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GYNECOLOGIC ONCOLOGY

Impact of gene polymorphisms on the systemic toxicity to paclitaxel/carboplatin chemotherapy for treatment of gynecologic cancers

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Abstract

Purpose Gynecologic malignancies are often detected in advanced stages, requiring chemotherapy with taxane/platinum combinations, which may cause severe toxicities, such as neutropenia and peripheral neuropathy. Gene polymorphisms are suspected as possible causes for the interindividual variability on chemotherapy toxicities.

Objective To evaluate the role of *ABCB1 1236C>T, 3435C>T; CYP2C8*3; CYP3A5*3C* variants on paclitaxel/carboplatin toxicities.

Methods A cohort of 503 gynecologic cancer patients treated with paclitaxel/carboplatin at the Brazilian National Cancer Institute (INCA-Brazil) was recruited (2013–2017). Polymorphisms were genotyped by real-time PCR, and toxicities were evaluated by patients' interviews at each chemotherapy cycle and by data collection from electronic records. The association of clinical features and genotypes with severe toxicities was estimated using Pearson's Chi square tests and multiple regression analyses, with calculation of adjusted odds ratios ($OR_{adjusted}$), and respective 95% confidence intervals (95% CI).

Results *CYP2C8*3* was significantly associated with increased risks of severe (grades 3–4) neutropenia ($OR_{adjusted}$ 2.11; 95% CI 1.24–3.6; dominant model) and severe thrombocytopenia ($OR_{adjusted}$ 4.93; 95% CI 1.69–14.35; recessive model), whereas *ABCB1* variant genotypes ($OR_{adjusted}$ 2.13; 95% CI 1.32–3.42), in association with *CYP2C8*3* wild type (GG) ($OR_{adjusted}$ 1.93; 95% CI 1.17–3.19), were predictive of severe fatigue.

Conclusions The present study suggests that *CYP2C8*3* is a potential predictor of hematological toxicities related to paclitaxel/carboplatin treatment. Since hematological toxicities, especially neutropenia, may lead to dose delay or treatment interruption, such prognostic evaluation may contribute to clinical management of selected patients with paclitaxel-based chemotherapy.

Keywords Gene polymorphisms · Ovarian cancer · Uterine cancers · Paclitaxel toxicity · *CYP2C8*3* · *ABCB1*

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Introduction

Gynecologic malignancies affect many women worldwide and are important causes of morbidity and mortality. The estimated global incidence for all cervical, corpus uteri and ovarian cancers was over a million cases in 2012, whereas their combined mortality accounted for approximately 14% of all female cancer deaths in the same period [1]. In the past 4 decades, the incidence rates of cervical cancer have shown a trend for decrease in most countries [2], mostly due to the introduction of screening policies [3]. Nevertheless, cervix cancer is still the 4th most common female cancer, with 527,600 new cases estimated in 2012. It is also the 4th most lethal female cancer, with 265,700 deaths worldwide (7.5% of all female cancer deaths) [1]. Incidence and mortality vary greatly across countries, with most new cases (83%) and deaths (87%) occurring in less developed regions [1]. Malignancies affecting corpus uteri or ovaries are the 6th and the 7th most incident cancers among women, with 319,600 and 238,700 new cases, respectively, estimated in 2012. Their mortality is lower as compared to cervical cancer: ovarian cancer accounted for 4.3%, whereas uterine cancer accounted to 2.1% of cancer deaths among women in 2012, respectively [1].

The therapeutic approaches of gynecologic cancers vary according to their clinical staging, which are based on tissue invasion, as proposed by FIGO (International Federation of Gynecology and Obstetrics) [4]. Locally advanced or metastatic diseases (stages II–IV) are usually treated with cytoreductive surgery plus neoadjuvant and/or adjuvant chemotherapy. The most common chemotherapeutic protocol consists of a combination of a taxane (usually paclitaxel), and a platinum compound (usually carboplatin), which is recommended both for curative or palliative intent [4].

Paclitaxel undergoes biotransformation into inactive compounds in the liver and is dose-normalized according to the body surface area (135–175 mg/m^2). Carboplatin, which is eliminated in the urine without metabolic processing, is dose-adjusted based on the patient's renal function to reach an area under the plasma concentration curve (AUC) > 5 [5, 6].

Despite the benefits of the paclitaxel/carboplatin chemotherapy to improve survival rates of gynecologic cancers [7–9], severe toxicities represent a clinically relevant concern. Thus, patients presenting myelosuppression and/or severe symptoms of peripheral neuropathy may require clinical interventions, including dose delay, dose reduction or even early cessation of the treatment [7–9]. Other common toxicities include fatigue, arthralgia, myalgia, and gastrointestinal discomfort, including nausea and vomiting [5, 7–9].

Susceptibility to adverse effects of paclitaxel and/or carboplatin differs greatly among patients, and it has been proposed that single nucleotide polymorphisms (SNPs) in genes related to the drugs' tissue distribution or systemic disposition could explain such interindividual variability [10–23].

Paclitaxel is metabolized to 6-α-hydroxypaclitaxel and to *p*-3′-hydroxypaclitaxel by CYP2C8 [18] and CYP3A4/3A5 in the liver [24–26], and is also a substrate of the ATP-driven efflux pump P-glycoprotein encoded by *ABCB1* gene [27]. Regarding the gene polymorphisms that may affect these proteins, *CYP2C8*3* has been associated with decreased 6α-hydroxypaclitaxel production in vitro [28]. *CYP2C8*3* is a variant allele formed by two SNPs, i.e. c.-416G>A (rs11572080) and c.1196A>G (rs10509681), which are in perfect linkage disequilibrium [29]. Although over 30 SNPs in the *CYP3A4* gene have been described, they do not seem to affect enzyme activity in vivo [30]. In contrast, the *CYP3A5*3* allele (rs7767746) is a result of a transition in intron 3 (*A6986G*) that causes a frameshift during translation, resulting in a truncated and non-functional splice variant, which accounts for low CYP3A5 activity [26]. Regarding the ABCB1 P-glycoprotein membrane transporter, two synonymous *ABCB1* polymorphisms, *C1236T* in exon 12 and *C3435T* in exon 26, have been shown to generate rare codons, which apparently compromise protein conformation, membrane stability and substrate recognition [31].

