT
					anyvariant	OS	1.4	0.9-2.2	0.09	553	Polterauer et al. [72]	Plat-based
					var/var	OS	-	-	NS	563	Hefler et al. [32]	Plat-based
					wt/var	OS	-	-	0.033	159	Smerdel et al. [98]	Carbo/CTX
		833061	–T460C	non-coding	anyvariant	PFS	1.1	0.7-1.6	0.8	553	Polterauer et al. [72]	Plat-based
					wt/var	PFS	-	-	0.14[b]	143	Steffensen et al. [48]	Carbo/PXT
					anyvariant	OS	0.8	0.5-1.3	0.4	553	Polterauer et al. [72]	Plat-based
					var/var	OS	-	-	NS	159	Smerdel et al. [98]	Carbo/CTX
		3025039	C936T	non-coding	anyvariant	PFS	0.9	0.7-1.3	0.7	553	Polterauer et al. [72]	Plat-based
					per-genotype	PFS	-	-	0.19[b]	143	Steffensen et al. [48]	Carbo/PXT
					anyvariant	OS	0.9	0.6-1.3	0.6	553	Polterauer et al. [72]	Plat-based
		699947	C2578A	non-coding	per-genotype	PFS	-	-	0.14[b]	143	Steffensen et al. [48]	Carbo/PXT
					anyvariant	OS	-	-	NS	563	Hefler et al. [32]	Plat-based
		1570360	– G1154A	non-coding	per-genotype	PFS	-	-	0.27[b]	143	Steffensen et al. [48]	Carbo/PXT
					anyvariant	OS	-	-	NS	563	Hefler et al. [32]	Plat-based
Cellcycleregulation	*CDKN1A*		C10971T		anyvariant	PFS	-	-	0.305[b]	454	Marsh et al. [4]	Carbo/Tax
					anyvariant	PFS/OS	-	-	NS	114	Santos et al. [74]	CDDP/PXT
	TP53	1042522	C215G	Arg72Pro	anyvariant	PFS	**decreased PFS**		**0.011**[b]	114	Santos et al.[74]	CDDP/PXT
					anyvariant	PFS	-	-	NS	454	Marsh et al. [4]	Carbo/Tax
					var/var	OS	**6.5**	**1.07-6.45**	**0.035**	103	Bartel et al. [27]	Plat-based
					anyvariant	OS	-	-	NS	112	Concin et al. [83]	Carbo
					NI	OS	-	-	NS	29	Morari et al. [41]	Plat-based
					anyvariant	OS	-	-	0.32[b]	114	Santos et al. [74]	CDDP/PXT
					NI	PFS/OS	-	-	NS	100	Khrunin et al. [24]	CDDP/CTX

Statistically significant results are shown in bold. HR: Hazard Ratio (unless otherwise mentioned, results were adjusted, at least, for: age, histological type and FIGO staging); PFS: Progression-Free Survival; OS: Overall Survival; NS: Not Significant; BLM: Bleomycin; Carbo: Carboplatin; CDDP: Cisplatin; CTX: Cyclophosphamide; Plat: Platinum drugs; PXT: Paclitaxel; Tax: Taxane; VP: Etoposide

[a]Non-adjusted Cox model

[b]Log-Rank test

Table 2: Meta-analysis of reported associations between gene polymorphisms and ovarian cancer survival outcomes.

Gene	Polymorphism (rs)	PFS					OS				
		N	I^2	HR	95% CI	Author	N	I^2	HR	95% CI	Author
ABCB1	1128503	-	-	-	-	-	2257	24.5	1	0.83 - 1.19	Bergmann et al. [5]
											Johnatty et al. [63]
											Björn et al. [26]
	2032582	2519	57.4	1.05	0.86 - 1.27	Johnatty et al. [63]	2777	0	0.98	0.89 - 1.07	Bergmann et al. [5]
						Tecza et al. [76]					Johnatty et al. [63]
						Tian et al. [77]					Tian et al. [77]
											Björn et al. [26]
	1045642	2650	58.3	0.95	0.79 - 1.15	Johnatty et al. [63]	2650	0	0.97	0.89 - 1.05	Johnatty et al. [63]
						Tian et al. [77]					Tian et al. [77]
						Björn et al. [26]					Björn et al. [26]

