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Association of genetic polymorphism with the mutation status of the *BRCA*1/2 genes in spontaneous breast cancer

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Aim. To study ssociation of the *FGFR2* and *TOX3/LOC643714* genetic polymorphisms with the *BRCA1/2* mutation status in Ukrainian female breast cancer patients without ionizing radiation impact in their histories. **Methods.** Molecular genetics methods were used. Non-parametric data were evaluated using the two-way Fisher's Exact test. Statistical analysis was performed using the StatPlus Pro program package. **Results.** Association of genetic polymorphisms rs2981582 of the *FGFR2* gene and rs3803662 of the *TOX3/LOC643714* gene with the mutation status of the *BRCA1/2* genes in breast cancer patients non-treated with ionizing radiation in their histories was shown. The association between the minor genotype of the *TOX3/LOC643714* gene and the positive status of the *BRCA1* gene was found to be reliable. No statistic association was found between homozygotes for the major alleles and heterozygote polymorphisms of the *FGFR2, TOX3 / LOC643714* genes, with or without BRCA1/2 mutations ($p < 0.05$).

Keywords: breast cancer, genetic polymorphisms, *BRCA1/2* mutations.

Breast cancer is the most commonly occurring cancer among women world wide [1]. In Ukraine it accounts for over 20 % of all malignant tumors and is the second most frequent cause of cancer-related death [2].

Despite the fact that most cases of breast cancer are sporadic, 25 % of them are associated with hereditary inheritance factors of high penetrance genes for the development of breast cancer, and family history remains the best indicator of their individual risk [3]. Among the known predisposition genes, the *BRCA1* and *BRCA2* mutations have the strongest influence on the susceptibility of the disease and the risk of developing breast cancer to 85 % of the mutation carriers [4, 5].

Though the effect of high penetrance gene mutations is noticeable, they account for only about 25 % of family risk and less than 5 % of the overall incidence of breast cancer, since their frequency in the general population is very low [6]. As a result of the combination of several common low penetrance genes, each of which increases the risk of breast cancer, the odds ratio (OR) is 1.2–1.5 [7.8]. According to the polygonal model of inheritance, a large number of low penetrance genes may have a communicative effect on the risk [9] and the disease manifestation [10, 11].

Single nucleotide polymorphism (SNPs) associated with the risk of various types of cancer has been identified through Genome-wide association study (GWAS). More than 22 studies have been conducted to study breast cancer in different populations, where more than 36 loci have been associated with the hereditary predisposition to this disease [12].

Antoniou A. *et al.* suggested that the hereditary predisposition to breast cancer in the carriers of mutations in the *BRCA1* and *BRCA2* genes may be explained in a polygenic model with a large number of low penetrance alleles, each of which slightly increases the risk, but their cumulative effect becomes quite pronounced [13]. The hypothesis "common disease – common variant" was formulated, according to which the hereditary predisposition to common diseases (including oncology) is caused by many genetic variants, often found in the population [14].

GWAS has identified the genetic susceptibility loci associated with breast cancer risk [15–17]. Today low penetrance SNPs [18] with a weak association with the breast cancer risk compared to high penetrance mutations such as *BRCA1* or *BRCA2* is identified [19]. Though each option with low penetrance gives only a small increase in breast cancer, a combination of individual choices can act cumulatively leading to an increased risk (some of which are listed in Table 1). Such combinations may be useful tools for the identification of women with relative risk and prevention in the population. Relations likely are situated in the range of 1.1–1.3 and 1.2–1.6 for hetero- and homozygous genotypes respectively [8, 23, 24]. The important fact is that although mutations in the genes *BRCA1*, *BRCA2* cause an increased risk of breast cancer, Baynes S. demonstrated that there is no association between genetic polymorphisms and mutations in the genes *BRCA1*, *BRCA2* (separately and in combination) with the risk of breast cancer [17, 25].

The aim of the work was to establish the association of genetic polymorphisms of the *FGFR2*, *TOX3 / LOC*643714 genes carriership with mutation status of the *BRCA*1/2 genes in Ukrainian women with breast cancer who do not have an ionizing radiation history.