Considering the potential impact of the above genes and their functional SNPs on the clinical effects of taxane-based chemotherapeutic protocols, the present work aimed to evaluate the potential role of *CYP2C8*3*, *CYP3A5*3*, *ABCB1 C1236T* and *ABCB1 C3425T* as prognostic biomarkers of individual susceptibility to paclitaxel/carboplatin toxicities among patients with gynecologic cancers.

Methods

Subjects and study design

The study population consisted of an on-going prospective hospital-based cohort of Brazilian women with an initial diagnosis of gynecologic cancer at any clinical stage. The study was conducted at the Hospital do Câncer II, a reference hospital for treatment of gynecologic malignancies, which is part of the Instituto Nacional do Câncer (INCA), the National Cancer Institute of Brazil. Patients were recruited during the period between November 2013 and March 2017, when assigned for adjuvant, neoadjuvant or palliative chemotherapy with the combination of paclitaxel (175 mg/m^2) and carboplatin (AUC 5–6, using Calvert's formula). All patients assigned to receive or already under paclitaxel/carboplatin chemotherapy for less than three cycles were considered eligible and consulted regarding their interest in participating in the study.

The study protocol was approved by the Ethics Committees of the Brazilian National Cancer Institute (INCA 20406413.6.0000.5274) and of the National School of Public Health (FIOCRUZ/CAAE 58944216.0.0000.5240), and all participants gave written consent. The authors complied with the Brazilian regulation of clinical research, and the study was conducted following the international precepts of ethics in research, including the 1964 Helsinki Declaration and its later amendments, and of good clinical practice.

Collection of clinical and histopathological data

A total of 503 patients with gynecologic cancers were included. The major cancer locations were ovaries ($N=195$), corpus uteri ($N=132$) and cervix ($N=173$). Three patients had tumors located in the vulva or vagina. A first interview was conducted to obtain information on the patient's clinical history and life-style habits. The variables considered for clinical history were age at diagnosis, menopausal status, and comorbidities, including any pre-existing chronic condition under medical treatment. Obesity was the only exception, being defined based on the body mass index (BMI), which was calculated as the weight (kg) divided by the square of height (m^2). Patients were considered obese if they had a BMI ≥ 30 [32].

Subsequent interviews were conducted at each chemotherapy cycle, to obtain individual reports about adverse events experienced during inter-cycle periods, as well as the use of any supporting medication. Additionally, both electronic and written medical records were consulted to collect data about hematological evaluations performed immediately (usually 1–2 days) before each chemotherapy cycle, as well as any adverse event or clinical intervention possibly related to chemotherapy (dose delays, dose reductions or treatment interruptions) occurring between or after cycles.

Adverse events, i.e., neurotoxicity, gastrointestinal and hematological toxicities, were graded following the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Grade 0 defines the absence of adverse effects, whereas grades 1, 2, 3 and 4 correspond to mild, moderate, severe and very severe events, respectively.

Regarding clinical interventions, dose delay was characterized as any temporary suspension (at least 1 day) of a previously scheduled chemotherapy cycle, affecting both paclitaxel and carboplatin simultaneously. Dose reductions varied from 15 to 25% reduction in the prescribed dose of paclitaxel, since the adjustment of carboplatin dosage followed the Calvert's formula with no additional corrections. Treatment interruption consisted of cessation of the originally prescribed chemotherapeutic protocol or permanent discontinuation of either chemotherapeutic drug.

Genotyping analyses

Peripheral blood samples (3 mL) were collected from all subjects, and DNA was extracted using the Blood Genomic Prep Mini Spin Kit (GE Healthcare, Buckinghamshire, UK), following the procedures recommended by the manufacturer. DNA could be obtained for 490 patients.

Genotyping was conducted with Taqman assays using Real-Time Polymerase Chain Reaction (real-time PCR 7500 Applied Biosystem, USA) for four polymorphisms from two genes involved in taxane pharmacokinetics (*ABCB1 C1236T* (rs1128503), *ABCB1 C3435T* (rs1045642), *CYP2C8*3* (rs11572080) and *CYP3A5*3* (rs776746). All genotyping analyses were carried out with control samples that were sequenced. Among the 503 enrolled patients, 459 (91.2%) were successfully genotyped for *ABCB1 C1236T*, 476 (94.6%) for *ABCB1 C3435T,* 476 (94.6%) for *CYP3A5*3 A6986G* and 472 (93.8%) for *CYP2C8*3 G416A*.

Statistics

A descriptive study of the cohort was conducted, presenting median values for continuous variables or relative frequencies for each categorical variable. Allelic and genotypic frequencies were derived by gene counting, and the adherence to the Hardy–Weinberg principle was evaluated by the Chi square test for goodness-of-fit, which compares the observed and expected frequencies of genotypic distribution. Although cancer patients do not strictly fit into the conditions for the Hardy–Weinberg principle, this evaluation intends to detect any major deviation that could indicate detection errors.

Individual features (clinical and histopathological variables and genotypes) were evaluated for their association with the occurrence of severe toxicities using Pearson's Chi square tests which compares proportions of events according to categorical characteristics within a population. Significant associations ($P<0.05$) were further tested in multivariable logistic analyses, using the "Enter" method, for calculation of adjusted odds ratios ($OR_{adjusted}$) and respective 95% confidence intervals (95% CI). Wald Chi square test was used to identify independent predictors ($P<0.05$), and the final regression models were tested with the Hosmer–Lemeshow (H–L) test. Only the variables that contributed to increase the p value of the H–L test were maintained in the final model. All statistical analyses were conducted in SPSS 20 for Windows (SPSS Inc., Chicago, Illinois) or GraphPad Prism 5.0 (GraphPad Software, La Jolla, CA, USA). All statistical analyses were carried out using SPSS software package version 20.0 (SPSS).

Results

Characteristics of the study population

Table 1 describes the clinical and histopathological characteristics in the overall population and in the three major cancer subsets. Patients with corpus uteri cancer were older (median age of 63 years) than patients with ovarian or cervical cancer (median ages of 56 or 51 years, respectively) and consequently presented with more comorbidities, especially hypertension and obesity. Regardless of the cancer location, most patients (83.1%) were in advanced stages (FIGO 3–4) and received paclitaxel/carboplatin as palliative chemotherapy (61.4%). The proportion of palliative treatment was particularly high among patients with cervix cancer (91.9%), to whom platinum/taxane combinations are usually reserved for second-line treatment, whereas platinum/radiotherapy protocols are often preferred as the first therapeutic approach.

