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THE CONTRIBUTION OF GENETIC POLYMORPHISMS OF XENOBIOTIC-METABOLIZING ENZYMES IN THE RISK OF BREAST CANCER DEVELOPMENT IN WOMEN

Summary. *Breast cancer (BC) is multifactor disease, the occurrence of which is considered as a result of the number factors interaction, including genetic. Polymorphism of genes encoding for detoxification xenobiotics enzymes may be associated with increased risk of various diseases, including BC.* ***Aim:*** *to evaluate the contribution of polymorphic variants G1934A, G681A, C430T, A1075C and C3435T of CYP2D6, CYP2C19, CYP2C9 and MDR1 genes in the BC risk in women.* ***Object and methods:*** *the study enrolled 67 patients with histologically verified BC diagnosis of stages I and II, that had burdened by heredity. The control group was represented by women without cancer pathology with unburdened by heredity (n = 300). Genotyping of the C430T, A1075C, G681A, G1934A and C3435T polymorphic variants of CYP2C9, CYP2C19, CYP2D6, and MDR1 genes was performed by PCR-RFLP.* ***Results:*** *it was established that the 1934AA genotype by G1934A polymorphic variant of CYP2D6 gene contributes to the risk of BC developing, and in combination with other genotypes of xenobiotic-metabolizing enzymes genes this risk increases significantly. «Wild-type» (1934GG) genotype by polymorphic variant G1934A of CYP2D6 gene shows a pronounced protective effect in the risk of BC development in women.* ***Conclusion:*** *the study revealed that genotypes for investigational polymorphic variants of xenobiotics detoxification system genes in various combinations increased BC risk in women with aggravated heredity.*

Breast cancer (BC) is multifactor disease, which occurrence is considered to be the result of interaction between series of genetic and environmental factors, including geographical, social, industrial, etc. [1]. The basis of tumor process independently from localization of tumor is cells malignant transformation as a result of abnormality cellular cycle regulation and apoptosis depression [2]. Molecular pathogenesis of oncological diseases includes large amount of genetic and epigenetic events, which cause the oncogenes activation and inactivation of tumor suppression genes [3, 4].

At the same time, modifying impact on the functioning of oncosuppressors genes may have such factors, as xenobiotics detoxification enzymes genes, which are responsible for metabolism (activation and inactivation) of wide range endo- and exobiotics, including carcinogens [5, 6]. The main enzymes of I phase xenobiotics detoxification are enzymes of cytochrome P450 superfamily. It is expected that the cytochrome P450 gene polymorphism may affect the risk a number malignant neoplasms, including BC. To the system of detoxification is also referred ATP-dependent transporter — P-glycoprotein, which realizes energy-dependent transport of substances in cells.

CYP2D6 gene (according to the electronic systematization of genes — OMIM*124030) is localized on the chromosome 22q13.1. In *CYP2D6* gene (product— cytochrome P450 2D6) mostly in our region is detected allele variant *4 — single nucleotide replacement G1934A (rs3892097) on the boundary between intron 3 and exon 4, presence of which causes the incorrect splicing of mRNA, that results in a reading frame shift, premature completion of the translation and formation of the defective protein product devoid of enzymatic activity [7].

Cytochrome P450 2C19 gene — *CYP2C19* (OMIM*124020) is localized on the chromosome 10q24.1-q24.3. Allele variant *2 of *CYP2C19* gene (rs4244285), which in literature is marked also as *CYP2C19m1* and is typical only for Europeans, is formed by replacement of guanine (G) by adenine (A) in 681 position of 5th exon «wild type» (*CYP2C19*1* — G681) and creates aberrant splicing site [8]. Such single nucleotide replacement causes the displacement of mRNA reading frame, starting from 215 amino-acid residue, and untimely creates stop-codon on 20 amino-acid residues earlier that results in truncated, non-functional protein.