Methods

Patients. The main group of patients was formed from 62 women aged 35-60 and diagnosed to have breast cancer, which was confirmed histologically. To determine the specifics of the clinical course of the disease, the history of the disease and medical records of the patients were studied; the computer database was created. The study included women without ionizing radiation and anamnesis. The studied cohort of women was divided according to their mutated status into *BRCA*1/2positive and negative ones. For molecular genetic stu-

Table 1. **SNPs – low penentrance markers of genetic predisposition to breast cancer with *BRCA1* and *BRCA2* gene mutations carriers**

Polymorphism	Locus	Gene	Protein function	OR for minor allele	Association in different groups of patients	Risk modification in the *BRCA1* and *BRCA2* gene mutations carriers [20, 21]	
						BRCA1	*BRCA2*
rs2981582	10q26	*FGFR2*	recipe for growth of fibroblasts	1,26 [8, 17]	Breast cancer in postmenopause [17], stronger associations with ER-positive and PR-positive breast tumors [22]	no	yes
rs3803662	16q12.1	*TOX3*	DNA-dependent regulation of the transcription	1,28[23] 1,20[8]	Stronger associations with ER-positive breast tumors [23]	yes	yes

dies, the samples of peripheral blood were used.

DNA isolation. DNA isolation was carried out with the standard method using the NeoPrep^{100} DNA Magnet kit (NeoGene, Ukraine). Also, the genomic DNA was extracted from formalin-fixed and paraffin-embedded tissues using a Quiamp DNA Mini Kit DNA kit (Quiagen, Hilden, Germany).

Allelic-specific PCR. The genotyping of the polymorphic markers rs2981582 of the gene *FGFR2* and rs3803662 of the *TOX3 / LOC*643714 gene was performed by allelic-specific PCR with real-time detection on the LightCycler II amplifier (Roche, Switzerland) using specific primers and probes. The probes have a fluorescence modification and a gummy dye (quencher) that suppresses fluorescence until the DNA polymerase, due to its exonuclear activity, releases fluorochrome in the process of elongating the PCR product. Each step was accompanied by the registration of the fluorescence signal in the bands corresponding to fluorores fluorescence intervals. Primers for the determination of the studied polymorphisms of the *FGFR2, TOX3 / LOC*643714 genes synthesized by the TIB MOLBIOL company (Germany) are presented in Table 2.

The reaction mixture consisted of probes manufactured by Roche Diagnostics (Germany). Amplification was performed under the following conditions: initial denaturation for 10 min at 95 °C; 45 amplification cycles that exponentially increase the number of ampli-

Table 2. **Primers to define the genes *FGFR2*, *TOX3/LOC643714* polymorphisms being studied**

Polymorphism	Primer	Sequence (5' ® 3')
rs2981582 of the *FGFR2* gene	Upstream	CATCGCCACTTAATGAACCTGTTTG
	Downstream	GGAGAGTCCACCTGGTGCCTGCCTG
rs3803662 of the *TOX3/LOC643714* gene	Upstream	CTCTCCTTAATGCCTCTATAGCTGTC
	Downstream	CTTAGCGAAGAATAAAACTGTGGAC

cons for molecular analysis and include denaturation at 95 °C – 10 sec, reoccurring at 60 °C – 10 sec, synthesis at 72 °C 15 sec; melting at 95 °C – 20 sec, 40 °C – 40 sec; cooling at 40 °C – 30 sec.

At the end of the amplification reaction, the accounting and analysis of the results were made in accordance with the manufacturer's recommendations.

The search for mutations was done using the PCR method and the analysis of the melting point Tm of the amplicons obtained. The PCR reaction was performed using TIB MOLBIOL (Germany) reagents. The displacement of Tm indicated changes in the nucleic acid sequence of the amplicon. The Tm analysis was performed using Light Cycler Software (build 4.1.1.21.) (Roche, Switzerland).

Statistic. The obtained results were processed using variation statistic methods, adopted for biological research and recommended for the processing of the results of molecular genetic studies using the StatPlus Pro package.

Results

Antoniou A. C. and Easton D. F. made the hypothesis that the risk of developing breast cancer in the carriers of mutations in the *BRCA1 and BRCA2* genes is modified by genetic factors [7]. The multicentre studies conducted by Antoniou A.C. *et al.* who included in total more than 25,000 mutation carriers in the *BRCA1* and *BRCA2* [20, 21] genes showed a modifying role of the common low penetrance genetic variants associated with the risk of development in the general population (Table 1) .