Genotypic distributions (Fig. 1) fitted Hardy–Weinberg equilibrium except for *CYP3A5*3 (A6986G)* in ovarian cancer ($P = 0.005$), *CYP2C8*3 G416A* in cervix cancer ($P = 0.008$) and *ABCB1 C1236T* in corpus uteri cancer ($P = 0.03$). Despite these specific lacks of adherence to Hardy–Weinberg equilibrium, no significant differences

Table 1 Clinical and histopathological characteristics among gynecologic cancer patients

	All cancer locations[a]		Ovarian		Cervix		Corpus uteri	
N	503		195		173		132	
Age (median/range)	57	22–84	56	23–83	51	22–80	63	26–84
Categorical variables	*N*	%	*N*	%	*N*	%	*N*	%
Age (years)								
22–35	19	3.8	6	3.1	11	6.4	2	1.5
36–50	120	23.9	45	23.1	65	37.6	10	7.6
51–65	217	43.1	91	46.7	67	38.7	59	44.7
> 65	147	29.2	53	27.2	30	17.3	61	46.2
FIGO stage								
I	42	8.3	13	6.7	15	8.7	14	10.6
II	41	8.2	9	4.6	21	12.1	11	8.3
III	201	40.0	91	46.7	43	24.9	67	50.8
IV	217	43.1	81	41.5	93	53.8	40	30.3
Not informed	2	0.4	1	0.5	1	0.6	0	0
Treatment type								
Neoadjuvant	59	11.7	51	26.2	2	1.2	6	4.5
Adjuvant	135	26.8	56	28.7	12	6.9	67	50.8
Palliative	309	61.4	88	45.1	159	91.9	59	44.7
Previous treatment								
None	364	72.4	155	79.5	87	50.3	121	91.7
Platinum/radiotherapy	80	15.9	1	0.5	73	42.2	5	3.8
Platinum/taxanes	53	10.5	36	18.5	12	6.9	4	3
Platinum/taxanes/radiotherapy	2	0.4	1	0.5	1	0.6	0	0
Platinum	2	0.4	1	0.5	0	0	1	0.8
Taxanes	1	0.2	1	0.5	0	0	0	0
Radiotherapy	1	0.2	0	0	0	0	1	0.8
Comorbidities[b]								
None	176	35.0	71	36.4	79	45.7	26	19.7
Hypertension	219	43.5	76	39	60	34.7	81	61.4
Obesity	137	27.2	41	21	42	24.3	53	40.2
Gastritis	77	15.3	32	16.4	21	12.1	24	18.2
Arthrosis	73	14.5	26	13.3	14	8.1	33	25
Diabetes	68	13.5	22	11.3	18	10.4	27	10.5

[a]Overall population included three cases of vulva and vagina cancer

[b]Percentages exceed 100% because patients could present two or more comorbidities simultaneously