ERCC1	11615	1415	65.8	0.99	0.74 - 1.33	Caiola et al. [29]	1475	67.3	1	0.70 - 1.43	Caiola et al. [29]
						Fleming et al. [13]					Krivak et al. [23]
						Krivak et al. [23]					Smith et al. [46]
						Smith et al. [46]					Steffensen et al. [47]
						Steffensen et al. [100]					Yan et al. [84]
						Yan et al. [84]					
	3212986	1463	0	1.32	1.12 - 1.55	Caiola et al. [29]	1246	0	1.55	1.23 - 1.97	Caiola et al. [29]
						Fleming et al. [13]					Krivak et al. [23]
						Kim et al. [16]					Moxley et al. [20]
						Krivak et al. [23]					Steffensen et al. [100]
						Moxley et al. [20]					Yan et al. [84]
						Steffensen et al. [100]					
						Yan et al. [84]					
ERCC2	1799793	763	0	0.81	0.68 - 0.97	Fleming et al. [13]	-	-	-	-	-
						Kang et al. [65]					
						Lambrechts et al. [67]					
						Saldivar et al. [44]					
	13181	530	19.8	0.99	0.71 - 1.38	Fleming et al. [13]	5644	46.9	1.04	0.68 - 1.59	Kang et al. [65]
						Kang et al. [65]					Saldivar et al. [44]
						Khruninet al. [24]					White et al. [50]
						Saldivar et al. [44]					
GSTM1	Null genotype	447	64.6	1.01	0.59 - 1.72	Beeghly et al. [28]	1106	58.8	1.11	0.76 - 1.63	Beeghly et al. [28]
						Carron et al. [86]					Cong et al. [12]
						Howells et al. [87]					Nagle et al. [18]
											Pereira et al. [82]
											Carron et al. [86]
											Howells et al. [87]
											Zhai et al. [17]
GSTP1	1695	-	-	-	-	-	906	14.3	0.91	0.71 - 1.15	Beeghly et al. [28]
											Cong et al. [12]
											Nagle et al. [18]
											Carron et al. [86]
											Zhai et al. [17]
GSTT1	Null genotype	447	0	1.37	1.0 - 1.88	Beeghly et al. [28]	804	71.3	1.03	0.69 - 1.53	Beeghly et al. [28]
						Carron et al. [86]					Kim et al. [16]
						Howells et al. [87]					Nagle et al. [18]
											Carron et al. [86]
											Howells et al. [87]
XRCC1	25487	-	-	-	-	-	1116	74.8	1.13	0.65 - 1.97	Cheng et al. [30]
											Kang et al. [65]
											Li & Li [68]
											Miao et al. [70]
											Zhai et al. [17]
	25489	-	-	-	-	-	1053	0	1.12	0.76 - 1.63	Cheng et al. [30]
											Kang et al. [65]
											Li & Li [68]
											Miao et al. [70]

XRCC1	1799782	-	-	-	-	-	904	52.3	0.98	0.57 - 1.67	Cheng et al. [30]
											Li & Li [68]
											Miao et al. [70]
											Zhai et al. [17]

Statistically significant results are shown in bold. PFS: Progression-Free Survival; OS: Overall Survival; I2: Heterogeneity Test; HR: Hazard Ratio; 3'-UTR: 3'-Untraslated Region

Table 3: Associations between high gene expression in ovarian tumors and survival outcomes according to data compiled in GEO platform [10].

Gene	PFS (N=1435)			OS (N=1656)		
	HR	95% CI	P	HR	95% CI	P
ABCB1	0.81	0.70 - 0.94	0.0051	1.02	0.89 - 1.17	0.77
ABCC2	0.85	0.74 - 0.96	0.011	0.94	0.82 - 1.08	0.36
ABCG2	0.91	0.80 - 1.04	0.015	1.04	0.91 - 1.19	0.58
CDKN1A	0.85	0.74 - 0.96	0.012	0.87	0.76 - 1.0	0.05
CD3EAP	0.86	0.74 - 0.99	0.036	0.9	0.77 - 1.05	0.17
ERCC1	1.21	1.04 - 1.40	0.011	1.21	1.03 - 1.41	0.017
ERCC2	1.15	1.01 - 1.32	0.036	1.11	0.95 - 1.28	0.18
GSTM1	0.79	0.69 - 0.91	0.00077	0.92	0.79 - 1.06	0.23
GSTP1	0.84	0.74 - 0.96	0.0093	0.82	0.72 - 0.94	0.0057
GSTT1	1.11	0.98 - 1.27	0.11	1.08	0.92 - 1.27	0.34
TP53	0.81	0.71 - 0.92	0.0014	0.88	0.77 - 1.02	0.082
VEGFA	1.28	1.13 - 1.46	0.00016	1.01	0.88 - 1.15	0.94
XPG	1.23	1.08 - 1.40	0.0014	1.07	0.93 - 1.23	0.36
XRCC1	1.19	1.04 - 1.35	0.0087	1.03	0.89 - 1.18	0.7

Statistically significant results are shown in bold. PFS: Progression-free survival; OS: Overall survival; HR: Hazard Ratio

significant results of GSTP1A313G or GSTM1 null genotype on ovarian cancer OS, except for a borderline increased risk of disease progression in association with GSTT1 null genotype. The evaluation of the impact of tumor expression profiles indicates that high GSTP1 mRNA expression is associated with better survival outcomes. Unfortunately, there was no available online data on mRNA expression of GSTM1 or GSTT1.

