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Anthracycline-Induced Cardiotoxicity: the Role of Genetic Predictors

Aim	To evaluate the predictive significance of gene polymorphism in endothelin-1 type 2A receptor, NADPH oxidase, p53 protein, endothelial nitric oxide synthase, caspase 8, interleukin-1β, tumor necrosis factor-α, superoxide dismutase-2, glutathione peroxidase-1, β1-adrenoceptor, angiotensin-converting enzyme, and matrix metalloproteinase-3 (MMP-3) genes in evaluating the risk of anthracycline-induced cardiotoxicity (AIC) in women without concurrent cardiovascular diseases (CVD).
Material and Methods	This study included 176 women aged 45.0 [42.0; 50.0] years with breast cancer without concurrent CVD who were scheduled for polychemotherapy (PCT) with anthracycline antibiotics. Echocardiography was performed for all patients at baseline and at 12 months after the end of PCT course. Genetic polymorphism was determined with the polymerase chain reaction.
Results	At 12 months, all patients were in remission of the underlying disease. They were retrospectively included into 2 groups: 1st group, 52 patients with AIC and 2nd group, 124 women without AIC symptoms. The development of AIC was associated with the presence of the p53 protein gene Arg/Arg genotype (odds ratio (OR), 2.972; p=0.001), NOS3 gene T/T genotype (OR, 3.059; p=0.018), NADPH oxidase gene T/T genotype (OR, 2.753; p=0.008), GPX1 gene C/C genotype (OR, 2.345; p=0.007), MMP-3 gene 5A/5A genotype (OR, 2.753; p=0.008), and ADRB1 gene G/G genotype (OR, 3.271; p=0.043).
Conclusion	Evaluation of genetic polymorphism in p53 protein (rs1042522), NOS3 (rs1799983), NADPH-oxidase (rs4673), GPX1 (rs1050450), ADRB1 (Arg389Gly, rs1801253), and MMP-3 (rs3025058) genes can be recommended for use prior to starting chemotherapy in women with breast cancer without CVD for assessing the risk of AIC. A maximum risk of cardiotoxicity is associated with the presence of the p53 protein gene Arg/Arg genotype and NOS3 gene T/T genotype.

Keywords	Anthracycline-induced cardiotoxicity; genetic polymorphism; prognosis; breast cancer; chemotherapy
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Introduction

A number of anticancer treatments are currently used for malignant tumors, which have high efficacy but a significant potential for cardiotoxicity: cyclophosphamide, doxorubicin, trastuzumab, fluorouracil, cisplatin, agents that inhibit the immune system (blockers of cytotoxic T-lymphocyte-associated protein-4, programmed type 1 cell death protein, and programmed cell death receptor ligand) [1]. Due to their efficacy associated with higher 5 year survival in some cancers by more than 80% and economic availability [2], anthracyclines remain one of the most potent and often administered chemotherapeutic agents for the treatment of hematological and solid tumors [3–5]. At the same time, the clinical use of anthracyclines is limited by their cardiotoxicity, such as heart failure (HF) [6, 7], the prevalence of which can be as high as 57% and depends on such factors as age, cumulative dose, history of cardiovascular diseases (CVDs), etc. [8]. It is discussed that the mechanisms of anthracycline-induced cardiotoxicity (AIC) are implemented through mitochondrial dysfunction (mitochondrial NADH dehydrogenase) [9], abnormal iron homeostasis [3, 10], generation of oxidative stress by NRF2 and reactive oxygen species with nitric oxide mediated by neuronal NO-synthase enzymes [3, 11], and development of endothelial dysfunction [12], stimulation of apoptosis (induction of heat shock proteins and p53) [13, 14], pyroptosis (activation of pro-inflammatory molecules) [15] and various caspases [16], and through induction of the signaling pathway of interstitial and perivascular fibrosis involving matrix

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metalloproteinases [17, 18] and transforming growth factor beta (TFG-β) [19]. However, the main ways of initiating this severe complication are not yet known.