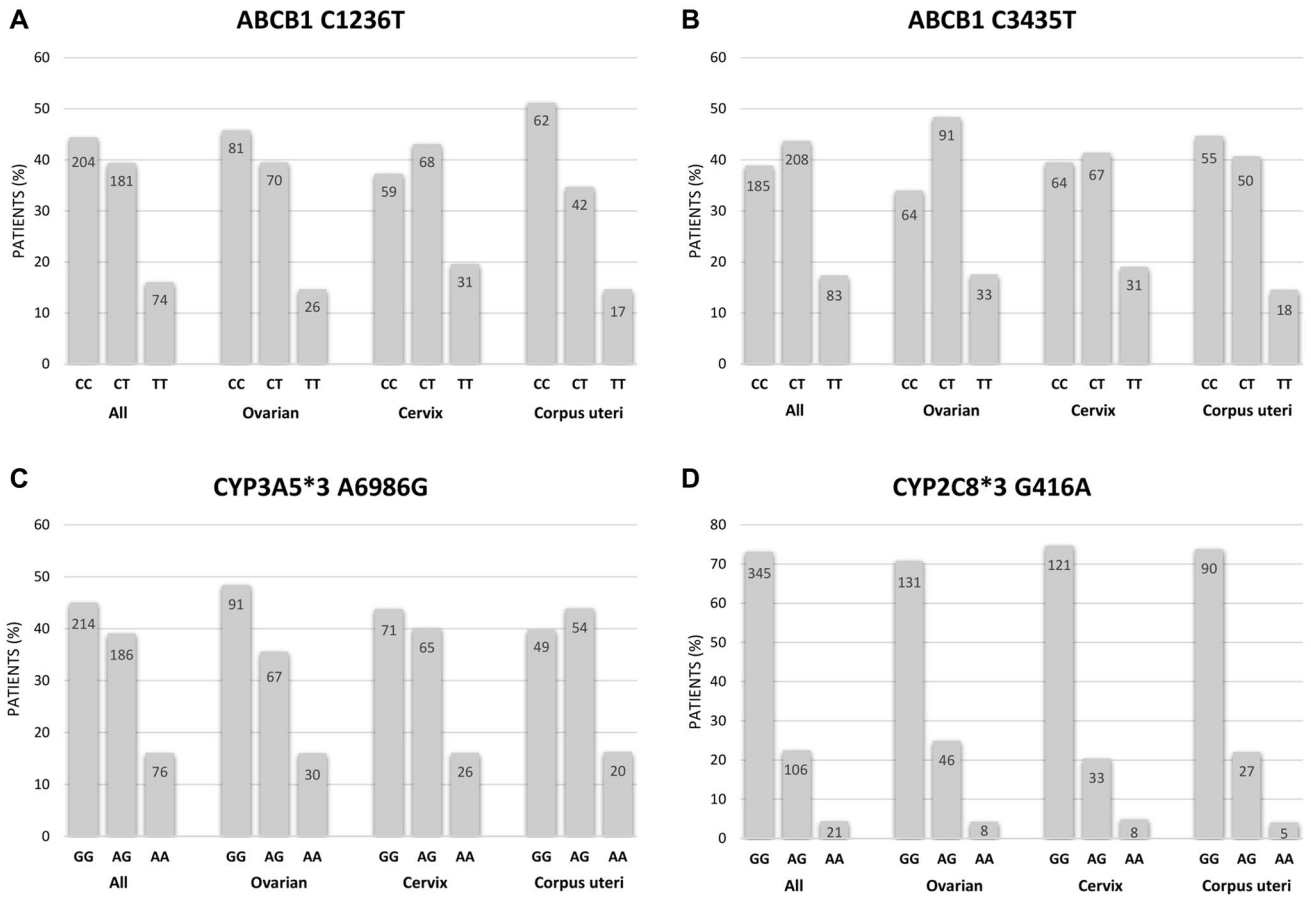

Fig. 1 Genotypic distributions of *ABCB1 C1236T* (**a**), *ABCB1 C3435T* (**b**), *CYP3A5*3 A6986G* (**c**) and *CYP2C8*3 G416A* (**d**) among all patients of the study and in each of the three major gynecological cancer subsets. Numbers inside the bars correspond to the total number of individuals in each category

in the allelic frequencies or genotypic distributions were observed for any of the analyzed SNPs among the three subsets of gynecologic cancer patients.

Toxicities

Figure 2 shows the frequencies of chemotherapy-induced toxicities in the overall population, with the distribution of grades 1–4 for each corresponding adverse effect. The distribution of severe toxicities (grades 3–4), as well as of related clinical interventions, in the overall study population and in the three gynecologic cancer subsets is presented in Fig. 3.

Fatigue was the most frequent toxicity, with severe adverse effects (grades 3–4) being reported by almost 30% of patients. Neuropathy was also quite frequent, with severe adverse effects affecting approximately 20% of patients. The occurrence of severe fatigue or neuropathy following carboplatin/paclitaxel chemotherapy was similar among patients with ovarian, cervix or corpus uteri cancer, independently of the differences in age or in the prevalence of comorbidities among the three gynecologic cancers. In contrast, the frequencies of severe hematological toxicities, which ranged from approximately 9% (thrombocytopenia) to 15% (neutropenia) in the overall population, differed among the three major gynecologic cancers. Thus, severe anemia and thrombocytopenia were more common in patients with cervix cancer than among those with ovarian or corpus uteri cancer, whereas severe neutropenia was more frequent among patients with ovarian cancer. Among patients with severe neutropenia in the overall population ($N=77$), there were four cases of febrile neutropenia, but no cases of neutropenic sepsis. Finally, severe vomiting was the least frequent toxicity, affecting less than 5% of patients, with no significant differences in its incidence among the three major gynecologic cancers.

Regarding clinical interventions, there were 153 cases of dose reduction, 124 patients with dose delays, and 112 treatment interruptions. Among the latter, 93 patients had both drugs suspended, whereas other cases had only paclitaxel ($N=8$) or carboplatin ($N=11$) suspended. These 11 cases of carboplatin interruption were mostly due to infusion reactions ($N=8$); one patient was submitted to a nephrostomy

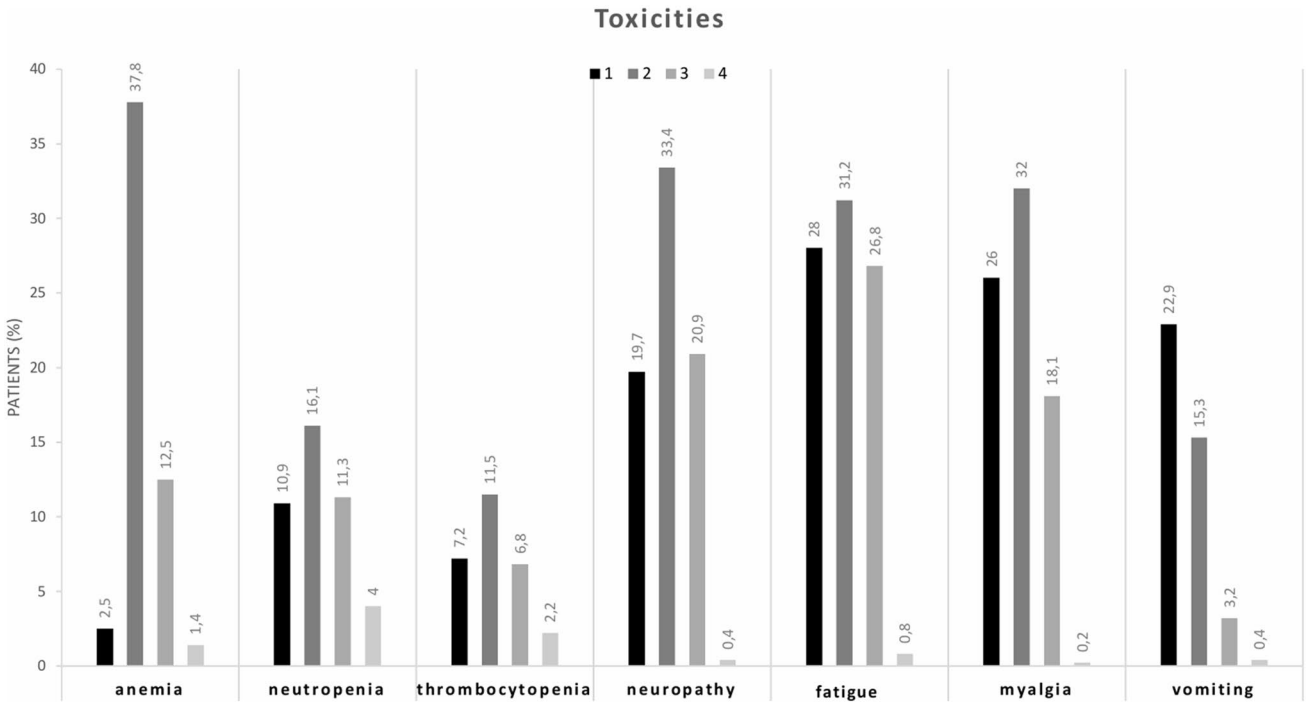

Fig. 2 Frequencies of paclitaxel/carboplatin-induced toxicities in all gynecologic cancer patients, with distribution of grades 1–4 for each toxicity

and two other cases presented several toxicities, but it was not clear why only carboplatin was interrupted. Additionally, blood transfusions ($N=19$) were prescribed in some cases of severe anemia ($N=70$), and two patients among those with severe neutropenia ($N=77$) received granulocyte colony-stimulation factors.