CYP2C9 gene (OMIM*601130) is localized on the chromosome 10q24 and encodes cytochrome P450 2C9 (CYP2C9 enzyme). Today are known two allele variants, which are significant for Caucasians population: *2 and *3. Allele *1 is «wild type» and encodes normal protein. Allele *2 contains replacement of C430T, that causes the replacement of arginine by cysteine in position 144 of amino-acid sequence (R144C, rs1799853). Allele *3 is determined by nucleotide replace-

ment A1075C, that causes replacement of isoleucine by leucine in position 359 of amino-acid sequence (I359L, rs1057910). Both variants are associated with significant decrease of enzyme activity [9].

Multidrug resistance 1 gene (*MDR1)*, which is localized on the chromosome 7 (7q21.1), encodes P-glycoprotein (P-gp) — ATP-dependent transporter. It has been proved that polymorphism C3435T (rs1045642) in 26th exon influences the P-gp expression. Action of P-gp is aimed on the regulation of substances entering speed (endo- and exogenous origin), including drugs, and their excretion from cells and, thus, it determines the bioavailability of many drugs, which are applied regularly at different pathologies. Alterations of P-gp function may cause the development of autointoxication that, in turn, may influence the development of different pathological states (including malignant neoplasms); drug resistance may be the result of its hyperactivation.

The interrelation between features of female sex hormones metabolism and risk of hormone-dependent breast tumors, endometrial and ovarian tumors for a long time has been considered to be proved [6]. Polymorphic variants of genes, which products participate in synthesis of androgens and estrogens (CYP450), can increase risk of neoplasms reproductive system development [13]. Coding proper enzymes (for example, aromatase), they can influence the generation of estrogens.

Earlier we have studied overall alleles and genotypes frequency according to the polymorphic variants of most significant of xenobiotics detoxification system genes [11]. Also we has been determined the connection of genotypes frequency by polymorphic variant G1934A of *CYP2D6* gene with increased risk of BC in women [12]. Since frequency of genotypes according to the polymorphic variants of xenobiotics detoxification system genes for Ukrainian population is quite high, it has been decided to carry out comprehensive analysis of involvement of these genes in the risk factors of BC in women.

The aim of this study was to evaluate contribution of polymorphic variants G1934A, G681A, C430T, A1075C and C3435T of *CYP2D6, CYP2C19, CYP2C9* and *MDR1* genes to the risk of BC in women.

PATIENTS AND METHODS

Protocol of study has been approved by the Ethics Committee of SI «Institute of Genetic and Regenerative Medicine of NAMS». All individuals enrolled in study group have signed informed consent for the participation in study. The main group included 67 patients aged from 18 to 80 (mean age — 44.8 ± 13.6) with histologically verified diagnosis of BC of I and II stage burdened by heredity (patients who have 2 or more BC cases among the relatives of I–II degree of kin) and have been receiving treatment in Kyiv City Clinical Oncological Centre. Control group was represented by 300 women without oncological pathology with unburdened heredity (mean age 46.1 ± 16.6). The inquiry of all, who participated in study, with entering the information in the developed by us card and further analysis of pedigree, has been carried out.

As material for molecular-genetic studies has been taken peripheral blood, which was kept in closed systems for venous blood sampling with potassium salt of ethylene ethylenediaminetetraacetic acid (EDTA) as anticoagulant. Genomic DNA was extracted with use of commercial kit «DNA-sorb-B»(Central Research Institute of Epidemiology of Ministry of Health of RF). Genotyping by polymorphic variants C430T, A1075C, G681A, G1934A and C3435T of *CYP2C9, CYP2C19, CYP2D6* and *MDR1* genes has been carried out by method of polymerase chain reaction. A product of DNA amplification fragments of *CYP2C19, CYP2D6* and *MDR1* genes subject to hydrolytic cleavage by SmaI, BstNI (MvaI) and MboI («Fermentas», Lithuania) endonucleases of restriction, correspondently. Detection of allele-specific amplification and restriction fragment length polymorphism products has been carried out by method of horizontal electrophoresis in 2% (2.5% for *CYP2C9*) agarose gel, which contained ethidium bromide. Visualization of results has been carried out in ultraviolet light with the help of automatic Vi-Tran system in transilluminator «Biocom» (RF). Lengths of amplification and restriction fragments have been analyzed by comparison with marker DNA.