It takes time to trigger the molecular mechanisms of cardiotoxicity, which is why the initial stages of AIC are often asymptomatic, and screening based on the measurement of left ventricular ejection fraction (LVEF) has certain limitations in the symptom-free stages. This explains the significant delay between the completion of polychemotherapy (PCT) and the development of myocardial remodeling and cardiovascular dysfunction [20]. Another likely mechanism is the repeated induction of cardiomyocyte death with limited regenerative capacity [21] during PCT and impaired expression of cardiac genes. Thus, as well as molecular mechanisms, the pathogenesis of cardiotoxicity involves changes in the expression of specific genes initiating structural and functional changes in the myocardium, including genes that control the activity of the components of the renin-angiotensin system, electron transport chain, fibrosis, etc. [1, 17–19].

Objective

Comprehensive assessment of the prognostic significance of polymorphisms of genes responsible for the main mechanisms of initiation of cardiotoxicity: genes of endothelin-1 type 2A receptor, NADPH oxidase, p53 protein, endothelial nitric oxide synthase, caspase-8, interleukin-1 beta, tumor necrosis factor alpha, superoxide dismutase-2, glutathione peroxidase-1, beta-1 adrenoceptor, angiotensin-converting enzyme, and matrix metalloproteinase-3 in the assessment of the risk of AIC in female patients without concomitant CVDs.

Material and Methods

This was a prospective observational single-center study approved by the local ethics committee of the Research Institute for Cardiology of Tomsk National Research Medical Center (Minutes No. 207 dated December 23, 2020).

The study included 176 female patients of a mean age of 45.0 [42.0; 50.0] years, with breast cancer (BC) and without CVDs. The women were undergoing chemotherapy. PCT for BC included a combination of doxorubicin and cyclophosphamide (AC regimen) or a combination of doxorubicin, cyclophosphamide, and docetaxel (TAC regimen). The cumulative dose of doxorubicin was 300–360 mg/m^2.

The exclusion criteria were diabetes mellitus, coronary artery disease, arterial hypertension, valvular heart disease, and cardiomyopathies of any origin. The absence of CVDs was confirmed by anamnestic data and the findings of electrocardiography, echocardiography, and coronary angiography.

All patients underwent echocardiography, general clinical examinations, and the serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) were determined (Biomedica immunoassays).

A decrease in LVEF 12 months after the completion of chemotherapy by ≥ 10% of the baseline, the appearance of clinical signs of HF, and an elevation in NT-proBNP levels ≥125 pg/mL were the criteria for the development of AIC.

Genetic materials were collected from all patients followed by typing of alleles of endothelin-1 receptors type 2A (EDNRA, C+70G, rs5335), NADPH oxydase (C242T, rs4673), p53 protein (Arg72Pro exon 4, rs1042522), endothelial nitric oxide synthase NOS3 (Glu298Asp, rs1799983), caspase 8 (CASP8, rs3834129 and rs1045485), interleukin-1 beta (Il-1β, rs1143634), superoxide dismutase-2 (SOD2, rs4880), tumor necrosis factor alpha (TNF-α, rs1800629), angiotensin-converting enzyme (ACE, I/D, rs4343), glutathione peroxidase-1 (GPX1, rs1050450), adrenergic receptor beta 1, Arg389Gly, rs1801253), matrix metalloproteinase-3 (MMP-3, rs3025058).

Genotyping was performed by real-time polymerase chain reaction with primers matched using the single nucleotide polymorphism database (dbSNP; http://www.ncbi.nlm.nih.gov/snp). DNA was isolated from buccal epithelial cells using the phenol chloroform extraction method.

The data obtained were analyzed using Statistica (StatSoft, Inc.) and MedCalc 11.5.0.0. The quantitative variables were presented as the medians and the interquartile ranges (Me [25th percentile; 75th percentile]). Statistical hypotheses were tested for the comparison of two independent samples using the Mann-Whitney test. The qualitative variables were examined using the contingency table analysis and Pearson's chi-square test. The odds ratios (OR) and 95% confidence intervals (CI) were calculated using logistic regression to identify factors having a significant impact on the course and prognosis of the disease. Multivariate regression analysis was used to select genes having the most significant roles in the development of AIC. The critical significance value for all the statistical analysis procedures used was p=0.05.

Hardy-Weinberg equilibrium was used to control the results of genotyping. Compliance with Hardy-Weinberg equilibrium was assessed using Fisher's exact test using the online instrument of the Institute of Human Genetics (http://ihg2.helmholtz-muenchen.de/cgi-bin/hw/hwa1.pl).