Figure 3b shows the frequencies of the three major clinical interventions (dose delay, dose reduction or treatment interruption) in the overall study population and in each of the three major gynecological cancer subsets. The data indicate similar frequencies among the three cancer subsets, except for dose reduction, which was less common among ovarian cancer patients, as compared to cervix or corpus uteri cancers

Next, we evaluated the association between severe toxicities and each of the three major clinical interventions. In the case of treatment interruption, only the cases including paclitaxel interruption ($N=101$) were considered for analysis. The results observed within the overall study population (Table 2) indicate no significant associations for fatigue, neuropathy or vomiting, whereas all three hematological toxicities (anemia, thrombocytopenia and neutropenia) were associated with the requirement for at least one clinical intervention to the chemotherapeutic protocol. The lack of association between severe neuropathy and clinical interventions to the chemotherapeutic protocol is probably due to the use of gabapentin or classical analgesics which were prescribed to all affected patients with intent to mitigate pain and allow treatment continuation without adjustments in the chemotherapeutic dose.

Severe anemia was associated with dose delay and treatment interruption; severe neutropenia significantly led to dose delay and dose reduction, whereas severe thrombocytopenia increased the requirement of all three interventions. The associations between hematological toxicities and clinical interventions could also be observed within the three cancer subsets (Table 3). Thus, all three hematological toxicities led to increased frequency of dose delay among patients with cervix or corpus uteri cancer. Higher demands of dose reduction were observed for severe neutropenia in ovarian cancer or for severe thrombocytopenia in both ovarian and cervix cancer, whereas severe anemia increased the frequency of treatment interruption among patients with cervical cancer.

Genotypes and clinical predictors of severe toxicities to paclitaxel/carboplatin chemotherapy

Table 4 shows the final multivariable regression models, indicating which variables, either clinical features or genotypes were independent predictors of severe toxicities to paclitaxel/carboplatin chemotherapy in gynecologic cancer patients. It is noticeable that all models presented high P values for the H–L test indicating robust predictions.

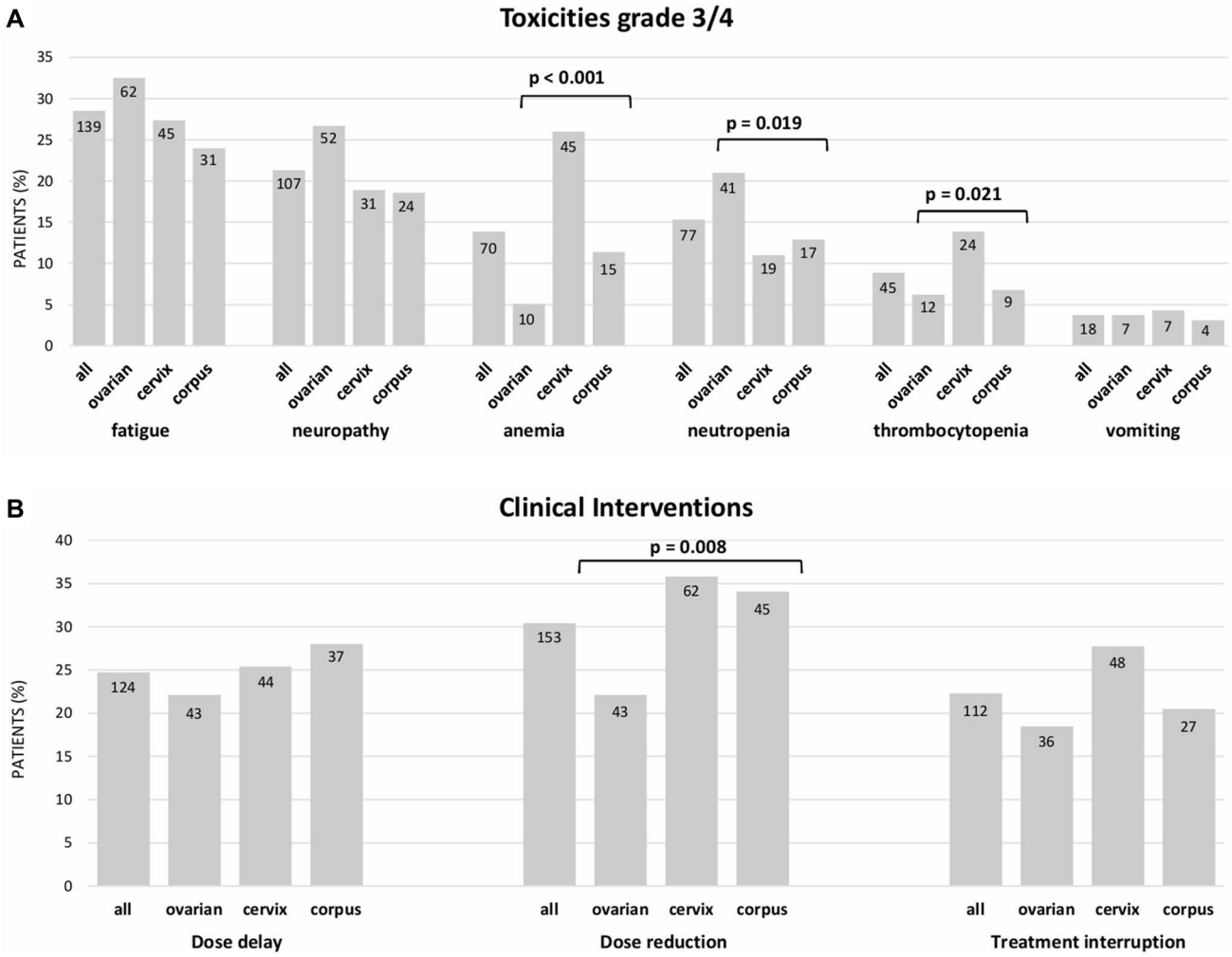

Fig. 3 **a** Frequencies of severe toxicities (grades 3–4) among all patients of the study and in each of the three major gynecological cancer subsets. **b** Frequencies of clinical interventions among all patients of the study and within each of the three major gynecological cancer subsets. Numbers inside the bars correspond to the total number of individuals in each category. *P* values were obtained with Chi square test

