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Review Article

Genetic Polymorphisms as Treatment Biomarkers for Gynecological Malignancies Treated With Carboplatin and Paclitaxel: A Systematic Review

Nadine de Godoy Torso, MSc[1], Yasmim Gabriele Matos, PharmB[1], Giovana Fernanda Santos Fidelis, BPharm[1], Carolina Dagli-Hernandez, PhD[2,3], Marília Berlofa Visacri, PhD[3], Eder de Carvalho Pincinato, PhD[1], Jefman Efendi Marzuki, MD[4,5,6], Baharuddin Baharuddin, MSc[4,7,8], Paulo Caleb J.L. Santos, PhD[9], Patricia Moriel, PhD[2,*]

[1] School of Medical Sciences, Universidade Estadual de Campinas, Campinas, Brazil
[2] Faculty of Pharmaceutical Sciences, Universidade Estadual de Campinas, Campinas, Brazil
[3] Department of Pharmacy, Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, Brazil
[4] Department of Biomedical Science, Faculty of Medicine, University of Surabaya, Surabaya, Indonesia
[5] Clinical Pharmacology Department, Faculty of Medicine, University of Surabaya, Surabaya, Indonesia
[6] Ubaya Hospital, Surabaya, Indonesia
[7] Medical Biochemistry Laboratory, Faculty of Medicine, University of Surabaya, Surabaya, Indonesia
[8] Center of Excellence for Higher Education Science and Technology, Food Products and Health Supplements for Degenerative Conditions, University of Surabaya, Surabaya, Indonesia
[9] Department of Pharmacology, Universidade Federal de São Paulo (EPM-Unifesp), São Paulo, Brazil

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ABSTRACT

Purpose: Gynecological tumors, which correspond to the group of neoplasms that affect the female reproductive system, have high incidence and mortality rates. This systematic review aimed to summarize the most recent advances in identifying pharmacogenetic variants associated with the clinical outcomes of carboplatin-paclitaxel chemotherapy in these patients.

Methods: A comprehensive literature search was conducted across eight databases to identify studies published up to July 17, 2024. Two reviewers independently selected the studies and extracted the data; disagreements were resolved by two additional reviewers.

Findings: Out of the 2375 records that were found, only 20 met the eligibility criteria. The main findings were: (1) The three most extensively investigated genes were ATP binding cassette subfamily C member 1 (*ABCB1*), cytochrome P450 2C8 (*CYP2C8*), and glutathione S-transferase P1 (*GSTP1*); (2) three variants, rs1128503 (*ABCB1*), rs10509681 and rs11572080 (*CYPC28*), appear to have a significant association with important adverse drug reactions (in particular, neutropenia, thrombocytopenia, and peripheral sensory neuropathy). Others, as is the case with rs1045642 (*ABCB1*) and rs1695 (*GSTP1*), have inconsistent results, and the extent to which these results can be extrapolated is still limited; and (c) most of the included studies concerned Asian or European patients.

Implications: Therefore, future research should include more extensive analyses with more inclusive cohorts. As a limitation of the study, a meta-analysis was not possible due to the significant heterogeneity among the studies.

Introduction

Gynecological cancers correspond to the group of neoplasms that affect the female reproductive system, encompassing tumors of the ovary, endometrium (corpus uteri), cervix, and vulva, and less frequently, tumors of the vagina and fallopian tube.[1] With a significant global impact on women's health, gynecological cancers were among the 15 most prevalent cancers for this group in 2022, both in terms of incidence and mortality.[2]

The higher mortality rates may be partly attributed to the challenging process of diagnosis. The symptoms, which may include changes in bowel habits, abdominal distension, and associated pain, are common

* Address correspondence to: Patricia Moriel, PhD, Faculty of Pharmaceutical Sciences, Universidade Estadual de Campinas, Campinas 13083-970, Brazil.
E-mail address: patricia.moriel@fcf.unicamp.br (P. Moriel).

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but nonspecific symptoms of these malignancies. Therefore, it is challenging to discern between chronic symptoms and the ones that could potentially indicate the development of a tumor.[3–5] For these reasons, most patients are diagnosed with advanced or metastatic disease, for which surgery in isolation is not appropriate.

According to the International Federation of Gynecology and Obstetrics (FIGO), the most recommended treatment regimen for recurrent or advanced stages of these tumors consists of adjuvant chemotherapy with the association of a platinum derivative and a taxane.[1] As previous clinical studies have shown, the combination of paclitaxel with carboplatin is preferred to cisplatin, due to its higher safety profile, as carboplatin has fewer nonhematological adverse drug reactions (ADRs) than its precursor cisplatin.[6–8] However, despite the positive therapeutic effectiveness,[9] these two agents have well-established ADRs profiles in clinical practice. While the carboplatin myelosuppressive effects lead to hematologic ADRs, paclitaxel is most associated with peripheral neuropathy, characterized by damage or loss of function of peripheral sensory nerves.[8,10]

Although several factors contribute to interindividual differences in the incidence and severity of ADRs, it is well-recognized that genetic variations are a significant component.[11,12] Among them, single-nucleotide variants (SNVs) can be highlighted as the most common genetic variations across the human genome. Therefore, genetic variants in genes implicated with the pharmacokinetics or pharmacodynamics of these chemotherapeutic agents could induce substantial alterations in the transcription of essential proteins for both biological processes.[13]

Chemotherapy-induced ADRs are known to significantly impair patients' quality of life and treatment success, resulting in dose delays, dose reductions, or discontinuation. Identifying the main SNVs associated with interindividual variations of ADRs may provide a better understanding of cancer treatment, being especially important in the context of personalized medicine in clinical practice. Therefore, this systematic review aimed to provide a comprehensive overview of pharmacogenetic variants associated with the clinical outcomes of carboplatin-paclitaxel chemotherapy in patients with gynecological tumors.

Materials and Methods

This review followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA) 2020 checklist and reporting guideline.[14] The review protocol was registered in Open Science Framework (https://doi.org/10.17605/OSF.IO/Q3SX7, last updated on May 08, 2024).

Search Strategy

A systematic review was conducted to answer the precise question: Which polymorphisms have already demonstrated significant associations with clinical outcomes in patients with gynecological cancers treated with carboplatin and paclitaxel? To answer this question, a comprehensive literature search was executed using eight databases (PubMed, PubMed Central, BIREME, Web of Science, Scopus, Embase, Cochrane Library, and ProQuest) to retrieve pertinent studies published in peer-reviewed journals up to July 17, 2024, without language restriction. The complete search strategy employed for each database can be found in **Supplemental (Online Only) File 1**. To ensure search sensitivity, the authors selected four articles a priori, all subsequently retrieved through the search. Additionally, the reference lists of recovered publications were consulted to identify studies possibly overlooked in the database searches.

Eligibility Criteria

The inclusion criteria were organized according to the PECOS (population, exposure, comparator, outcomes, and study design) acronym, as follows:

- "P" (population): gynecologic cancer patients (exclusively tumors of the ovary, cervix, endometrium, or vulva) who were treated with carboplatin and paclitaxel;
- "E" (exposure): altered alleles of genetic polymorphisms (regardless of the gene) associated with carboplatin and paclitaxel treatment;
- "C" (comparator): reference alleles of the genetic polymorphisms;
- "O" (outcomes): the primary outcomes of interest were: response to chemotherapy, progression-free survival (PFS), overall survival (OS), and/or ADRs (especially neurotoxicity and myelosuppression). These two ADRs were chosen as primary outcomes because they are common in chemotherapy treatment with carboplatin and paclitaxel;
- "S" (studies design): cohort, case-control, and cross-sectional studies. The criteria for noninclusion comprised books/book chapters, editorials, comments, conference proceedings or abstracts, literature reviews, and guidelines, as well as research published in non-Romance languages or for which access to full text was not possible.