Statistical processing of obtained results has been carried out with use of application program package Statistica 10.0 («StatSoft Inc.», USA) and MS Excel. For comparison of genotype frequency distribution and their compounds in study groups has been used Pearson's chi-squared test (χ^2). When the volume of sampling did not exceed 10 cases, has been used Yates' correction for continuity. Odds ratio (OR) with 95% confidence interval (CI) has been used for evaluation of relative risk of disease development for each genotype and their combinations. Analysis of gene-gene interactions has been carried out with the help of Multifactor Dimensionality Reduction (MDR) bioinformatic method proposed by M.D. Ritchie and co-authors [13] with the aim of modeling genome interactions of high order, which are impossible to evaluate with the help of parametric methods that are traditionally used in genetic epidemiology. In all types of analysis, values $p < 0.05$ were considered significant.

RESULTS AND DISCUSSION

During our research the genotyping by studied polymorphic variants of *CYP2D6, CYP2C19, CYP2C9* and *MDR1* genes in the main and control group of women has been carried out. Obtained genotypes frequency for BC patients and women of control group has been compared with use of statistical methods. Results of analysis has showed that frequency of genotype 1934AA by polymorphic variant G1934A of *CYP2D6* gene is significantly higher in group of BC patients compared with control group (Table 1) that significantly increases of BC risk and does not contradict data obtained by us earlier [11].

At the same time, genotype 1934GG of gene *CYP2D6* decreases this risk almost two times, i.e. has protective effect. Also it has been determined that genotype 681GG of gene *CYP2C19* significantly more often is found in women with BC compared with control group. For the rest of polymorphic variants of studied genes has not been detected statistically significant difference in distribution of genotypes frequency in compared groups ($p > 0.05$).

Associations, detected by us allowed to explain the genetic component of BC development in women, and since significant distinctions have been determined not for all studied genes, we have decided to analyze combinations of genotypes by studied polymorphic variants. At first we analyzed paired genotypes combinations of *CYP2D6* gene with polymorphic variants of *CYP2C9, CYP2C19* and *MDR1* genes in compared groups. Totally in analysis have been included 36 possible paired combinations. The detected significant distinctions between compared groups are represented in Table 2.

As show the results of comparison of paired genotypes combinations of *CYP2D6* gene with other studied genes, risk of BC compared with control has 8 times increased at such genotypes combination as *CYP2D6* (1934AA)/*CYP2C19* (681GG), while the risk of BC was 5 times decrease (protective effect) for 1934GG genotype of *CYP2D6* gene in combination with heterozygous genotype by polymorphic variant G681A of *CYP2C19* gene.

Analyzing genotypes frequency of paired compounds, we made certain that generated combination 1934AA(*CYP2D6*)/430CC (*CYP2C9*) does not change risk of BC if to be compared with data in Table 1 for genotype 1934AA of *CYP2D6* gene (OR = 7.28 in both cases). Also modifying influence of 1075AA genotype of *CYP2C9* gene on the risk of BC development at interaction with 1934GG and 1934AA genotypes of *CYP2D6* gene was noticed, that caused the decrease (OR = 0.46) and increase (OR = 7.98) of risk correspondently. The significant increase of 1934AA/3435CT combination genotypes frequency in group of women with BC in contrast to the control has been determined. OR index for this compound has constituted 18.98, but had wide limits 95% CI that can be explained by small volume of sampling.

Next we have analyzed combinations of 3 genotypes by studied polymorphic variants of *CYP2C9, CYP2C19* and *MDR1* genes with polymorphic variant G1934A of *CYP2D6* gene. Totally have been studied 243 combinations of genotypes, significant differences in frequency of their distribution in compared groups have been determined for combinations of genotypes represented in Table 3.

Analyzing data of Tables 1–3, we have determined that protective effect of genotypes combination 1934GG (*CYP2D6*)/681GA (*CYP2C19*) insignificantly increases at annexation by 1075AA genotype of *CYP2C9* gene (OR = 0.18) and decreases in combination with 430CC genotype of *CYP2C9* gene (OR = 0.28). Also it has been noticed that 1934AA variant of *CYP2D6* gene in combination with other genotypes of studied genes influences the significant increase of BC risk in women.