Table 2 Associations between severe toxicities (grades 3–4) and clinical interventions among all gynecologic cancer patients ($N=503$)

Severe toxicities	Dose delay ($N=124$)		Dose reduction ($N=153$)		Treatment interruption ($N=101$)[a]	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
Anemia	**3.12 (1.85–5.27)**	**< 0.001**	1.32 (0.78–2.25)	0.3	**3.82 (2.23 – 6.54)**	**< 0.001**
Neutropenia	**3.85 (2.32–6.38)**	**< 0.001**	**1.90 (1.16–3.15)**	**0.011**	0.95 (0.52–1.76)	0.887
Thrombocytopenia	**12.64 (6.16–25.9)**	**< 0.001**	**3.95 (2.1–7.42)**	**< 0.001**	**2.42 (1.26–4.66)**	**0.008**
Fatigue	0.75 (0.47–1.21)	0.247	1.11 (0.72–1.69)	0.635	1.01 (0.60–1.69)	0.965
Neuropathy	0.89 (0.53–1.51)	0.683	1.14 (0.71–1.83)	0.587	1.16 (0.67–2.00)	0.590
Vomiting	1.08 (0.37–3.19)	0.883	1.38 (0.51–3.73)	0.527	1.81 (0.63–5.23)	0.270

Significant associations are presented in bold font

OR odds ratio, *CI* confidence interval, *PP* value for univariate logistic regression

[a]Cases of paclitaxel/carboplatin or only paclitaxel treatment interruption

Table 3 Associations between severe toxicities and clinical interventions in the three major cancer subsets

Tumor location	Toxicities	Dose delay		Dose reduction		Treatment interruption[a]	
		OR (CI)	*P*	OR (CI)	*P*	OR (CI)	*P*
Ovaries	Anemia	3.81 (0.99–14.66)	0.051	0.56 (0.07–4.68)	0.597	2.87 (0.69–11.88)	0.145
	Neutropenia	2.16 (0.93–5.01)	0.072	**2.84 (1.29–6.24)**	**0.009**	1.38 (0.54–3.53)	0.502
	Thrombocytopenia	**11.35 (2.81–47.78)**	**0.001**	**3.95 (1.12–13.93)**	**0.033**	2.21 (0.55–8.73)	0.259
Cervix	Anemia	**2.77 (1.15–6.69)**	**0.023**	0.94 (0.43–2.02)	0.869	**4.53 (2.17–9.44)**	**< 0.000**
	Neutropenia	**5.00 (1.58–15.83)**	**0.006**	1.30 (0.47–3.64)	0.612	0.68 (0.22–2.19)	0.527
	Thrombocytopenia	**13.67 (4.45–42.02)**	**0.000**	**4.40 (1.67–11.59)**	**0.003**	1.75 (0.71–4.33)	0.224
Corpus uteri	Anemia	**3.44 (1.01–11.72)**	**0.048**	1.25 (0.39–3.98)	0.704	1.57 (0.46–5.39)	0.474
	Neutropenia	**10.86 (3.36–35.09)**	**0.000**	1.45 (0.51–4.12)	0.488	1.30 (0.38–4.37)	0.671
	Thrombocytopenia	**5.06 (1.05–24.41)**	**0.043**	1.49 (0.36–6.23)	0.584	3.67 (0.91–14.79)	0.067

Significant associations are presented in bold font

OR odds ratio, *CI* confidence interval, *PP* value for univariate logistic regression

[a]Cases of paclitaxel/carboplatin or only paclitaxel treatment interruption

Table 4 Multivariable logistic regression models of severe toxicities among gynecologic cancer patients

Severe toxicity (grades 3–4)	Predictors	OR	95% CI	*P* (HL)
Anemia	Cervix cancer	2.89	1.56–5.38	0.864
	Previous radiotherapy	2.44	1.27–4.67	
Neutropenia	*CYP2C8*3 GA + AA*	2.11	1.24–3.6	0.648
	Ovarian cancer	2.10	1.25–3.52	
	Adjuvant treatment	1.91	1.11–3.28	
Thrombocytopenia	Previous radiotherapy	4.14	2.07–8.27	0.924
	*CYP2C8*3 AA*	4.93	1.69–14.35	
	ABCB1 3435 CC	1.98	1.01–3.86	
Fatigue	*CYP2C8*3 GG*	1.93	1.17–3.19	0.663
	ABCB1 any variant	2.13	1.32–3.42	
Neuropathy	Diabetes	1.77	1.01–3.13	

OR odds ratio, *CI* confidence interval, *PP* value for multivariable regression analysis, *HL* Hosmer–Lemeshow test

Anemia and neuropathy were not affected by gene polymorphisms. The risk of severe anemia was increased for cervix cancer patients, as well as for those who were exposed to previous radiotherapy, whereas diabetes was the only independent predictor of severe neuropathy and yet with borderline statistical significance ($P = 0.048$).

In contrast, severe neutropenia was more likely to affect patients with *CYP2C8*3* variant genotypes as well as those with ovarian cancer patients or who were under adjuvant chemotherapy. The independent predictors of severe thrombocytopenia were previous radiotherapy, *CYP2C8*3* double variant homozygous genotype (*AA*) and *ABCB1 C3435T* wild-type genotype. Finally, the combination of any *ABCB1* variant genotypes and wild-type *CYP2C8* was predictive of severe fatigue.

Discussion

The present study is the first pharmacogenetic study of taxane/platinum-based protocols for gynecologic cancer among Brazilians. It involved a relatively large ($N = 503$) prospective cohort, composed mostly of patients with ovarian, cervix and corpus uteri tumors. Previous pharmacogenetic studies of taxane- or platinum-based protocols for gynecologic cancer usually restricted their analyses to ovarian tumors [10, 12–22], with sample sizes varying from 31 [14] to 914 [20], although only 4 [16–18, 20] presented larger cohorts than ours (195 patients with ovarian cancer). The study by Uchiyama et al. [23] was the only to include any gynecologic tumors but with a very restricted

sample size ($N = 42$). Regarding the population origin, such previous studies were conducted with individuals from Europe [10, 12–14, 16–18, 20, 22], Asia [15, 19, 23] or North America [21]. In the last case, as well as in the studies conducted in Europe, all subjects were identified as Caucasians. In contrast with this ethnic distinction, Brazil is well known for its very heterogeneous and admixed population, formed mostly by a tri-hybrid composite of Amerindians, Europeans and Sub-Saharan Africans [33].