Results

All patients had remission of BC 12 months after the completion of chemotherapy and were retrospectively

divided into 2 groups: Group 1 included 52 patients with AIC, Group 2 consisted of 124 patients without AIC (Table 1).

The groups did not differ significantly in the main clinical and demographic characteristics. The analysis depending on the type of treatment received showed no differences in the incidence of AIC.

Baseline echocardiographic parameters did not differ between the groups. Twelve months after the completion of chemotherapy, in Group 1, LVEF decreased by 16.8% (p<0.001); LV end-systolic dimension increased by 13.7%, LV end-diastolic dimension increased by 15.1% compared to the inclusion data, and these parameters did not change statistically significantly in Group 2 (Table 2).

In Group 1, the frequency of T/T genotypes of NADPH oxidase gene (p = 0.006), T/T of the NOS3 gene rs179998 (p=0.014), Arg/Arg of the p53 gene (p=0.008), C/C of the GPX1 gene (p=0.019), G/G of the ADRB1 gene (p=0.013), 5A/5A of the MMP-3 gene (p=0.006) was statistically significantly higher than in Group 2 (Table 3).

The presence of genotypes of the following genes increased the likelihood of AIC more than 2-fold: genotype C/C of the GPX1 gene – 2.3 (OR 2.346; p=0.001), genotype 5A/5A of the MMP-3 gene – 2.8 (OR 2.753; p=0.008), genotype T/T of the NADPH oxidase gene – 2.8 (OR 2.753; p = 0.008); genotype Arg/Arg of the protein p53 gene – 2.9 (OR 2.972; p = 0.001), genotype T/T of the NOS3 gene – 3.1 (OR 3.059; p=0.018), and genotype G/G of the ADRB1 gene – 3.3 (OR 3.271; p=0.043) (Table 4).

It was found that the Pro/Pro genotype of the p53 gene was statistically significantly associated with the absence of AIC (OR 0.510; p = 0.031). This means that this genotype can produce a cardioprotective effect.

The comparison of gene polymorphisms using multivariate regression analysis found that the Arg/Arg genotype of the p53 gene (OR 3.12; 95% CI 2.73–11.13;

Table 1. Clinical and demographic characteristics of patients

Parameter	Group 1 (n = 52)	Group 2 (n = 124)	p
Age, years	45 [42; 47]	45 [42; 50]	0.557
Cumulative dose of doxorubicin, mg/m²	360 [300; 360]	360 [300; 360]	0.818
Chemotherapy regimen, n (%)			
AC regimen	29 (55.8)	74 (59.7)	0.631
TAC regimen	23 (44.2)	50 (40.3)	0.654
BC stage 2A–2B, n (%)	32 (61.5)	77 (62.1)	0.467
BC stage 3A–3B, n (%)	20 (38.5)	47 (37.9)	0.972
Body mass index, kg/m²	24.7 [21.8; 25.8]	23.0 [21.1; 25.6]	0.255
Smoking, n (%)	7 (13.5)	20 (16.1)	0.654
COPD, n (%)	5 (9.6)	10 (8.1)	0.737
Postmenopause, n (%)	38 (73.1)	88 (71.0)	0.987
Total cholesterol, mmol/L	5.2 [4.85; 5.7]	5.25 [4.8; 5.7]	0.882
Glucose, mmol/L	4.8 [4.3; 5.25]	4.7 [4.3; 5.3]	0.541
Creatinine, μmol/L	75 [68; 86]	77 [71; 86.5]	0.619
GFR, mL/min/1.73m²	89 [78; 96]	88 [76; 98]	0.876
Hemoglobin, g/dL	109.5 [100; 117]	109.5 [99; 117.5]	0.798

AC regimen is the combination of doxorubicin and cyclophosphamide; TAC regimen is the combination of doxorubicin, cyclophosphamide, and docetaxel; BC, breast cancer; GFR, glomerular filtration rate (CKD-EPI).