Studies were selected for inclusion in this systematic review through a multi-step process. First, the retrieved studies were imported into EndNote® to remove duplicates. The remaining studies were allocated to the free tool Rayyan®,[15] where two review authors (N.d.G.T. and Y.G.M.) independently screened and analyzed the titles and abstracts. Any discrepancies were discussed with two additional reviewers (P.M. and M.B.V.). If the title and abstract failed to provide sufficient details to ensure proper exclusion, the full text was also reviewed to clarify any uncertainties and reach the final decision.

The studies chosen by this initial analysis were then subjected to a comprehensive and critical article reading. This was also independently conducted by two reviewers (N.d.G.T. and Y.G.M.), and any inconsistencies were discussed with the third and fourth reviewers (P.M. and M.B.V.).

Data Extraction and Analysis

Two reviewers (N.d.G.T. and Y.G.M.) independently extracted the data from each included study, and disagreements were once more discussed with two additional reviewers (G.F.S.F. and C.D.H.). The collected information was recorded in a Microsoft Word® predefined table, which included: first author, year of publication, country of origin, study design, sample size, age (mean or median), population diagnosis, outcome (ADRs or effectivity), criteria assessment, genotype methods, Hardy–Weinberg equilibrium (HWE), gene of the polymorphism, Single Nucleotide Polymorphism database identifiers (dbSNP ID), genotype, and allele frequencies. Results or discussions originating from other studies were not collected.

Quality Assessment

The evaluation of the methodological quality of the included studies was carried out by two reviewers (N.d.G.T. and Y.G.M.) independently, according to the Newcastle–Ottawa scale (NOS)[16]; disagreements were resolved by discussion with the third and fourth reviewers (G.F.S.F. and P.M.). Three primary domains were evaluated in each study: sample selection (four aspects), comparability of cohorts (one aspect), and outcome quality (three aspects), and the maximum NOS scores for each domain were four, two, and three stars, respectively. Therefore, each study could receive a maximum of nine stars. Finally, the present review adopted the following classification of the overall NOS methodological quality: high quality (≥7 stars), moderate quality (4–6 stars), or low quality (<4 stars).

Evidence Synthesis

Meta-analyses could not be performed due to the significant heterogeneity among the included studies. Instead, the body of evidence was categorized according to the outcome assessed (ADRs, effectiveness, or

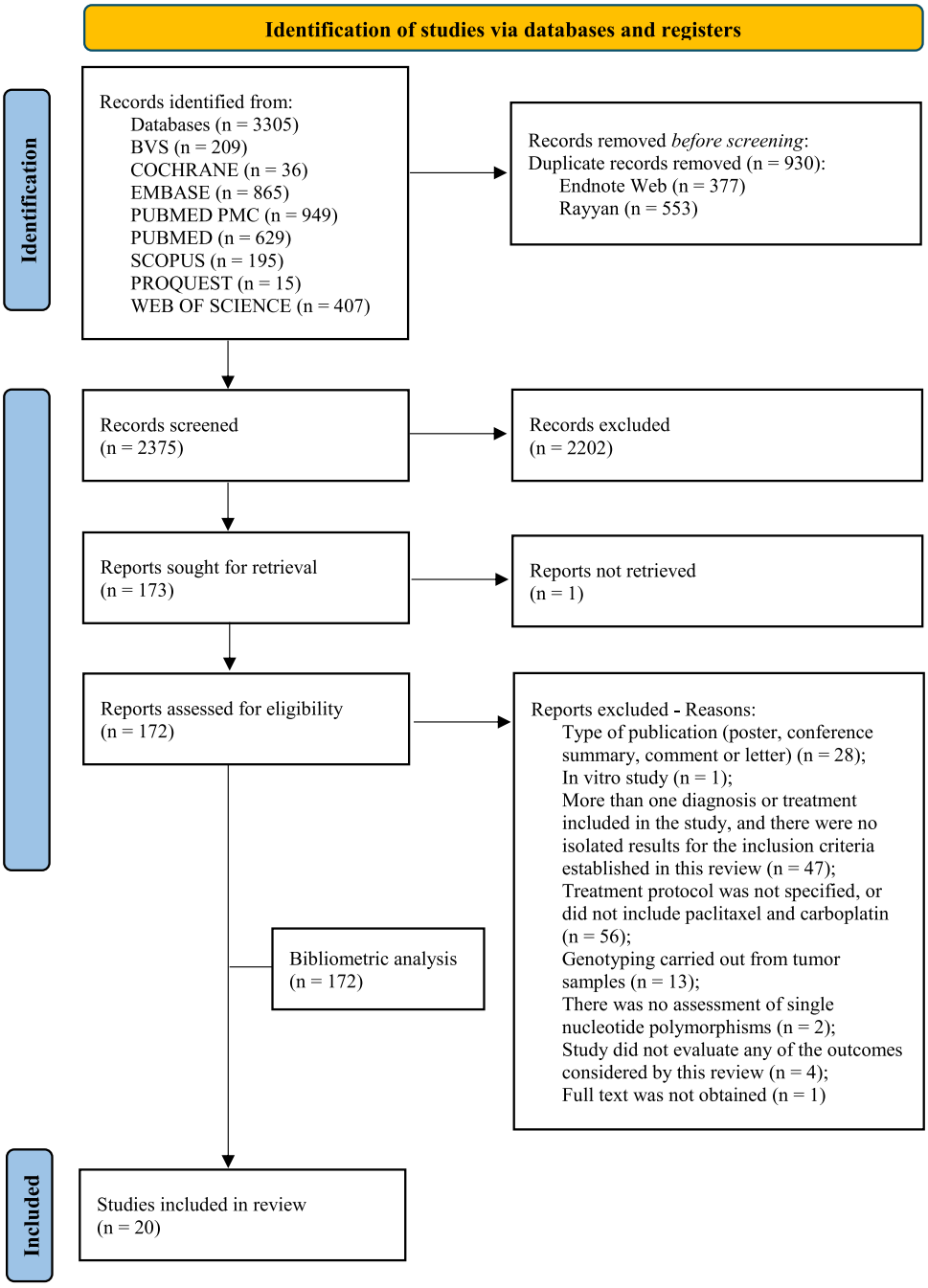

Figure 1. Flow diagram indicating databases that were searched, registers recovered, and specific reasons for exclusion from the present systematic review.

both), and the results were reported using the narrative synthesis approach, supported by structured tables. Those genetic variants reported to deviate from HWE were not included in the subsequent analyses performed in the present systematic review.

In the case of included studies that considered more than one treatment protocol, only the data related to patients treated with carboplatin and paclitaxel were considered and extracted. Studies in which it was not possible to collect such data in isolation were not included.

Bibliometric Analysis

Following the systematic literature review, 172 eligible studies were analyzed using bibliometric techniques, focusing on keyword co-occurrence as the primary unit of analysis. The goal was to identify clusters of related genes, topic relationships, and trends in pharmacogenomic research concerning gynecological cancers. Each node in the analysis represents a gene derived from the keywords, and the connections between them reflect their co-occurrence in the literature. Clustering techniques were employed to optimize the visualization and reveal key genetic interactions relevant to the field. This allowed for a deeper understanding of how different genes are associated with pharmacogenomics, particularly in the context of carboplatin and paclitaxel treatments.

The clustering approach also provided insights into emerging trends, highlighting genes frequently studied together and those that were gaining attention in recent research. By focusing on these clusters, the analysis reveals potential genetic biomarkers linked to treatment responses or ADRs in patients undergoing chemotherapy for gynecological malignancies.