The allele frequencies described here are mostly within the ranges reported for a healthy Brazilian sample of both men and women from the southeast region of Brazil where Rio de Janeiro is located [34]. The only exception was *CYP2C8*3*, with an allelic frequency of 15.7% (13.5–18.1%) in our population which was significantly higher from the estimated value of 10.96% (8.3–13.7%) for the Brazilian southeast region [34]. Nevertheless, the frequency of *CYP2C8*3* in our population is within the values reported in other studies involving gynecologic cancer patients from Europe (9.7–16.8%) [10, 12, 13, 20]. Although the genotypic distributions did not always fit Hardy–Weinberg equilibrium (e.g. *CYP3A5*3* in ovarian cancer, *CYP2C8*3* in cervix cancer and *ABCB1 C1236T* in corpus uteri cancer), this result does not reflect a genotyping error, since it was not consistent through the different groups of gynecologic cancer, and all analyses were carried out with control samples. It is important to stress that cancer patients do not fit into the premises for Hardy–Weinberg equilibrium, e.g. gynecological cancers affect only women, and more frequently at older ages; there are recognized gene mutations that may favor cancer susceptibility, such as the association between *BRCA1* and ovarian cancer (ref). In addition, it is possible that variant genotypes may also favor cancer susceptibilities or progression, or even segregate with a particular phenotype due to linkage disequilibrium with another genetic determinant. All these possibilities could lead to deviations from Hardy–Weinberg equilibrium or to differences in genotypic distribution among the three cancer subsets.

The comparison of pharmacogenetic studies of taxane/platinum-based protocols in ovarian cancer patients indicates similar clinical characteristics regarding histological types, tumor staging and chemotherapeutic protocols. Nevertheless, the frequencies of severe hematological toxicities (grades 3–4) reported in previous studies were higher: 18% [21], 48% [14], 53% [15], 56% [22] or 95% [16] for neutropenia; 18% [16] for thrombocytopenia (grades 3–4); and 22% [16] for anemia. Such higher frequencies of hematological toxicities are possibly due to the moment of blood collection. In our study, blood cell counts were evaluated at about 20 days after chemotherapy, while other ovarian cancer studies had myelosuppression evaluated between 1 and 2 weeks after chemotherapy [14–16], which is the expected nadir of neutrophil, platelets and red blood cells counts [35]. In addition, the frequencies reported here for neutropenia, anemia, and thrombocytopenia were different in the three cancer subsets. Anemia and thrombocytopenia were more frequent in patients with cervix cancer, probably as a consequence of previous use of local radiotherapy, which might lead to vaginal bleeding. Accordingly, previous radiotherapy was an independent predictor of both anemia and thrombocytopenia in the final multivariable models. In contrast, neutropenia was more frequent in ovarian cancer and was also associated with adjuvant chemotherapy. We have no explanation for this finding, since the chemotherapeutic doses were not different in adjuvant, neoadjuvant or palliative conducts.

Severe neuropathy was described with an incidence of 5.8% in two previous studies [17, 18], while our population had a frequency of 21.3%. The higher frequency of severe neuropathy in our population appears to be related with diabetes, which was the only independent predictor of this toxicity in our study.

Severe emesis was reported with variable incidences among gynecologic cancer patients receiving taxane- or platinum-based protocols: 3% [21], 25% [22] or 38% [22]. Such variability might be due to a different antiemetic routine preceding and/or following chemotherapy sessions. In our study, all patients received dexamethasone immediately before and after chemotherapy and ondansetron after chemotherapy and were also advised to use metoclopramide in case of severe nausea or emesis in the inter-cycle period. Finally, there are no previous reports regarding the incidence of fatigue among gynecologic cancer patients, although it is recognized as a common toxicity of taxane-based protocols [5].

Regarding the potential of gene polymorphisms as prognostic predictors of severe toxicities to paclitaxel/carboplatin chemotherapy, the results of our final multivariable models point to *CYP2C8**3 and to *ABCB1* variant genotypes as possibly interesting targets, whereas *CYP3A5*3* showed no significant risk associations with any of the evaluated toxicities. In summary, *CYP2C8*3* was significantly associated with higher risk of severe neutropenia and thrombocytopenia, whereas the presence of any *ABCB1* variant genotypes seemed to favor the occurrence of severe fatigue. When the three cancer subsets were evaluated separately, only the association between *CYP2C8*3AA* genotype and severe thrombocytopenia was maintained for both ovarian and corpus uteri cancer. The lack of significant associations when the three tumor subsets are considered separately may reflect cancer specificities but might also be due to low statistical power within subgroups.

The comparison of our results with previous pharmacogenetic studies about the toxicity of taxane/platinum protocols indicates no consensus. First, our data suggest no significant impact of *CYP3A5*3* on the risk of taxane/platinum

toxicities, which is in accordance with the findings from most studies involving various types of cancer in different ethnic groups [16, 20, 21, 36–42]. However, there have been some reports of decreased neutropenia [43] or leucopenia [14, 15] in association with *CYP3A5*3*, whereas Leskelä et al. reported lower risk of neurotoxicity for *CYP3A5*3* [44] and proposed that paclitaxel neurotoxicity could be mediated by some of its metabolites [44].

Although *CYP3A5*3* codes for a truncated and non-functional splice variant [26], the translation to CYP3A5 protein is highly modulated by diet [45] and xenobiotics [46], which might attenuate the functional impact of *CYP3A5*3* polymorphism. In addition, *CYP3A5*3* is the major allele among Europeans and North-American Caucasians, with frequencies in the range of 66–94% [14, 20, 21], which can compromise the detection of any significant functional effect. Finally, paclitaxel is also a substrate to CYP2C8, which may compensate its metabolic rate [47].