Table 2. Changes in the echocardiographic parameters and levels of NT-proBNP

Parameter	Group 1 (n = 52)	Group 2 (n = 124)	p	Group 1 (n = 52)	Group 2 (n = 124)	p
LVEF, %	65.5 [62; 70]	67.0 [62; 70]	0.663	54.5 [51.5; 58]*	66 [63; 69]	< 0.001
LA, mm	28 [26; 31]	28 [25.5; 31]	0.871	30 [28; 32]*	29 [27; 31]	0.064
EDD, mm	44 [42; 48.5]	45.5 [43; 49]	0.284	51 [49; 54.5]*	47 [44; 49]	< 0.001
ESD, mm	28 [26; 31]	28 [26; 31]	0.764	33 [31; 35]*	29 [27; 31]	< 0.001
IVS, mm	10 [9; 11]	10 [9; 11]	0.992	10.5 [10; 11]	10 [9; 11]	0.041
LVPW, mm	10 [10; 11]	10 [10; 11]	0.774	11 [10; 12]	10.5 [10; 11]	0.008
NT-proBNP, pg/mL	49.65 [41.65; 56.9]	46.95 [40.6; 56.35]	0.604	295.3 [197; 370.4]*	57.4 [45.7; 70.3]	< 0.001

NT-proBNP, N-terminal pro-brain natriuretic peptide; LVPW, left ventricular posterior wall;

* Statistically significant differences (p<0.05) compared to the baseline.

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Table 3. Frequency of genotypes and gene alleles depending on the development of anthracycline-induced cardiotoxicity

Gene	Alleles and genotypes	Group 1 (n = 52)	Group 2 (n = 124)	χ^2	p
NADPH oxidase (C242T, rs4673)	C/C	13 (25.0)	43 (34.7)	1.34	0.246
	C/T	21 (40.4)	61 (49.2)	1.142	0.85
	T/T	18 (34.6)	20 (16.1)	7.395	0.006
NOS3 (rs1799983)	G/G	22 (42.3)	72 (58.1)	3.65	0.058
	G/T	19 (36.5)	42 (34.7)	0.115	0.734
	T/T	11 (21.5)	10 (8.1)	5.97	0.014
EDNRA (C+70G, rs5335)	G/G	10 (19.2)	22 (17.7)	0.102	0.775
	C/G	28 (53.8)	71 (57.3)	0.173	0.677
	C/C	14 (26.9)	31 (25.0)	0.123	0.702
P53 (Arg72Pro exon 4, rs1042522)	Arg/Arg	30 (57.7)	38 (30.6)	11.05	0.008
	Arg/Pro	16 (30.7)	53 (42.7)	2.2	0.137
	Pro/Pro	6 (11.5)	33 (26.6)	4.8	0.028
CASP8 (rs3834129)	del/del	17 (32.7)	41 (33.1)	0.002	0.961
	ins/del	24 (46.1)	60 (48.4)	0.073	0.786
	ins/ins	11 (21.2)	23 (18.5)	0.159	0.689
CASP8 (rs1045485)	G/G	40 (76.9)	93 (75.0)	0.073	0.786
	G/C	10 (19.2)	28 (22.6)	0.242	0.622
	C/C	2 (3.9)	3 (2.4)	0.041	0.840
GPX1 (rs1050450)	C/C	32 (61.5)	65 (52.4)	5.48	0.019
	C/T	17 (32.7)	53 (42.7)	2.43	0.118
	T/T	3 (5.7)	6 (4.8)	2.58	0.107
SOD2 (rs4880)	C/C	10 (19.2)	41 (33.1)	3.406	0.064
	C/T	25 (48.1)	59 (44.6)	0.003	0.952
	T/T	17 (32.7)	24 (19.4)	3.641	0.056
TNF-α (rs1800629)	G/G	41 (78.8)	95 (76.6)	0.104	0.747
	G/A	9 (17.3)	25 (20.2)	0.114	0.661
	A/A	2 (3.8)	4 (3.2)	0.428	0.836
Interleukin-1β (rs1143634)	C/C	29 (55.8)	61 (49.2)	0.634	0.425
	C/T	18 (34.6)	48 (38.7)	0.262	0.608
	T/T	5 (9.6)	15 (12.1)	0.224	0.636
ACE (I/D, rs4343)	G/G	18 (34.6)	43 (34.7)	0.004	0.976
	G/A	25 (48.1)	59 (47.6)	0.012	0.786
	A/A	9 (17.3)	22 (16.1)	0.154	0.655
ADRB1 (Arg389Gly, rs1801253)	G/G	40 (76.9)	93 (75.0)	3.773	0.013
	G/C	10 (19.2)	28 (22.6)	0.242	0.622
	C/C	2 (1.9)	3 (2.4)	0.041	0.840
MMP-3 (5A/6A, rs3025058)	5A/5A	18 (34.6)	20 (16.1)	7.395	0.006
	5A/6A	21 (40.4)	61 (49.2)	1.142	0.285
	6A/6A	13 (25.0)	43 (34.7)	1.34	0.246

p=0.005) and the T/T genotype of the NOS3 gene (OR 4.49; 95% CI 1.94–7.23; p<0.0001) had the most significant roles with respect to the risk of developing AIC.