A previous meta-analysis by Assis et al. [102] found a significantly lower risk of death associated with GSTM1 null genotype compared to wild-type carriers, but only when restricting the analysis to advanced stages of ovarian cancer (HRadj =0.68; 95% CI = 0.48-0.97) or to patients treated only with platinum-based chemotherapy (HRadj =0.61; 95% CI = 0.39-0.94). Regarding GSTT1, Assis et al. [102] found GSTT1-null genotype to be significantly associated with a lower risk of disease progression (HRadj =0.60; 95% CI = 0.38-0.93), but only in the subgroup of patients submitted to platinum-based chemotherapy (n=142). The original studies included by Assis et al. [102] are the same that were considered here. Differences in the findings are due to subgroup analyses, and reflect the variability of inclusion criteria and statistical analyses of survival outcomes among the original studies. Despite such differences and possible slight effects of GST variants on patients' response to chemotherapy, no clear predictive role can be attributed that may influence prognostic evaluation of ovarian cancer.

The lack of statistically significant associations in the current meta-analyses for polymorphisms involved with the pharmacokinetics of taxanes and platinum drugs should not be regarded as definitive. First, the number of studies with available quantitative data from multivariate statistical analysis was quite limited (3 to 4 studies for each polymorphism). Second, most studies were retrospective, i.e. not specifically designed to evaluate the effects of gene polymorphisms. Third, the results across studies were expressed using different genetic models of inheritance and different combinations of genotypes, which were grouped for the current meta-analyses. In addition, no additional adjustments for potential confounding variables were performed in meta-analyses, since only final aggregated data from original studies were available. Finally, the most common chemotherapeutic drugs, i.e. carboplatin and paclitaxel, have their pharmacokinetics affected by multiple enzymes, which limits the likelihood of establishing the role of single genetic variants.

In addition to genes coding for proteins involved with the pharmacokinetics of taxanes and platinum drugs, polymorphisms in genes related to cellular mechanisms of DNA repair have also been explored for their possible contribution as pharmacogenetic targets to guide ovarian cancer chemotherapy. Polymorphisms in ERCC1, ERCC2 and in XRCC1 have been explored by various authors, and could be included in the present meta-analysis evaluation [13,16,20,23,29,30,35,46,47,65,68,70,84,100]. Significant results were found only for ERCC1 C8092A (rs3212986), which increased the risk of disease progression and death, as well as for ERCC2 C862A (rs1799793), which favored progression-free survival. The polymorphisms in XRCC1 (rs25487, rs25489, rs1799782) showed no significant results in the meta-analysis, which could be performed only for OS since only Kang et al. [65] presented HR data for the impact of XRCC1 rs25487 and rs25489 on PFS.

The apparently beneficial effect of ERCC2 C862A (rs1799793) in reducing the risk of disease progression was suggested independently by several authors, and appears to be related to a reduction in the capacity of DNA repair by tumor cells, resulting in increased DNA

damage and enhanced cytotoxic effect of cisplatin [13,24,44,65,67]. As the available online data regarding the ERCC2 mRNA expression in ovarian tumors suggests no significant impacts on survival outcomes and ERCC2 C862A is a non-synonym polymorphism that leads to amino acid change, its effect is more likely to involve altered ERCC2 function in tumor cells.

The gene polymorphism with most promising potential to identify patients at higher risk of treatment failure seems to be ERCC1 C8092A (rs3212986). It was associated with increased risk of disease progression [16,23], and of death in independent studies [16,23,35], and such associations were confirmed in the current meta-analyses. A previous meta-analysis conducted by Yan et al. [51] also reported that the variant genotypes of ERCC1 C8092A were associated with worse OS among ovarian cancer patients, whereas the homozygous variant genotype AA was also associated with worse PFS. The authors also included ERCC1C118T polymorphism (rs11615) in their meta-analyses, and in agreement with our present data, found no association with the clinical outcomes of ovarian cancer patients treated with platinum-based chemotherapy. In comparison with the work by Yan et al. [51], the current meta-analyses included two other studies, which were published afterwards [13,29]. Therefore, the number of ovarian cancer patients evaluated for the impact of ERCC1 C8092A on survival outcomes was expanded from 1102 to 1463 for the analysis of PFS or from 984 to 1246 for the analysis of OS. Regarding the meta-analyses for ERCC1C118T polymorphism (rs11615), the number of ovarian cancer patients evaluated was expanded from 877 to 1415 for the analysis of PFS or from 977 to 1475 for the OS.