Regarding *ABCB1*, we found that both *ABCB1 C1236T* and *C3435T* were associated with severe fatigue. The only pharmacogenetic study about this toxicity in platinum/taxane protocols was the report by Pérez-Ramírez et al. [48], who evaluated 141 patients with lung cancer. The authors found no association between *ABCB1* polymorphisms and fatigue, but only 23.4% of patients received the paclitaxel/carboplatin chemotherapy, and the incidence of severe fatigue (grades 3–4) was very low (2.13%) when compared to our study (27.6%). Regarding other toxicities, *ABCB1 C1236T* has been associated with severe anemia in ovarian cancer ($n=290$) [16], whereas *ABCB1 C3435T* has been associated with severe neutropenia in patients with ovarian ($n=86$) [10], breast ($n=216$) [49] or other solid tumors ($n=33$–58) [40, 42]. In contrast, however, most studies evaluating *ABCB1* variants in ovarian cancer [10, 12, 13, 20, 21] or other tumors treated with taxane/platinum protocols [11, 44, 48, 50–54] found no significant risk associations for any toxicity.

According to our results, the most promising pharmacogenetic predictor of paclitaxel/carboplatin toxicity is *CYP2C8*3*, which was associated with higher risk of severe neutropenia and thrombocytopenia among patients with either ovarian or corpus uteri tumors. CYP2C8 is responsible for the biotransformation of paclitaxel [24], and *CYP2C8*3* variant has been associated with lower clearance in vivo [12, 55], resulting in increased drug exposure [55], which could justify a higher degree of toxicity when *CYP2C8*3* carriers are exposed to paclitaxel-based treatment. In accordance with this functional rationale, Gréen et al., in a small study involving 33 ovarian cancer patients, reported an increased risk of both neurotoxicity and thrombocytopenia for *CYP2C8*3* heterozygotes [14]. Nevertheless, most pharmacogenetic studies with ovarian cancer [10, 13, 20, 56] or other solid tumors [38, 41, 44, 57–59] do not corroborate an increased risk of hematological toxicity for *CYP2C8*3* carriers exposed to taxane-based protocols.

One possible explanation for the lack of a detectable adverse hematological effect of *CYP2C8*3* in such previous studies is that cell counts were usually conducted at the expected nadir after each chemotherapeutic cycle. As a consequence, the high incidences of anemia and leucopenia reported in such studies might be reflecting a transient myelosuppressive effect that is rather common for most patients under taxane/platinum protocols, since both drugs are cytotoxic. The functional impact of *CYP2C8*3* on paclitaxel pharmacokinetics is more likely to compromise the patient's ability to recover from myelosuppression, potentially resulting in delayed anemia, neutropenia or thrombocytopenia.

Regarding the risk of neurotoxicity, two studies on breast cancer [60, 61] and a study with various solid tumors [44] (ovarian, $n=24$; breast $n=38$ and lung cancer, $n=39$) reported a higher incidence of neuropathy for *CYP2C8*3* carriers, whereas other studies involving ovarian cancer [10, 13, 14, 20, 56], breast cancer [58] or other solid tumors [41, 59] indicate no association between *CYP2C8*3* and neurotoxicity. Taxane-related neurotoxicity is dose-cumulative, and the discrepancies among such studies might be related to differences in chemotherapeutic protocols. Thus, severe neuropathy appears to be more frequent with weekly paclitaxel 80–90 mg/m^2 regimens [44], which are common for breast cancer, than with the combination of paclitaxel at 175 mg/m^2 and carboplatin (AUC 5 or 6) every 21 days, which is the standard treatment of ovarian and lung tumors. Due to this higher exposure to paclitaxel, breast cancer patients are possibly more susceptible to a functional impact of *CYP2C8*3* on paclitaxel pharmacokinetics affecting the risk of neurotoxicity. Accordingly, the only breast cancer study reporting no association between *CYP2C8*3* and neurotoxicity had 26% of patients receiving paclitaxel, while 74% received docetaxel [58]. In contrast, the breast cancer studies with significant impact of *CYP2C8*3* on the incidence of taxane-related neuropathy used weekly paclitaxel regimens [60, 61]. In our study, the only independent variable significantly associated with severe neuropathy was diabetes, possibly indicating a causal mechanism not related to paclitaxel exposure and, therefore, not likely to be affected by *CYP2C8*3*.

Conclusions

The present study suggests that *CYP2C8*3* is a potential predictor of hematological toxicities, namely neutropenia and thrombocytopenia, following paclitaxel/carboplatin chemotherapy in gynecologic cancer patients. As strong points of the current evaluation, the study was conducted in a relatively large cohort of an ethnically heterogeneous population, with different gynecologic tumors, and the finding

was confirmed in multivariable analysis, including clinical characteristics and with independent validations for both ovarian cancer and corpus uteri tumors. In contrast, most of the previous pharmacogenetic studies focused on univariate analysis of randomly selected variables, while other varying circumstances that are likely to affect the susceptibility to chemotherapeutic toxicities were not explored.

Since hematological toxicities, especially neutropenia, may lead to treatment delay or even interruption, the evaluation of prognostic factors may contribute to guide the therapeutic conduct as well as the follow-up of patients at higher susceptibility. In this regard, it would be also interesting to evaluate the prognostic impact of *CYP2C8*3* on survival outcomes. Unfortunately, the current study was not originally designed with this intent; the three cancer subsets have different prognosis, and the use of the paclitaxel/carboplatin combination is used at different stages of the disease in each case. Therefore, the survival analyses should be conducted in each cancer subset separately, but the number of available cases in the three sub-cohorts is below the limit for adequate statistical power. In view of these limitations, we could not include prognosis evaluation in the current study. We are now planning new design strategies so that we can pursue this evaluation.

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Author contributions CLC: data curation, formal analysis, investigation, methodology, project administration, software, visualization, writing—original draft and review. LCCJ: data curation, investigation, methodology, and visualization. LVL: data curation, investigation, methodology, and visualization. KSS: data curation, software, and visualization. TSLS: data curation and visualization. RV-J: conceptualization, funding acquisition, methodology (selection and development); project administration; resources; supervision; validation; visualization; and writing (review and editing).

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

Ethical standards The study was conducted following the international precepts of ethics in research, including the 1964 Helsinki Declaration and its later amendments, and of good clinical practice. The authors complied with the Brazilian regulation of clinical research. The study protocol was approved by the Ethics Committees of the Brazilian National Cancer Institute (INCA 20406413.6.0000.5274) and of the National School of Public Health (FIOCRUZ/CAAE 58944216.0.0000.5240), and all participants gave written consent to participate.

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