Discussion

There are many gene polymorphisms that can be involved in the pathogenesis of AIC by affecting the balance between the efficacy and toxicity of doxorubicin [1, 21]. However, the evidence from large fundamental studies involving large numbers of patients is clearly insufficient, thus, there is a need for research in this area [1]. From the perspective of personalized medicine, finding possible predictors for cardiotoxicity is crucial for patients who are at a high risk of developing AIC during the administration current anticancer drugs [22, 23]. The studies of pharmacogenetic interventions in patients with cancer showed that many biomarkers (primarily those that regulate oxidative stress, inflammation, autophagy, apoptosis, and metabolism) contribute most to the pathogenesis of cardiotoxicity [9–13, 15, 16, 18, 19]. We studied polymorphisms of the most promising genes of the main possible mechanisms of the development of AIC and showed that the genotypes Arg/Arg of the p53 gene (p=0.005) and T/T of the NOS3 gene (p<0.0001), and genotypes C/C of the GPX1 gene (p=0.001), 5A/5A of the MMP-3 gene (p = 0.008), T/T of the NADPH oxidase gene (p = 0.008), and G/G of

Table 4. Table 4. Likelihood of anthracycline-induced cardiotoxicity depending on the presence of genotypes and gene alleles

Gene	Genotype	Odds ratio	95% CI	p
NADPH oxidase (C242T, rs4673)	C/C	0.6508	0.3137–1.3499	0.248
	C/T	0.6996	0.3629–1.3487	0.286
	T/T	2.7529	1.3066–5.8005	0.008
NOS3 (rs1799983)	G/G	0.5296	0.2749–1.0203	0.057
	G/T	1.1241	0.5718–2.2099	0.734
	T/T	3.0585	1.2094–7.7348	0.018
P53 (Arg72Pro exon 4, rs1042522)	Arg/Arg	2.9720	1.9181–8.9283	0.001
	Arg/Pro	1.1109	0.9032–1.1981	0.812
	Pro/Pro	0.5101	0.1721–1.0187	0.031
GPX1 (rs1050450)	C/C	2.3459	2.0198–6.8163	0.001
	C/T	1.0128	0.8271–1.1921	0.818
	T/T	0.9981	0.8899–1.1029	0.901
ADRB1 (Arg389Gly, rs1801253)	G/G	3.2712	1.8063–8.1045	0.043
	G/C	0.9811	0.9182–1.1721	0.712
	C/C	1.0189	0.8711–1.6181	0.919
MMP-3 (5A/6A, rs3025058)	5A/5A	2.7529	1.3066–5.8005	0.008
	5A/6A	0.6996	0.3629–1.3487	0.286
	6A/6A	0.6508	0.3137–1.3499	0.248

the ADRB1 gene (p = 0.043) were potential predictors of AIC in female patients with BC and without concomitant CVDs.

The p53 gene regulates many cell functions, including the mitotic cycle, DNA repair, cell differentiation and apoptosis, with subsequent production of pro-apoptotic factors, such as Fas, FasL and c-Myc, responsible for myocardial cell death [13, 23]. McSweeney et al. (2019) [14] analyzed the contribution of 1290 genes to the mechanisms of AIC development. They showed that the external apoptosis pathway with the activation of the p53 gene was the most significant cluster of gene ontology. We also showed that the development of AIC is mainly associated with the presence of the Arg/Arg genotype of the p53 gene (OR 2.972; p=0.001), and the Pro/Pro genotype of the p53 gene was a protective factor (OR 0.510; p = 0.031).