The meta-analysis by Assis et al. [102] also evaluated ERCC1 polymorphisms under different subgroup analyses. Regarding ERCC1C8092A (rs3212986), the authors also found higher risks of death and of disease progression in association with variant genotypes under the dominant model of inheritance. Regarding ERCC1C118T (rs11615), the authors reported no impact for on the risk of progression, but a marginally protective effect regarding the risk of death when considering the dominant model of inheritance for the subgroup submitted to the specific platinum-paclitaxel combination (n=352; HRadj = 0.71; 95% CI = 0.52-0.98; P=0.04).

The ERCC1C8092A polymorphism occurs within a 3'-untranslated region that has been shown to be involved in translational repression of ERCC1 mRNA [103]. More recently, Yu et al. [104] have shown that the rs3212986. A variant might change ERCC1 mRNA structure, leading to a stem-loop chain within its upstream sequence that would be unfolded. In addition, rs3212986 also affects the opposite orientated, adjacent coding region of CD3EAP, which may lead to amino acid substitutions or to a gained stop codon at position 504 [https://www.ncbi.nlm.nih.gov/snp/rs3212986]. Yu et al. used cell lines transfected with CC or AA variants of both ERCC1 and CD3EAP to evaluate their impact on the repair efficiency of DNA damage. The authors reported reduced DNA repair associated with ERCC1 (AA), but not with CD3EAP (AA) overexpressed cells, suggesting that the major effect of rs3213986 polymorphism was driven by regulating ERCC1 3'-untranslated region [104]. Such cellular effects of ERCC1C8092A polymorphism in reducing the repair efficiency of DNA damage appear to be contradictory with its prognostic prediction of worse outcomes in ovarian cancer patients treated with platinum-based protocols.

Regarding the prognostic effects of ERCC1 expression in ovarian tumors, both ERCC1 mRNA [105], and protein expression [47,106] have been found to be inversely correlated with response to platinum based chemotherapy. In addition, Smith et al. found that high ERCC1 mRNA was associated with higher risk of disease progression, although only in ovarian cancer patients treated with a platinum regimen not including paclitaxel [97]. Steffensen et al. [47] evaluated ERCC1 protein levels in ovarian tumors by immunohistochemistry, and found that ERCC1 positivity was a highly significant predictor of early disease recurrence (75% of the patients with positive ERCC1 relapsed within 6 months as compared to 26.7% of those with negative staining for ERCC1), resulting in a significant reduction in PFS. However, the authors found no significant association with overall survival. The only independent finding in apparent discrepancy is that of Codegoni et al. [107], who showed a negative correlation (p=0.037) between the expression of ERCC1 and mortality, i.e. patients with higher tumor expression of ERCC1 had longer survival. Nevertheless, the work was based on a very small cohort (33 patients). The current analysis of compiled online mRNA data available at the GEO platform confirms the significant deleterious impact of high ERCC1mRNAexpression on both PFS and OS, whereas CD3EAP mRNA showed only a borderline protective effect on PFS and no significant impact on OS.

Taken together, the results indicate that evaluation of individual genotype of ERCC1 rs3212986 or quantification of tumor ERCC1 mRNA may contribute for prognostic evaluation of ovarian cancer patients, especially those under platinum-based protocols, in order to identify patients at higher risk of disease progression or death. It would be interesting to study these two variables together, and evaluate if they might have additive prognostic contributions or if high tumor ERCC1 mRNA might be already associated with ERCC1 rs3212986 polymorphism, perhaps as a compensation of reduced mRNA activity.

Conclusion

The data compiled in this review suggest that ERCC1 C8092A (rs3212986) and ERCC2 C862A (rs1799793) may contribute as prognostic factors of survival outcomes for ovarian cancer patients treated with chemotherapeutic protocols based on taxane and platinum compounds either alone or in combination. Variant genotypes of ERCC2 C862A suggest more favorable prognosis, with reduced risk of disease progression, whereas ERCC1 C8092A increases the risks of disease progression and death. Quantification of tumor mRNA levels of ERCC1 and GSTP1 may also contribute as prognostic factors: the first indicates higher risks of disease progression and death, whereas the second favors better survival outcomes.

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