Results

The initial search identified 3305 studies from multiple databases, with 930 overlapping references. From the remaining 2375 articles,

2202 were excluded after reviewing their titles and abstracts. The full text of the remaining 173 articles was thoroughly reviewed, and the main reasons for excluding 152 of them were: (1) The treatment protocol was not specified or did not include paclitaxel and carboplatin; (2) multiple diagnoses or treatments were included in the study without providing isolated results for the specific ones considered in this review; and (3) the publication type did not meet the inclusion criteria of this review. Only one of the 173 articles identified for potential inclusion was excluded, as the full-text article was not obtainable with reasonable effort.[17]

Thus, a total of 20 studies[11,18–35] met the eligibility criteria and were included in this systematic review (Figure 1). **Supplemental (Online Only) Table SI** provides a reference list of the studies excluded during the full-text review, together with the specific reasons for their exclusion.

Characteristics of Included Studies

All included studies were published in English between 2006 and 2024. They were all cohort studies, 12 of which were prospective, and the remaining were retrospective cohorts. Most of them included populations from Asian cohorts,[19,26,28–31,35] followed by European-origin populations[11,20,32]; six of them were multicentric studies.[22–25,27,33] The number of participants ranged from 33 to 1244, and the average age within the studies ranged from 48 to 65 years.

Among the studies that included an unique histological subtype, epithelial ovarian cancer was the most extensively investigated (11 out of the 20 articles included in this review); only one study consisted exclusively of patients with squamous cervical cancer.[26] The remaining articles involved more than one diagnosis and included patients with corpus uteri, cervical, fallopian tube, vaginal, vulvar, or peritoneal cancer.

In terms of outcomes, seven studies assessed only ADRs,[11,18,25,32,33,35,36] seven focused only on treatment effectiveness (response to chemotherapy, platinum-resistance, PFS, or OS),[20,22,24,26–28,34] and six of them evaluated both outcomes.[19,21,23,29–31] The most commonly studied ADRs were peripheral neuropathy and myelosuppression (including neutropenia and thrombocytopenia), which is expected, as these are the two main adverse events associated with the combination of carboplatin and paclitaxel. The main criteria used in the studies to characterize ADR severity were the Common Toxicity Criteria for Adverse Events (CTCAE) (versions 2.0, 3.0, 4.0, 4.03, and 5.0), but inconsistencies were found regarding the time interval evaluated. Some studies assessed the baseline and each treatment cycle, while others assessed the period after the first chemotherapy and the last cycle containing paclitaxel.

Among the 12 studies assessing treatment effectiveness, PFS and OS were the two most investigated outcomes,[19,21–24,27,28,34] followed by platinum-resistance (evaluated in three studies).[20,28,31] Three studies[26,29,31] assessed general response to chemotherapy (according to Response Evaluation Criteria in Solid Tumors, RECIST[37]), one of which[21] also classified in accordance with platinum response (classified as Patch et al[38]).

As for the treatment regimens, neither the dose (paclitaxel doses ranged from 135 to 175 mg/m^2) nor the total number of treatment cycles observed was consistent among the studies (the minimum period followed was two cycles[26] and the longest one was nine cycles[33]). A summary of the characteristics for all the 20 studies is presented in Table 1.

Genes and Their Genetic Variants

In total, the included studies analyzed 76 SNVs across 33 different genes (the complete list of variants and their respective genes can be found in **Supplemental [Online Only] Table SII**). This systematic review will concentrate mainly on those polymorphisms significantly associated with either chemotherapy-induced ADRs or treatment effectiveness (listed, respectively, in Tables 2 and 3).

Apart from two studies that did not specify the sample source,[22,24] all included studies extracted DNA from blood samples. The main genotyping method employed was PCR (18 of the 20 included articles), whether it was conventional PCR or qPCR. The other two studies used pyrosequencing[23] and targeted resequencing.[19]

Regarding HWE, 15 studies tested for adherence to HWE and reported the results. One of the studies was not in accordance with the HWE,[35] possibly because of the small sample size, and, therefore, this study was not included in the further evidence syntheses of this systematic review. However, the remaining four did not report on HWE testing[22,30–32] (**Supplemental [Online Only] Table SII**). Testing for deviation from the HWE can serve as an essential methodological quality control, highlighting genotyping errors, population stratification, and other biases.[41]

Owing to the high heterogeneity of the studies included in this review, it was not possible to conduct a meta-analysis for any of the genes that were evaluated by at least two different studies, even with reasonable effort. There was a high discrepancy in terms of: (1) CTCAE version used to characterize ADR severity (specifically, different CTCAE versions defined ADR severity inconsistently, resulting in different metrics for the same outcome); and (2) inconsistent reporting of primary results by the studies. In this last instance, some studies only reported the odds ratio, while others provided genotype and ADR frequencies independently. Therefore, it was not possible to associate these data and conduct the meta-analysis. As for the studies that had therapeutic effectiveness as one of their outcomes (response to chemotherapy, PFS, or OS), each polymorphism was assessed by only one study, which also made a quantitative synthesis unfeasible (Table 3).

ADR and Genetic Variants

The three most extensively investigated genes (and for which a greater number of significant associations were found) were ATP binding cassette subfamily C member 1 (*ABCB1*), cytochrome P450 2C8 (*CYP2C8*), and glutathione S-transferase P1 (*GSTP1*), with five,[18,21,23,33,36] four,[18,30,32,42] and two[19,21] different studies, respectively, examining each of them. Therefore, this review will concentrate on polymorphisms in those three genes, as the other genes and polymorphisms were each evaluated by only one study. Figure 2 provides an overview of the polymorphisms investigated.

In the first case, *ABCB1*, only the SNVs rs1045642[18,21,23,33,36] and rs1128503[18,21,33,36] were assessed by multiple studies, while rs2032582[33] and rs2229109[23] were assessed by only a single study each (Table 2). Another two cohort studies also assessed rs1045642,[11,34] although they did not find any association between this polymorphism and either PFS or OS, nor did it influence the clearance of paclitaxel.

Association analyses between outcomes and *ABCB1* polymorphisms were heterogeneous. Five studies assessed myelosuppression,[18,21,23,33,36] three addressed gastrointestinal ADRs,[18,33,36] and three examined neurological ADRs.[21,33] Less frequent outcomes (hearing loss, alopecia, and renal and hepatic ADRs) were each reported by only one study.

As for the *CYP2C8*, rs11572080[11,18] was the only polymorphism with significant associations found by multiple studies; the four remaining (rs10509681, rs1113129, rs17110453, and star allele *1D) were reviewed by a single study each.[11,23,30,32] Once more, *CYP2C8* association analysis demonstrated substantial variability: five studies investigated myelosuppression, with an emphasis on neutropenia occurrence,[11,18,23,30,32] four studies focused on neurological ADRs,[11,18,30,32] and one evaluated gastrointestinal ADRs.[11]

Lastly, for the *GSTP1* gene, rs1695 was the only polymorphism assessed by multiple studies.[19,21] Both investigations centered mainly on myelosuppression outcomes (neutropenia, thrombocytopenia, and anemia),[19,21] and one study also assessed peripheral neuropathy.[21]

Table 1
Characteristics of studies included in this systematic review.