It is important that the relative risk for these genetic variants in the group of patients with mutations in the *BRCA1* and *BRCA2* genes coincides with the risk for the population as a whole, although it is a significant factor that modifies the risk of developing breast cancer. Thus, the data obtained most fit to a simple multiplicative interaction model, in which the effect of each variant is independent; the accurate assessment of the risk is made taking into account the contribution of high-penetrance mutations [26]. Patients with mutations in the *BRCA2* in postmenopause [17], stronger associations with ER-positive and PR-positive breast tumors [22].

As a result of molecular-genetic analysis of DNA in women with breast cancer without radiation history, the association of carriership of genetic polymorphisms rs2981582 of the *FGFR2* gene, rs3803662 of the *TOX3/ LOC643714* gene with mutation status of the genes *BRCA1/2* was established.

Among the patients without breast cancer who had molecular genetic determination of genotypes of rs2981582 polymorphism of [the] *FGFR2* gene, 5 of 62 subjects had positive status of the *BRCA1* gene. The *BRCA2* mutations were not found in the studied cohort.

In the cohort of patients without a radiation history, which managed to successfully amplify the rs3803662 polymorphism of the *TOX3 / LOC643714* gene, four *BRCA1*-positive mutations were identified among 41 patients. Instead, the *BRCA2* mutation was not found in the studied group.

Having applied Fisher's ratio test we managed to calculate the association among the *BRCA1 / 2* gene status indicators, depending on the variants of the genetic polymorphisms rs2981582 of the *FGFR2* gene, rs3803662 of the *TOX3 / LOC643714* gene.

Table 3. **Distribution of genetic polymorphisms genotypes of rs2981582 of the *FGFR2* gene, rs3803662 of the *TOX3 / LOC643714* gene depending on the status of *BRCA1/2* genes in women with breast cancer without ionizing radiation history**

Breast cancer patients without IR in history	SNPs:	rs2981582			rs3803662		
	Gene:	*FGFR2*			*TOX3/ LOC643714*		
	Number of Patients	n=62			n=41		
	SNP genotypes:	CC	CT	TT	CC	CT	TT
BRCA-positive		3	0	2	0	1	3
BRCA-negative		25	23	9	26	5	6

We obtained the following results: Fisher's ratio test with the association of genetic polymorphism rs2981582 of the *FGFR2* gene and rs3803662 of the *TOX3 / LOC643714* gene with positive status of the *BRCA1* gene was 0.212, $p < 0.05$ and 0.028, $p > 0.05$, respectively.

No association of the rs2981582 genotypes of the *FGFR2* gene with positive or negative status of the *BRCA1/2* genes was found in the cohort of patients with breast cancer without ionizing radiation impact in their history.

Instead, we revealed an association with the *BRCA1*-positive status of the minor allele in the *TT* polymorphism rs3803662 of the *TOX3 / LOC643714* gene among patients with breast cancer without ionizing radiation in their history (Fisher's ratio test – 0.028, $p > 0.05$).

The results of the correlation of the genetic polymorphisms rs2981582 of the *FGFR2* gene and rs3803662 of the gene *TOX3 / LOC643714* among patients with breast cancer without ionizing radiation in their history are presented in Table 4.

No statistic association was found among homozygotes for major alleles and heterozygote polymorphisms of the *FGFR2, TOX3 / LOC643714* genes, with or without *BRCA1 / 2* mutations ($p < 0.05$).

Thus, by comparing and analyzing the data of the molecular study, regarding the genetic polymorphism rs2981582 of the FGFR2 gene, with a positive and negative *BRCA*-status, no significant difference has been found between the indices.

According to the literature, the genetic polymorphism rs2981582 of the *FGFR2* gene was significantly associated with the *BRCA2* mutation ($p = 2 \times 10\text{-}8$) [27]. Latif *et al.* have also found that in the breast cancer patients who were *TT* genotype carriers the *FGFR2* gene was associated with the positive status of the *BRCA2* mutation.

In the mutation carriers, *BRCA1* and *BRCA2* were associated with the genetic polymorphism rs3803662 of the *TOX3* / *LOC643714* gene and an increased risk of breast cancer ($p = 0.004$ and 0.009 respectively) [28].