Analysis of genotypes combination with polymorphic variant G1934A of *CYP2D6* gene with other studied genes (4 genotypes) have been studied 324 combinations. Obtained significant differences in compared groups are represented in Table 4. For combinations of 4 genotypes is also confirmed protective effect for 1934GG genotype of *CYP2D6* gene, but only in one combination (*2D6*(1934GG)/*2C19*(681GA)/*2C9*2*(430CC)/*2C9*3*(1075AA)), that is associated with almost 5 times decrease risk of BC development.

Frequency of genotype combinations 1934AA of *CYP2D6* gene with genotypes by polymorphic variants of *CYP2C9* and *CYP2C19* genes prevailed among BC patients that 9.5 times increased risk of BC development. Combinations, which included heterozygous genotype with polymorphic variant C3435T of gene *MDR1,* also caused the risk increase, but these data were not taken

Table 1

Significant differences in distribution of genotypes frequency by studied polymorphic variants in compared groups

Genotype (gene)	BC		Control		Results of statistical analysis			
	n	%	n	%	χ^2	OR	95% CI	p
1934GG (*CYP2D6*)	33	49.25	196	65.33	**6.04**	**0.52**	**0.3–0.88**	**0.01**
1934AA (*CYP2D6*)	6	8.96	4	1.33	**9.3**	**7.28**	**1.99–26.57**	**0.002**
681GG (*CYP2C19*)	56	83.58	215	71.67	**4.17**	**2.01**	**1.01–4.03**	**0.04**

Table 2

Significant differences in distribution of paired genotypes combinations frequency of *CYP2D6* gene with other studied polymorphic variants in compared groups

Genotypes combination	BC		Control		Results of statistical analysis			
	n	%	n	%	χ^2	OR	95% CI	p
CYP2D6/CYP2C19								
1934GG/681GA	3	4.48	47	15.67	**7.59**	**0.2**	**0.06–0.65**	**0.001**
1934AA/681GG	5	7.46	3	1.00	**7.91**	**7.98**	**1.86–34.28**	**0.006**
CYP2D6/CYP2C9*2								
1934AA/430CC	6	8.96	4	1.33	**9.3**	**7.28**	**1.99–26.57**	**0.003**
CYP2D6/CYP2C9*3								
1934GG/1075AA	25	37.31	169	56.33	**7.95**	**0.46**	**0.27–0.8**	**0.006**
1934AA/1075AA	5	7.46	3	1.00	**7.91**	**7.98**	**1.86–34.28**	**0.006**
CYP2D6/MDR1								
1934AA/3435CT	4	5.97	1	0.33	**9.09**	**18.98**	**2.09–172.72**	**0.004**

Table 3

Significant differences in distribution of three genotypes combination frequency by polymorphic variants of *CYP2D6*, *CYP2C9*, *CYP2C19* and *MDR1* genes in compared groups

Genotypes combination	BC		Control		Results of statistical analysis			
	n	%	n	%	χ2	p	OR	95% CI
2D6 (1934AA) / *2C19* (681GG) / *MDR1* (3435CT)	3	4.48	1	0.33	**5.3**	**0.02**	**14.02**	**1.43–136.92**
2D6 (1934AA) / *2C19* (681GG) / *2C9* (1075AA)	4	5.97	2	0.67	**6.57**	**0.01**	**9.46**	**1.7–52.78**
2D6 (1934GG) / *2C19* (681GA) / *2C9* (1075AA)	2	2.99	43	14.33	**5.54**	**0.007**	**0.18**	**0.04–0.78**
2D6 (1934AA) / *MDR1* (3435CT) / *2C9* (430CC)	4	5.97	1	0.33	**9.09**	**0.004**	**18.98**	**2.09–172.72**
2D6 (1934GG) / *2C9* (430CC) / *2C9* (1075AA)	21	31.34	141	47.00	**5.44**	**0.002**	**0.51**	**0.29–0.9**
2D6 (1934AA) / *2C9* (430CC) / *2C9* (1075AA)	5	7.46	1	0.33	**13.16**	**0.0009**	**24.11**	**2.77–210.00**
2D6 (1934GA) / *2C19* (681GG) / *2C9* (430CC)	20	29.85	53	17.67	**5.1**	**0.03**	**1.98**	**1.09–3.62**
2D6 (1934AA) / *2C19* (681GG) / *2C9* (430CC)	5	7.46	3	1.00	**7.91**	**0.006**	**7.98**	**1.86–34.28**
2D6 (1934GG) / *2C19* (681GA) / *2C9* (430CC)	3	4.48	43	14.33	**4**	**0.02**	**0.28**	**0.08–0.93**
2D6 (1934AA) / *MDR1* (3435CT) / *2C9* (1075AA)	4	5.97	1	0.33	**9.09**	**0.004**	**18.98**	**2.09–172.72**