Study	Country	Study design	Sample size (*n*)	Age, mean ± SD or median (range)	Population	Outcome (definition and criteria evaluation)	
						ADRs	Effectivity
Cervical cancer							
Guo et al[26]	China	Prospective (C)	110	48.9 (28–75)	Patients with squamous cervical cancer	NA	Response to chemotherapy (according to RECIST)
Ovarian cancer							
Bergmann et al[25]	Denmark and Sweden	Retrospective (C)	241	NR	Patients with ovarian cancer	Neuropathy (evaluated at baseline and at every treatment cycle, according to CTCAE, version 3.0)	NA
Ferracini et al[21]	Brazil	Prospective (C)	112	58 (22–87)	Patients with epithelial ovarian cancer	Myelosuppression (anemia, leukopenia, neutropenia, and thrombocytopenia) and neurotoxicity were evaluated in each treatment cycle (according to CTCAE, version 5.0). The highest grade of ADR over all courses for a patient was reported	PFS (time of diagnosis until relapse, progressive disease, or last follow-up) and OS time (time of diagnosis up to any cause of death or last follow-up) was estimated in months, from the date of diagnosis to the last follow-up visit, recurrence, or any cause of death Platinum response (refractory, primary resistant, sensitive, and acquired resistance was classified as Patch et al[38])
Gréen et al[32]	Sweden	Retrospective (C)	33	NR	Patients with ovarian cancer	Myelosuppression (leukopenia and neutropenia) were evaluated at baseline and whole treatment period (according to CTCAE, version 2.0) and neuropathy (according to Cassidy et al[39])	NA
Hu et al[35]	China	Prospective (C)	75	52.7 ± 12.1	Patients with epithelial ovarian cancer	Myelosuppression (leukopenia and neutropenia) were assessed every 3 days after drug administration (according to CTCAE, version 2.0) and neurotoxicity (according to WHO grading). The most severe adverse reaction for each patient was considered	NA
Huang et al[27]	Multicentric	Retrospective (C)	377 (Phase 1); 1326 (Phase 2)	NR (143–79)	Patients with invasive ovarian cancer	NA	PFS (different definitions, according to the clinical studies of participants' origin) and OS (interval between the date of diagnosis and death from any cause)
Johnatty et al[22]	Multicentric	Retrospective (C)	1098	NR	Patients with invasive epithelial ovarian cancer	NA	PFS (interval between the date of histological diagnosis and the first confirmed sign of disease progression or death), OS (interval between the date of histological diagnosis and death from any cause)
Kang et al[28]	South Korea	Prospective (C)	60	50 (15–73)	Patients with epithelial ovarian cancer	NA	Platinum-resistance (progression on platinum-based chemotherapy or recurrence within 6 months of completing therapy), OS (time interval between the date of surgery and the date of death) and platinum-free interval (interval between treatment commencement and the date when evidence of recurrence was obtained)

(*continued on next page*)

Table 1 (*continued*)

Study	Country	Study design	Sample size (*n*)	Age, mean ± SD or median (range)	Population	Outcome (definition and criteria evaluation)	
						ADRs	Effectivity
Park et al[30]	South Korea	Prospective (C)	43	57.6 ± 13.4	Patients with epithelial ovarian cancer	Myelosuppression (neutropenia) and neurotoxicity (according to CTCAE, version was not reported)	Disease-free interval (calculated from the time of surgery to the time of recurrence)
Sarkar et al[31]	India	Prospective (C)	80	49.15 ± 10.8	Patients with advanced ovarian cancer	Myelosuppression (anemia, leukopenia), nausea, vomiting, neuropathy, diarrhea, constipation, abdominal pain/swelling, and renal ADR (according to CTCAE version 4)	Clinical response assessed based on criteria from GCIG and RECIST. Responders were platinum sensitive, partial responders were developing platinum resistance, and nonresponders included patients with platinum-refractory status and stable or progressive disease
Steffensen et al[20]	Denmark	Retrospective (C)	143	65 (32–84)	Patients with epithelial ovarian cancer	NA	Recurrence of disease (defined according to GCIG CA125 criteria and/or radiological confirmation of tumor progression). Platinum resistance assessed by sensitivity to chemotherapy (time to recurrence ≥6 months after completion of platinum-based chemotherapy) and platinum resistance (recurrence ≤6 months after completion of chemotherapy or progression during the first-line platinum-based chemotherapy)
Ye et al[29]	China	Prospective (C)	122	51 (27–78)	Patients with ovarian cancer	Anaphylaxis, peripheral nerve toxicity, vomiting, diarrhea and leukocytosis (according to RECIST)	Tumor responses (categorized as complete response, partial response, stable disease, or progressive disease) (according to Clinical Curative Effect Criteria for Solid Tumors, by WHO)
Two or more gynecological malignancies							
Bergmann et al[33]	Denmark and Sweden	Prospective (C)	92	60.7 (32–79.4)	Patients with epithelial ovarian cancer, fallopian tube, or peritoneal cancer	Febrile neutropenia, myalgia, arthralgia, nausea, vomiting, mucositis, hearing loss, motor neuropathy, sensory neuropathy, and alopecia (according to CTCAE, version 3.0)	NA
Björn et al[23]	Sweden and Belgium	Retrospective (C)	265	56 (37–81)	Patients with epithelial ovarian cancer, fallopian tube cancer or primary peritoneal cancer	Myelosuppression (thrombocytopenia, leukopenia and neutropenia were evaluated at baseline, and at every treatment cycle (according to CTCAE, version 4.03)	PFS and OS (both measured from inclusion to an event, that is, confirmed progression with CT or death, respectively). CT scans were performed within the 6-week period before treatment, after cycles 3 and 6, every third month during the follow-up period, and when the patient left the study
Gréen et al[11]	Sweden	Prospective (C)	33	61 (36–75)	Patients with ovarian, corpus uteri, cervix uteri, or peritoneal cancer	Myelosuppression (anemia, leukopenia, neutropenia, and thrombocytopenia) and neurotoxicity were evaluated after the first chemotherapy cycle, and at the final cycle containing paclitaxel (according to CTCAE, version 2.0, and Cassidy et al[39])	NA

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Table 1 (*continued*)

Study	Country	Study design	Sample size (*n*)	Age, mean ± SD or median (range)	Population	Outcome (definition and criteria evaluation)	
						ADRs	Effectivity
da Costa Junior et al[36]	Brazil	Prospective (C)	507	57 (22–84)	Patients with ovarian, cervical, corpus uteri, vulvar, or vaginal cancer	Renal ADR (creatinine clearance using Cockroft-Gault), hepatic ADR (ALT, AST, and bilirubin concentrations in plasma), myelosuppression (anemia, neutropenia, and thrombocytopenia), gastrointestinal ADRs (nausea and vomiting) and myalgia were evaluated after every treatment cycle (according to CTCAE, version 5.0)	NA
de Castro et al[18]	Brazil	Prospective (C)	503	57 (22–84)	Patients with ovarian, cervical, corpus uteri, vulvar, or vaginal cancer	Neurotoxicity, gastrointestinal ADRs, and myelosuppression (anemia, neutropenia, thrombocytopenia) were evaluated at baseline, and at every treatment cycle (according to CTCAE, version 4.0)	NA
French et al[24]	Multicentric	Retrospective (C)	1244	NR	Patients with high grade serous epithelial ovarian, fallopian tube, or primary peritoneal invasive serous cancer	NA	PFS (time interval between the date of histologic diagnosis and the first confirmed sign of disease recurrence, or progression), and OS (time interval from date of diagnosis to time of last follow-up or time to death from any cause)
Johnatty et al[34]	Australia	Prospective (C)	309	58 (31.3–80.5)	Patients with primary invasive ovarian, peritoneal, or fallopian tube cancer	NA	PFS (time interval between the date of histologic diagnosis and the first confirmed sign of disease recurrence, or progression)
Yoshihama et al[19]	Japan	Retrospective (C)	320	Group 1 (cases): 54.5 (35–80) Group 2: (controls): 54 (27–80)	Patients with ovarian, fallopian tube, peritoneal, uterine, or cervical cancer	Myelosuppression (neutropenia, thrombocytopenia, and anemia) was assessed during the treatment period (according to CTCAE, version 4.0)	PFS (interval between the first day of chemotherapy administration and the day of the first relapse, progression, or death; relapse and progression were diagnosed by imaging or clinical symptoms), and OS (interval between the first day of chemotherapy administration and the date of death)

ADRs = adverse drug reactions; ALT = alanine aminotransferase; AST = aspartate aminotransferase; C = cohort study; CA-125 = cancer antigen 125; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; GCIG = Gynecologic Cancer Intergroup; n = absolute number of participants; NA = not applicable; NR = not reported; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors[40]; SD = standard deviation; WHO = World Health Organization.