According to the Antoniou A. C. et al., research for the rs2981582 polymorphisms of the

Table 4. **Frequency of genetic polymorphisms rs2981582 of the *FGFR2* gene, rs3803662 of the *TOX3/ LOC643714* gene in women with breast cancer without ionizing radiation history with different mutation status of the *BRCA1/2* genes**

Gene	SNP	V allele	Fisher's ratio test	p
FGFR2	rs2981582	T	0,212	p < 0,05
TOX3/LOC643714	rs3803662	T	0,028	p > 0,05

FGFR2 gene, an increased risk of breast cancer for *BRCA2* mutation carriers was found [21]. In the study conducted in the Chilean population of women with a family history of breast cancer, a correlation was found between the minor allele rs3803662 of the *TOX3/LOC643714* gene with the risk of developing breast cancer (OR = 1.57 95 % CI 1.25–1.95) [29].

However, in our study, we did not have patients with such mutations. According to the same authors, the close connection between the T/T genotype and the rs3803662 polymorphism of the *TOX3/LOC643714* gene with a positive mutation status of the *BRCA1* gene was proved, which was reflected in our study for spontaneous breast cancer ($p = 0.03$). The latter fact can be a consequence of the inherited gene linkage.

Conclusions

The association of the *TT* rs3803662 genotype of the *TOX3/LOC643714* gene with positive mutation status of the *BRCA1* gene ($p = 0.03$) was observed in women with breast cancer without ionizing radiation in their history.

No association was found between homozygotes for major alleles and heterozygote polymorphism of the *TOX3 / LOC643714* gene, and the presence or absence of the *BRCA2* mutations ($p < 0.05$).

No statistic association was found among homozygotes for major alleles and heterozygotes of the *FGFR2* polymorphism, with or without mutations in the *BRCA1* and *BRCA2* genes ($p < 0.05$).

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Визначення асоціації носійства генетичних поліморфізмів з мутаційним статусом генів *brca1/2* при спонтанному раку молочноїзалози

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Мета. Визначення асоціації носійства генетичних поліморфізмів генів *FGFR2, TOX3/LOC643714* з мутаційним статусом генів *BRCA1/2* у жінок України хворих на рак молочної залози, які не мають впливу іонізуючого випромінювання в анамнезі. **Методи.** Молекулярно-генетичні методи дослідження. Непараметричні дані оцінювали з використанням точного тесту Фішера в двобічному варіанті. Статистичний аналіз проводили з використанням пакету програми StatPlus Pro. **Результати.** Показано,що існують асоціації носійства генетичних поліморфізмів rs2981582 гена *FGFR2*, rs3803662 гена *TOX3/LOC643714* з мутаційним статусом генів *BRCA1/2* жінок хворих на РМЗ без іонізуючого випромінювання в анамнезі. **Висновки.** Серед досліджених генетичних поліморфізмів достовірним виявили асоціацію між мінорним генотипом *TT*гена *TOX3/LOC643714* та позитивним статусом гена *BRCA1.* Не знайдено статистичної асоціації серед гомозигот за мажорними алелями та гетерозигот поліморфізмів генів *FGFR2, TOX3/ LOC643714,* з наявністю або відсутністю мутацій *BRCA1/2 (*$p < 0,05$).

Ключові слова: рак молочної залози, генетичні поліморфізми, мутації *BRCA1/2.*

Определение ассоциации носительства генетических полиморфизмов с мутационным статусом генов brca1/2 при спонтанном раке молочной железы

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Цель. Проанализировать ассоциацию носительства генетических полиморфизмов генов *FGFR2, TOX3 / LOC643714* с мутационным статусом генов *BRCA1 / 2* у женщин Украины, больных раком молочной железы, не имеющих влияния ионизирующего излучения в анамнезе. **Методы.** Молекулярно-генетические методы исследования. Непараметрические данные оценивались с использованием точного теста Фишера в двустороннем варианте. Статистический анализ был проведен с использованием пакета программы StatPlus Pro. **Результаты.** Определена ассоциация носительства генетических полиморфизмов rs2981582 гена *FGFR2*, rs3803662 гена *TOX3 / LOC643714* с мутационным статусом генов *BRCA1 / 2* женщин, больных РМЖ, без ионизирующего излучения в анамнезе. **Выводы.** Среди исследованных генетических полиморфизмов была обнаружена ассоциация между минорным генотипом *TT*гена *TOX3 / LOC643714* и положительным статусом гена *BRCA1.* Не найдено статистической ассоциации среди гомозигот по мажорным аллелям и гетерозигот полиморфизмов генов *FGFR2, TOX3 / LOC643714*, с наличием или отсутствием мутаций *BRCA1/2* ($p < 0,05$).

Ключевые слова: рак молочной железы, генетические полиморфизмы, мутации *BRCA1/2.*

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