Table 4

Significant differences in 4 genotypes combinations frequency of *CYP2D6* gene with studied genes in compared groups

Genotypes combination	BC		Control		Results of statistical analysis			
	n	%	n	%	χ2	p	OR	CI
2D6 (1934GG) / *2C19* (681GA) / *2C9*2* (430CC) / *2C9*3* (1075AA)	2	2.99	39	13.00	**4.57**	**0.01**	**0.21**	**0.05–0.87**
2D6 (1934GA) / *2C19* (681AA) / *2C9*2* (430CC) / *2C9*3* (1075AA)	17	25.37	42	14.00	**5.45**	**0.02**	**2.09**	**1.1–3.96**
2D6 (1934AA) / *2C19* (681AA) / *2C9*2* (430CC) / *2C9*3* (1075AA)	4	5.97	2	0.67	**6.57**	**0.01**	**9.46**	**1.7–52.78**
2D6 (1934AA) / *2C19* (681AA) / *2C9*2* (430CC) / *MDR1* (3435CT)	3	4.48	1	0.33	**5.3**	**0.02**	**14.02**	**1.43–136.92**
2D6 (1934AA) / *2C19* (681AA) / *2C9*3* (1075AA) / *MDR1* (3435CT)	3	4.48	1	0.33	**5.3**	**0.02**	**14.02**	**1.43–136.92**
2D6 (1934AA) / *2C9*2* (430CC) / *2C9*3* (1075AA) / *MDR1* (3435CT)	4	5.97	1	0.33	**9.09**	**0.004**	**18.98**	**2.09–172.72**

into consideration, since they have to be verified on the larger groups of study.

At analysis of genotypes combinations, which contained 1934AA genotype of *CYP2D6* gene, has been confirmed their involvement in increase risk of BC development, but has been determined significant decrease of level of significance.

Analyzing genotypes combination of all studied polymorphic variants (243 combinations in 5th genotypes), we have determined significant increase risk of

BC development only for one genotypes combination — 1934AA (*2D6*) / 3435CT (*MDR1*) / 681GG (*2C19*) / 430CC (*2C9*) / 1075AA (*2C9*) (χ^2 = 5.3, p = 0.02, OR = 14.02 (95% CI 1.43–136.92). These results are the evidence that the main role in formation risk of BC development in women belongs to exactly 1934AA genotype of *CYP2D6* gene.

Next stage of study was carrying out modeling of interaction between studied genes in compared groups. For this purpose has been used MDR method, which allowed to conduct simultaneous analysis of many genes polymorphic variants, choosing such combinations, which have pathogenetic significance in development of disease.

For evaluation of interaction between genes polymorphic variants by MDR method has been used algorithm of exhaustive search, which evaluates all possible combinations of studied DNA-markers concerning the risk of BC development.

Testing balancing accuracy was highest (58.04%) for model, which included one gene — *CYP2D6* that confirms significance involvement of this gene in formation risk of BC development in women with burdened heredity, which was obtained with use of other statistical analysis methods. One more model of gene-gene interaction at BC development in women compared with control group has demonstrated 100% cross-validation consistency. It was five-locus model of gene-gene interaction *CYP2D6* (G1934A) / *MDR1* (C3435T) / *CYP2C9* (C430T) / *CYP2C9* (A1075C) / *CYP2C19* (G681A), which is characterized by accuracy of prediction 54.35%, but did not stand the permutation test and that is why it's not statistically significant.

With the help of MDR program for study groups has been built dendrogram, which reflects the pattern of gene-gene interaction of BC development in women (Figure).