Treatment Effectiveness and Genetic Variants

Twelve distinct studies evaluated the effectiveness of treatment, with 10 reporting significant associations with some of the polymorphisms considered. Nevertheless, the quantitative synthesis was unfeasible in all cases, as each association was verified by only one study (Table 3). The definition of treatment effectiveness outcomes also differed between the included studies. For instance, some studies considered the date of histologic diagnosis as the baseline for the time interval in OS and PFS, while others considered the first day of chemotherapy administration.

Quality of the Included Studies

One included cohort study was classified as low quality,[33] 14 were classified as moderate quality[11,19–21,25–32,35,36] and five were classified as high quality (with the highest score achieved being seven stars).[18,22–24,34] No study received a star in the "Representativeness of the exposed cohort" category (Table 4), often because the absence of a formal calculation for sampling power.

Bibliometric Analysis of Ovarian Cancer, Genes, and Polymorphism

The mapping results of 172 studies identified four main clusters: ovarian cancer, SNV, epithelial ovarian cancer, and polymorphism (**Supplemental [Online Only] Figure 1**). In the ovarian cancer cluster, the relationships formed are connected to several genes, including *ABCB1* and *CYP2C8*, consistent with this review. The inter-cluster relationships are also strong, with the ovarian cancer cluster overlapping with the polymorphism and SNV clusters.

The association of carboplatin and paclitaxel with other genes was also verified. Carboplatin was mainly associated with *ABCB1* and *GSTs,* while paclitaxel was mainly associated with *CYP2C8, CYP3A4,* and

Table 2
List of investigated genetic polymorphisms that showed significant association with chemotherapy-induced adverse reactions in this systematic review.

Genes	Polymorphism (dbSNP ID or position)	Studies										Total number of studies
		Bergmann et al[33]	Björn et al[23]	da Costa Junior et al[36]	de Castro et al[18]	Ferracini et al[21]	Gréen et al[11]	Gréen et al[32]	Park et al[30]	Sarkar et al[31]	Ye et al[29]	Yoshihama et al[19]	
ABCB1	rs1045642	x	x	x	x	x							5
	rs1128503	x		x	x	x							4
	rs2032582	x											1
	rs2229109		x										1
CYP2C8	rs11572080				x		x						2
	rs10509681						x						1
	rs1113129							x					1
	rs17110453								x				1
	*1D								x				1
GSTP1	rs1695					x						x	2
CYP3A5	rs776746							x					1
ABCC2	rs17222723	x											1
ABCC4	rs3765534											x	1
ABCC10	rs2125739	x											1
BUB3	rs11248416									x			1
	rs11248419									x			1
CYP2C18	rs117111102											x	1
CYP2C9	rs1057910											x	1
CYP2D6	rs1135823											x	1
CYP4B1	rs2297810											x	1
CYP4F2	rs2108622											x	1
	rs3093105											x	1
ERCC1	rs11615			x									1
NAT2	rs1799930											x	1
SLC15A1	rs2297322											x	1
SLC16A7	rs199876753											x	1
SLC22A2	rs160679680											x	1
SLC22A6	rs62752140											x	1
SLC28A1	rs8187758											x	1
	rs756890035											x	1
UGT1A6	rs1105879											x	1
	rs2070959											x	1
	rs6759892											x	1
UGT1A7	rs11692021											x	1
UGT1A8	rs1042597											x	1
USF1	rs2516839										x		1

Organized in descending order, beginning with the genes whose SNVs were evaluated by the largest number of studies.
ABCB1 = adenosine-triphosphate-binding cassette subfamily B member 1; *ABCC10* = adenosine-triphosphate-binding cassette subfamily C member 10; *ABCC2* = adenosine-triphosphate-binding cassette subfamily C member 2; *ABCC4* = adenosine-triphosphate-binding cassette subfamily C member 4; BUB3 = budding uninhibited by benzimidazoles 3; *CYP2C18* = cytochrome P450 family 2 subfamily C member 18; *CYP2C8* = cytochrome P450 family 2 subfamily C member 8; *CYP2C9* = cytochrome P450 family 2 subfamily C member 9; *CYP2D6* = cytochrome P450 family 2 subfamily D member 6; *CYP3A5* = cytochrome P450 family 3 subfamily A member 5; *CYP4B1* = cytochrome P450 family 4 subfamily B member 1; *CYP4F2* = cytochrome P450 family 4 subfamily F member 2; *ERCC1* = excision repair cross-complementation group 1; *GSTP1* = glutathione S-transferase pi 1; *NAT2* = N-Acetyltransferase 2; *SLC15A1* = solute carrier family 15 member 1; *SLC16A7* = solute carrier family 16 member 7; *SLC22A2* = solute carrier family 22 member 2; *SLC22A6* = solute carrier family 22 member 6; *SLC28A1* = solute carrier family 28 member 1; *UGT1A6* = UDP-glucuronosyltransferase family 1 member A6; *UGT1A7* = UDP-glucuronosyltransferase family 1 member A7; *UGT1A8* = UDP-glucuronosyltransferase family 1 member A8; *USF1* = upstream transcription factor 1.

CYP3A5. Genes associated with both drugs were *ABCB1, SLCO1B1, and ERCC1*.

Discussion

This systematic review aimed to provide a detailed synthesis of the genetic polymorphisms associated with ADRs and treatment effectiveness of carboplatin-paclitaxel chemotherapy in patients with gynecological malignancies. Therefore, the systematic research identified 20 studies, of which 11 reported significant SNV-ADR associations, and 10 showed SNV significant associations with treatment effectiveness.

Interindividual variability in response and ADRs to the same treatment emphasizes the importance of pharmacogenetic markers in personalized therapy. Therefore, understanding the increasing interest in genetic variants requires acknowledging that both carboplatin and paclitaxel undergo complex processes where genetic variants can interfere. SNVs in genes encoding transporters, metabolizing enzymes, or detoxification proteins can alter drug concentrations at the tumor site, thereby affecting both toxicity and efficacy.

Furthermore, depending on their genomic location, genetic variants have the potential to influence gene expression, as well as the protein structure, function, or expression levels.[43,44] In this regard, the articles included in this study mostly focused on two categories of SNVs: missense variants (rs1045642, rs10509681, rs11572080, and rs1695) and a synonymous variant (rs1128503) (Table 5 and Figure 3). In the first case, missense variants, a single base pair substitution occurs within a coding sequence, producing an amino acid other than the one predicted at that position, thus affecting protein activity. Downstream, it could also influence the key binding sites responsible for protein interactions. In the second scenario, if the variant is synonymous, it does not change the nature of the amino acid, but it may still affect the translation rates or mRNA half-life.[43,44] Because of all these implications, these SNVs are promising candidates for therapeutic biomarkers.

In most studies, the rationale for SNV selection was based on genes associated with either the pharmacokinetics or pharmacodynamics of carboplatin or paclitaxel. For this reason, the most extensively investigated genes were those encoding proteins involved in cellular transport (*ABCB1*), metabolism (*CYP2C8*), or detoxification (*GSTP1*) (Figure 2).

Table 3
Investigated genetic polymorphisms that were significantly associated with treatment effectiveness in this systematic review.