There is a hypothesis that doxorubicin changes the redox balance via several pathways [2, 3, 14]. Several studies found that a high risk of developing AIC and other cardiovascular complications after the administration of doxorubicin or daunorubicin, in both adults and children with cancer, is caused the presence of the T/T genotype of endothelial NO-synthase [11, 23, 24, 25]. Our findings allowed us to conclude that using doxorubicin in female patients with BC without CVDs is associated with a 3 fold risk of developing AIC in the presence of the T/T genotype of the NOS3 gene. The most likely mechanism of the AIC development seems to be the induction of necrosis and apoptosis triggered by the generation of reactive oxygen species, mediated by the stimulation of induced and endothelial NO-synthases, and the activation of lipid peroxidation followed by the development of oxidative stress in the mitochondria.

The catalytic activity of nicotinamide adenine dinucleotide phosphate (NADPH) and mitochondrial NADPH oxidase also contribute to the development of oxidative stress in cardiomyocytes [9]. The NADPH oxidase gene regulates the production of reactive oxygen species and is associated with the development of CVDs. Cascales et al. (2013) [26] found that NADPH oxidase polymorphism rs4673 was associated with a cardioprotective effect against focal myocardial necrosis (OR 0.11; 95% CI 0.20–0.63) and rs1883112 polymorphism was associated with the development of myocardial fibrosis (OR 5.11; 95% CI 1.59–16.43), however, the study included patients with risk factors or CVDs after PCT. The information obtained is also fair for patients without CVDs: we demonstrated that the presence of the T/T genotype of NADPH oxidase gene rs4673 was associated with a high risk of developing AIC.

Glutathione peroxidase (GPX) is the most common form of the enzyme, the genetic variability of which can lead to the accumulation of highly toxic oxidation products [27]. It has been shown earlier that allele T of Pro198 ^Leu (C>T) polymorphism of the GPX1 gene was associated with the manifestation of coronary artery disease, metabolic syndrome, early myocardial infarction and

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cardiovascular death, and ischemic stroke. Our data show that the carrier status of the C/C genotype of the GPX1 gene is associated in female patients with the development of AIC even in the absence of CVDs (OR 2.345; p=0.001).

The activation of metalloproteinases was shown in the experimental model in male Wistar rats to be one of the key events in the initiation and progression of AIC [17]. Matrix metalloproteinases are known as proteolytic system enzymes, angiogenic factors that act, due to certain features of domain structures, on collagen and proteoglycan matrix and regulate remodeling of vascular tissue [28], which results in the inclusion of changes in the expression of cardiac genes with the subsequent clinical manifestation of AIC. The results of our study are compatible: the risk of developing AIC increased 2.7-fold (OR 2.752; p=0.008) in women without CVDs who carry the 5A/5A genotype of the MMP-3 gene.

The protein produced by the ADRB1 gene is a target for beta-blockers and, therefore, is evaluated in most studies as a response to treatment with this group of drugs. However, the role of this gene in stratifying the risk of developing CVDs is also being actively evaluated. For example, in a study including more than 600 women referred for coronary angiography and followed up for 6 years, 115 patients who were carriers of the G/G genotype of the rs1801253 polymorphism developed acute myocardial infarction due to non-obstructive coronary artery disease in the follow-up period (OR 3.63; 95% CI 1.17–11.28) [29]. It was also found that ADRB1 polymorphism was associated with a high risk of developing arterial hypertension [30]. Patients with HFrEF who are homozygous for ADRB1 Ser49 are significantly more likely to recover LVEF than Gly49 carriers [31]. We were first to show the role of ADRB1 (Arg389Gly, rs1801253) in the pathogenesis of AIC. Thus, the carriership of the G/G genotype of ADRB1 increased 3.3-fold the likelihood of developing this pathology (OR 3.271; p=0.043).

Conclusion

Thus, based on the analysis of candidate genes, convincing evidence was obtained that the likelihood of developing anthracycline-induced cardiotoxicity is genetically determined. It was found that the presence of the Arg/Arg genotype of the p53 gene and the T/T of the NOS3 gene in female patients with breast cancer and without cardiovascular diseases is most associated with a high risk of cardiotoxicity. Our findings demonstrate that genetic factors can provide a more accurate classification of patients with a high likelihood of developing anthracycline-induced cardiotoxicity. This will help to make decisions on monitoring patients and, by improving the strategies for the prevention of cardiotoxicity, will prevent cardiovascular complications in cancer patients.

This pilot study was limited by the number of included patients, specificity of the sample (the study included patients with predefined clinical and demographic demographics and the absence of cardiovascular disease) and relatively short period of follow-up.

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