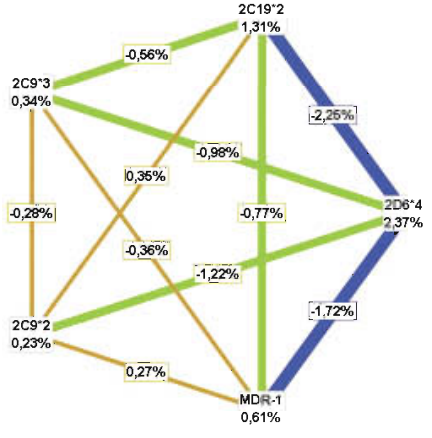

Figure. Dendrogram of gene-gene interactions at BC (blue and green colors are used for indication of antagonism between loci, brown — independence of particular loci effects)

Analyzing graphic presentation, we have determined that the most part of entropy at BC development in women was connect with polymorphic variant G1934A of *CYP2D6* gene and constitutes 2.37%, that finally confirms the role of exactly *CYP2D6* gene among other xenobiotics detoxification system genes in formation risk of BC development in women.

Thus, basing on the results of our study, we may state that *CYP2D6* and *CYP2C19* genes are involved in formation of BC development risk in women. Significance of these genes may be caused by participation of their products in metabolic transformation in woman's organism of both endogenous estradiol and wide spectrum of xenobiotics, including carcinogens [10].

CONCLUSION

1. 1934AA genotype by polymorphic variant G1934A of *CYP2D6* gene makes significant contribution to formation of BC risk, and this risk significantly increases in case of combination of this genotype with genotypes of other genes, which code enzymes of xenobiotics detoxification.

2. «Wild type» genotype (1934GG) by polymorphic variant G1934A of *CYP2D6* gene demonstrates apparent protective effect concerning of BC risk in women.

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ВНЕСОК ГЕНІВ СИСТЕМИ ДЕТОКСИКАЦІЇ КСЕНОБІОТИКІВ У ФОРМУВАННЯ РИЗИКУ РОЗВИТКУ РАКУ МОЛОЧНОЇ ЗАЛОЗИ У ЖІНОК

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Резюме. *Рак молочної залози (РМЗ) — це мультифакторне захворювання, виникнення якого розглядають як результат взаємодії низки чинників, у тому числі й генетичних. Поліморфізм генів, які кодують ферменти системи детоксикації ксенобіотиків, пов'язують із підвищеним ризиком розвитку ряду захворювань, зокрема РМЗ.* ***Мета:*** *оцінити внесок поліморфних варіантів (G1934A, G681A, C430T, A1075C та C3435T) генів CYP2D6, CYP2C19, CYP2C9 та MDR1 у формування ризику розвитку РМЗ у жінок.* ***Об'єкт і методи:*** *у дослідження включено 67 пацієнток із гістологічно підтвердженим діагнозом РМЗ I і II стадії, що мали обтяжену спадковість. Контрольна група була представлена жінками без онкологічної патології з необтяженою спадковістю (n = 300). Генотипування за поліморфними варіантами C430T, A1075C, G681A, G1934A і C3435T генів CYP2C9, CYP2C19, CYP2D6 та MDR1 проводили методом полімеразної ланцюгової реакції/поліморфізму довжин рестрикційних фрагментів.* ***Результати:*** *виявлено, що генотип 1934AA за поліморфним варіантом G1934A гена CYP2D6 зумовлює вагомий внесок у формування ризику розвитку РМЗ, а в сполученні з генотипами інших генів, які кодують ферменти детоксикації ксенобіотиків, цей ризик достовірно підвищується. «Дикий тип» (1934GG) за поліморфним варіантом G1934A гена CYP2D6 проявляє виражений протективний ефект стосовно ризику виникнення РМЗ у жінок.* ***Висновок:*** *у результаті дослідження показано, що генотипи за досліджуваними поліморфними варіантами генів системи детоксикації ксенобіотиків у різних комбінаціях впливають на підвищення ризику розвитку РМЗ у жінок з обтяженою спадковістю.*

Ключові слова: рак молочної залози, поліморфізм генів, ксенобіотики.

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