Genes	Polymorphism (dbSNP ID or position)	Studies										Total number of studies
		Björn et al[23]	French et al[24]	Guo et al[26]	Huang et al[27]	Johnatty et al[34]	Kang et al[28]	Park et al[30]	Steffensen et al[20]	Ye et al[29]	Yoshihama et al[19]	
ABCB1	rs1045642	x										1
	rs2032582					x						1
	rs2229109	x										1
Akt1	rs2498786			x								1
Akt2	rs10416620			x								1
	rs62107593			x								1
	rs34716810			x								1
CYP2C8	*1D							x				1
ERCC1	rs11615						x					1
GSTP1	rs1695										x	1
NRG3	rs1649942				x							1
PIK3CA	rs3729679			x								1
	rs12494623			x								1
TTC39B	rs7874043		x									1
	rs72700653		x									1
USF1	rs2516839									x		1
VEGF	Haplotype*								x			1

ABCB1 = adenosine-triphosphate-binding cassette subfamily B member 1; *Akt1* = AKT serine/threonine kinase 1; *Akt2* = AKT serine/threonine kinase 2; *CYP2C8* = cytochrome P450 family 2 subfamily C member 8; *ERCC1* = excision repair cross-complementation group 1; *GSTP1* = glutathione S-transferase pi 1; *NRG3* = neuregulin 3; *PIK3CA* = phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *TTC39B* = tetratricopeptide repeat domain 39B; *USF1* = upstream transcription factor 1; *VEGF* = vascular endothelial growth factor A.

* Haplotype (rs699947, rs1570360, rs833061, rs2010963, rs3025039).

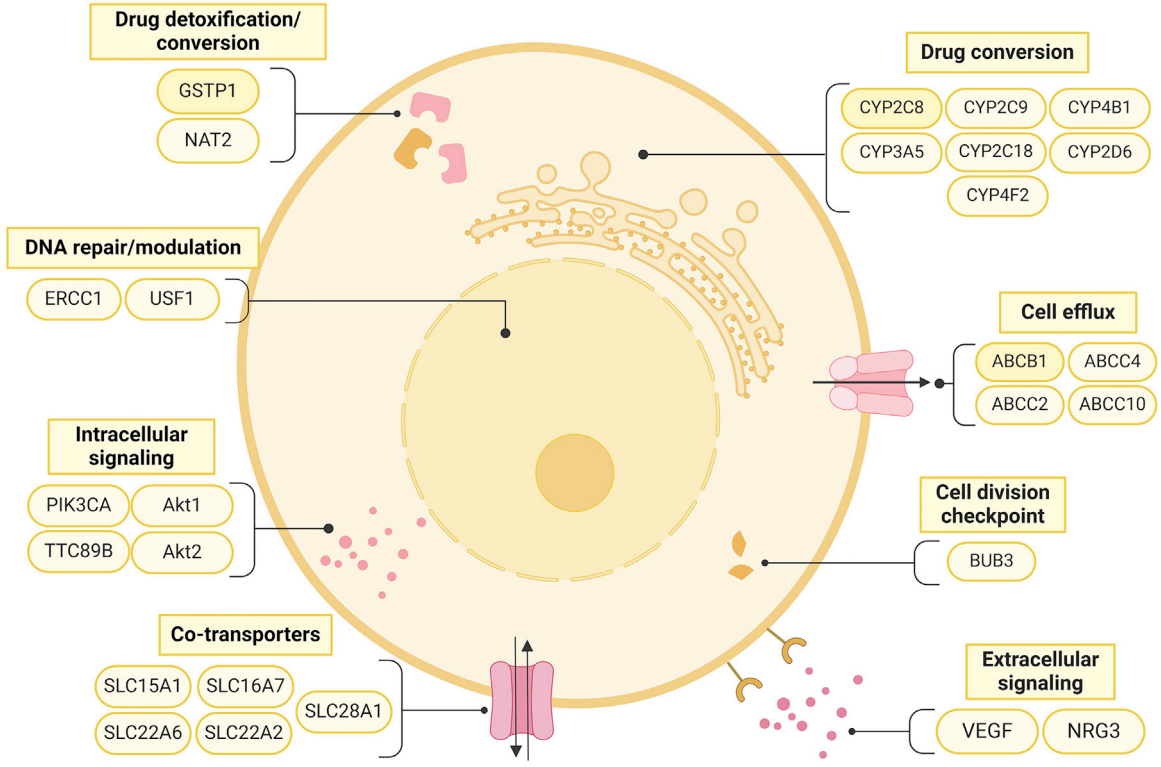

Figure 2. Protein products of the genes associated with ADRs or effectiveness, according to the studies included in this systematic review, in addition the biological processes in which they are involved. Created using BioRender.com.

The first one, the *ABCB1* gene, is a member of the ABC transporter superfamily and encodes phosphoglycoprotein (P-gp). The P-gp transmembrane transporter is an ATP-dependent efflux pump, which plays a significant role in the efflux of exogenous and endogenous substrates, including platinum and taxane drugs.[45] The main reason this gene was the subject of multiple investigations is that drug transporters modulate drug intracellular accumulation, which is mandatory for cytotoxicity effects. When P-gp activity increases, antitumor drugs can be actively released, reducing intracellular drug accumulation and contributing to chemoresistance.[46,47] SNVs in *ABCB1* may potentially influence the P-gp transport activity by altering the protein expression levels, stability, degradation, or substrate specificity.[48]

Four *ABCB1* SNVs were significantly associated with treatment-induced ADRs, although only two have shown significant results in more than one study (Table 2). The most extensively investigated was rs1045642 (c.3435C>T), which results in altered codons that compro-

Table 4
Results of quality assessment using the Newcastle–Ottawa scale (NOS) for cohort studies.

Studies	Selection				Comparability	Outcome			Total score
	Selection of the nonexposed cohort	Representativeness of the exposed cohort	Ascertainment exposure	Demonstration that the outcome was not present at start of study	Comparability of cohorts	Assessment of outcome	Follow-up for outcomes	Adequacy of follow-up of cohorts	
Bergmann et al[33]	*		*			*			3
Bergmann et al[25]	*		*	*		*	*	*	6
Björn et al[23]	*		*	*	*	*	*	*	7
Da Costa Junior et al[36]	*		*		*	*	*	*	6
de Castro et al[18]	*		*	*	*	*	*	*	7
Gréen et al[11]	*		*			*	*		4
Gréen et al[32]	*		*			*	*		4
Johnatty et al[34]	*		*	*	*	*	*	*	7
Johnatty et al[22]	*		*	*	*	*	*	*	7
Ferracini et al[21]	*		*		*	*	*		5
French et al[24]	*		*	*	*	*	*	*	7
Guo et al[26]	*		*	*		*	*		5
Huang et al[27]	*		*	*		*			4
Hu et al[35]	*		*		*	*	*	*	6
Kang et al[28]	*		*	*		*	*	*	6
Park et al[30]	*		*	*	*	*	*		6
Sarkar et al[31]	*		*			*	*	*	5
Steffensen et al[20]	*		*	*		*			4
Ye et al[29]	*		*	*		*	*	*	6
Yoshihama et al[19]	*		*		*	*	*	*	6

The studies are organized in the table in alphabetical order according to the last name of the first author.

Table 5
Details regarding the SNVs that have been extensively examined in the articles included in this systematic review.

Gene	dbSNP ID	Classification	Location	Reference allele > variant allele*
ABCB1	rs1045642	Missense variant	Chromosome 7	G > C, A, T
	rs1128503	Synonymous variant	Chromosome 7	A > G
CYP2C8	rs10509681	Missense variant	Chromosome 10	T > C
	rs11572080	Missense variant		C > A, T
GSTP1	rs1695	Missense variant	Chromosome 11	G > A, T

A = *adenine; ABCB1* = adenosine-triphosphate-binding cassette subfamily B member 1; C = *cytosine; CYP2C8* = cytochrome P450 family 2 subfamily C member 8; G = guanine; *GSTP* = glutathione S-transferase pi 1; T = thymine.
*According to Ensembl, considering forward strand.

mise protein conformation, membrane stability, and substrate recognition.[49] This SNV also appears to have implications on P-gp expression and substrate efflux.[50] Downstream, this indicates that P-gp alterations could impact therapeutic concentrations of relevant substrates, and, therefore, treatment outcomes.

Regarding hematological ADRs, Bergmann et al[33] observed that T-allele carriers experienced a considerable neutrophil decrease ($P = 0.03$), compared to CC or CT genotypes. This polymorphism has also been associated with severe neutropenia in patients with other solid tumors, including breast[51] and nonsmall cell lung cancer.[52] Controversially, in Björn et al,[23] it was verified that the haplotype encoded by rs1045642 (TT), rs1128503 (TT), and rs2032582 (TT) was associated with higher neutrophil values ($P = 0.039$) and lower neutrophil decrease ($P = 0.021$). Björn et al[23] were also able to verify that the variant rs1045642 (TT genotype) was significantly associated with increased PFS, as well as increased OS, compared to the wild-type.

Although paclitaxel treatment is widely recognized to cause peripheral sensory neuropathy,[53] only the study of Ferracini et al[21] demonstrated that TT carriers were at an increased risk of severe grades of neurotoxicity (OR: 3.61, $P = 0.03$). As nephrotoxicity is less frequently observed in carboplatin-treatment, and more commonly associated with its precursor cisplatin, only one study assessed renal ADRs. da Costa Junior et al[36] reported that the rs1128503 and rs1045642 were significantly associated with moderate-to-severe nephrotoxicity. In both polymorphisms, patients with the variant genotype (TT) were at a higher risk compared to the two other genotypes.[54]

Similar to rs1045642, the *ABCB1* rs1128503 (c.1236C>T) is responsible for differences in P-gp expression without altering the amino acid sequence.[49,50] This SNV was found to be particularly correlated with the two most critical adverse outcomes of the carboplatin-paclitaxel combination. First, its influence on neuroperipheral ADRs was assessed in the study conducted by de Castro et al,[18] where both rs1128503 and rs1045642 were associated with severe fatigue. In turn, its myelosuppressive effect was verified by Ferracini et al,[21] where a significant association between thrombocytopenia and the rs1128503 TT genotype was found. Similar findings were also indicated by de Castro et al,[18] but this time with rs1045642 polymorphism, which showed that CC genotype was an independent predictor of severe thrombocytopenia.[18]

Moving on to *CYP2C8*, the second gene with the highest number of statistical associations among the publications included. The *CYP2C8* gene is located in the human *CYP2C* subfamily cluster, along with three other highly homologous genes (*CYP2C18, CYP2C19,* and *CYP2C9*),[55] a cluster of polymorphic genes sharing significant sequence homology.[56,57] In terms of genome coding, *CYP2C8* is the shortest of the human CYP2C genes, consisting of only nine exons.[58,59] The CYP2C8 is among the CYP enzymes most abundantly expressed in hepatic tissue,[55,60] and it is known to be involved in the metabolism of over 100 drugs,[58] including paclitaxel.

One of the first studies to investigate the possible clinical significance of *CYP2C8* pharmacogenomics was done by Gréen et al.[42] Patients heterozygous for *CYP2C8*3* exhibited significantly lower clearance of paclitaxel, as compared to those homozygous for *CYP2C8*1* (the refer-

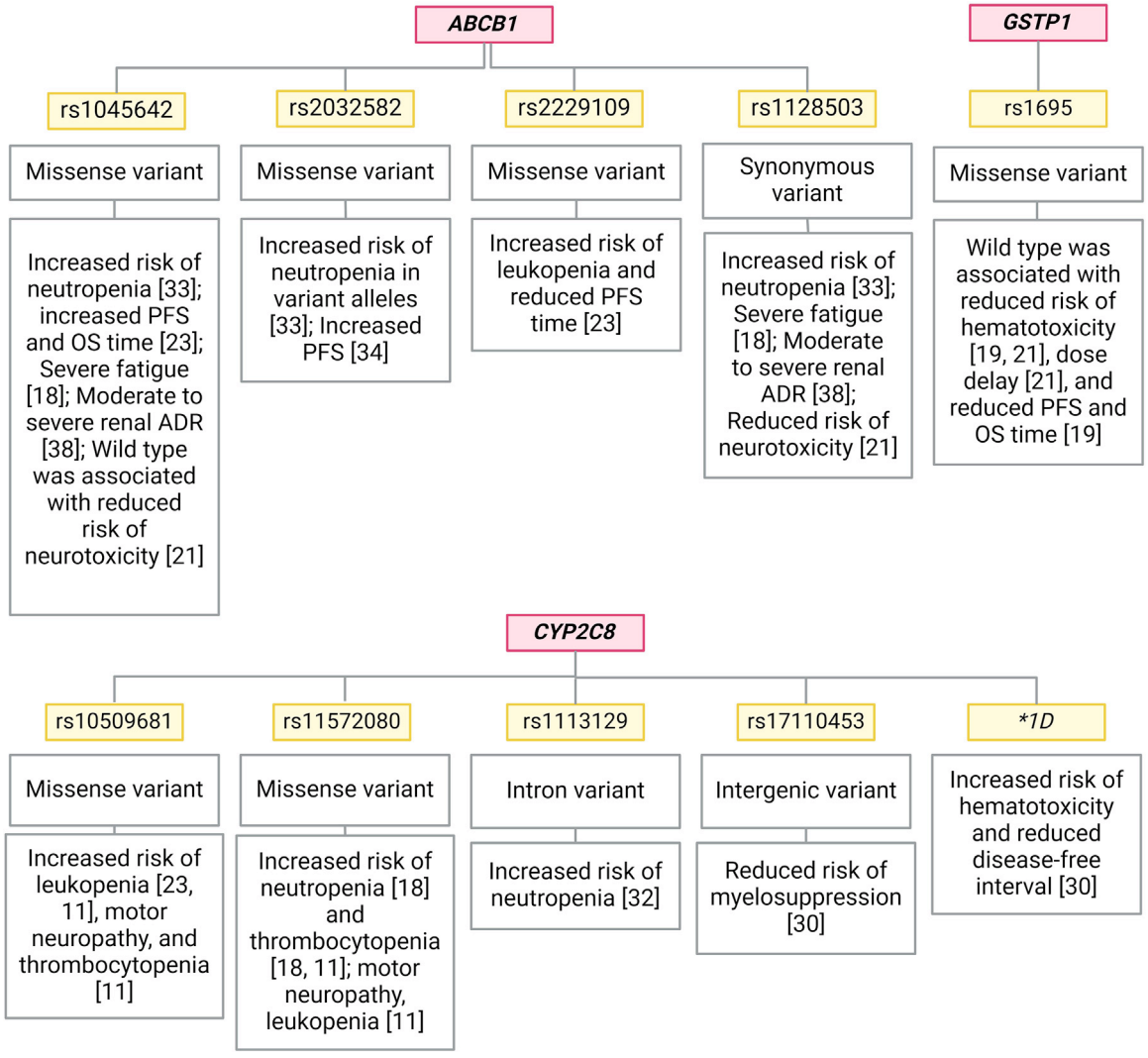

Figure 3. Synthesis of the most studied SNVs and their respective associations with.

ence allele of the gene). This finding suggests that *CYP2C8*3* may be responsible for reduced enzyme activity, impairing the metabolism of CYP2C8 substrates.[11] As a result, this genotype would also be associated with an increased risk of unfavorable outcomes associated with treatment.[33,57,61] A few years later, de Castro et al[18] also corroborated those findings by identifying *CYP2C8*3* as an independent predictor of severe thrombocytopenia.

Notably, as with other members of the CYP450 family, particular drugs may induce or inhibit this enzyme activity,[59] temporarily altering the phenotype of individuals under their use. Therefore, the concomitant administration of these medications must be taken into consideration. Nevertheless, none of the studies stated whether considered the concomitant consumption of medications with chemotherapy.

Finally, *GSTP1* was the gene with the third most extensive body of evidence showing associations with clinical outcomes. This gene, a member of the GSTs family, was the subject of some research because detoxification of platinum drugs occur through its interaction with the GST enzyme. The cytoplasmic GST catalyzes the binding of glutathione (GSH) to platinum. The formation of platinum-GSH conjugates results in drug inactivation, increased solubility, and excretion.[62] For this reason, its increased cellular expression has been previously observed in platinum-resistant cells.[63]

The rs1695 (c.313A>G) was the *GSTP1* variant considered by two of the included studies, a missense variant that seems to affect enzyme activity by changing the affinity of the enzyme with the substrate.[64] Ferracini et al[21] investigated the association this variant with hematologic and neurologic ADRs, treatment alterations, and disease prognosis in patients with epithelial ovarian cancer. Subjects carrying the variant allele had a reduced risk of developing anemia and thrombocytopenia.[21] In another research effort, Yoshihama et al[19] investigated this same relationship, but this time in a retrospective case-control study that also considered other gynecological cancers. But in contrast to the findings of Ferracini et al[21], AA homozygotes exhibited a significantly higher risk of severe myelosuppression (neutropenia, thrombocytopenia and anemia) compared to the G-allele carriers.[19] Furthermore, in terms of the effectiveness of treatment, patients with the AA genotype demonstrated significantly better PFS and OS than those with the AG or GG genotypes.[19]

Regarding the quality assessment by NOS criteria, the item "Representativeness of the exposed cohort" was the only one not scored by any of the studies. This trend may reflect a variety of reasons, two of which stand out. First, some investigations do not address sufficient details of the cohorts' characteristics or potential biases, which impairs a precise assessment of all NOS domains. Second, some studies had insufficient sample sizes to ensure appropriate statistical power to identify a genotype–phenotype association.[65] The number of publications reporting a sample size with previously established statistical significance is even more limited. Other common quality concerns included not demon-

strating that the outcome was not present at the baseline; lack of HWE testing, risking genotyping errors or population stratification; and not reporting key confounders (including concomitant medications), reducing confidence in genotype–phenotype associations. Despite the limitations, no study was removed from subsequent analyses because of poor quality.

The data inconsistencies regarding the same variant between different studies may be attributed to insufficient sample sizes and variations in chemotherapy doses or infusion periods, all of which could be confounding factors. It is also worth mentioning that most of the studies concerned Asian or European cohorts. Although researchers did not report information on the genomic ancestry of the samples, the fact that most current pharmacogenetic knowledge derives from an unrepresentative subsection of the global population indicates that global genetic diversity remains undercharacterized. This has two major implications. Firstly, the extrapolation of findings from homogeneous ethnic groups may not apply to populations with highly complex genetic patterns, as those with a history of miscegenation.[66–69] Secondly, the distribution of pharmacogenetic variants may differ considerably between populations.[66–69] Failing to account for these aspects risks misleading conclusions due to inappropriate cohort matching.

Although this systematic review was able to summarize the most significant findings, it does have certain limitations. It was not possible to perform a meta-analysis due to heterogeneity in the research in terms of the genes and subsequent genetic variants investigated, genotype classification, the selection and definition of outcomes, and the method used to classify ADRs. Therefore, to enable quantitative synthesis of evidence in future pharmacogenetic reviews, it would be interesting for studies to opt for consistent protocol standardization. Specifically, uniform definitions of time points (eg, adoption of the same baseline and endpoints for assessment of ADRs, PFS, and OS), incorporation of potential confounders (eg, co-medications, histological subtypes, prior treatments) into multivariable score models, and consistent genotyping methods would reduce inter-study variability. Moreover, if more than one treatment protocol was included in the study, consider presenting the results of each separately. Finally, we also reinforce the importance of following the recommendations of Reporting of Genetic Association studies (STREGA),[70] to ensure the methodological quality of investigations and standardize genetic association reporting.

Therefore, considering the current role of carboplatin and paclitaxel in gynecological malignancies, future research should further investigate the role and significance of *ABCB1, CYP2C8,* and *GSTP1* gene variants for patients undergoing this treatment. Translating these pharmacogenetic associations into clinical practice means, necessarily, consistently demonstrating the genotype predictive value for both safety and effectiveness. Ultimately, studies should also measure outcomes such as ADRs reduction, chemotherapy adherence, and cost-effectiveness to justify routine pre-treatment genotyping. Considering the promising findings mentioned here, addressing the potential of polymorphisms as therapeutic markers is of considerable interest for further investigations.

Conclusion

This systematic review included a total of 20 studies. The main strength of this review is the comprehensive overview and description of pharmacogenomic investigations to date. Three variants, rs1128503 (*ABCB1*), rs10509681, and rs11572080 (*CYPC28*), appear to have a significant association with important ADRs (in particular neutropenia, thrombocytopenia, and peripheral sensory neuropathy) in patients with gynecological tumors who undergo combined paclitaxel and carboplatin chemotherapy. Others, as is the case with rs1045642 (*ABCB1*) and rs1695 (*GSTP1*), have some conflicting results, and the extent to which these results can be extrapolated is still limited. Therefore, it is recommended that further studies should be more extensive, with more broadly inclusive analyses to support the clinical utility of the genetic markers as indicators of predisposition to ADRs, integrating them into clinical practice.

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Author contributions

Conceptualization, N.d.G.T., M.B.V., and P.M.; methodology, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., E.d.C.P., and P.M.; formal analysis, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., J.E.M., B., E.d.C.P., and P.M.; investigation, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., E.d.C.P., and P.M.; resources, E.d.C.P., P.C.J.L.S., and P.M.; data curation, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., E.d.C.P., and P.M.; writing—original draft preparation, N.d.G.T. and Y.G.M.; writing—review and editing, N.d.G.T., Y.G.M., G.F.S.F., C.D.H., M.B.V., P.C.J.L.S., E.d.C.P., and P.M.; visualization, P.M.; supervision, M.B.V., P.C.J.L.S., E.d.C.P., and P.M.; project administration, P.M.; funding acquisition, E.d.C.P., P.C.J.L.S., and P.M. All authors have read and agreed to the published version of the manuscript.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary materials

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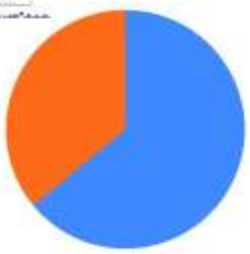

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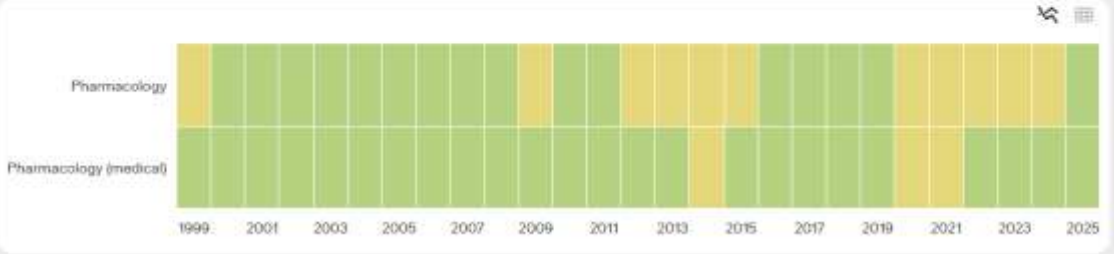
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