CHARACTERISTICS OF *BRCA*-ASSOCIATED BREAST CANCER IN THE POPULATION OF THE RUSSIAN FEDERATION

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"Standard" diagnostic panels allow identification of only a few of *BRCA1* and *BRCA2* gene mutations most common in a population. Therefore, tests relying on such panels may return false negative results, since the coding regions of these genes may have other defects. For breast cancer (BC) patients, false negative test results may translate into selection of inadequate therapy by their doctors. This study aimed to identify the features of *BRCA*-associated breast cancer in the population of the Russian Federation. The study included breast cancer patients (n = 4440). At the first stage, all patients were screened for the eight most common *BRCA1* and *BRCA2* genes mutations with the help of real-time PCR. Next, patients that exhibited clinical signs of a hereditary disease (CSHD) in the absence of common mutations (n = 290) had the entire coding regions of *BRCA1* and *BRCA2* genes studied with next generation sequencing (NGS). "Standard" mutations in the *BRCA1* and *BRCA2* genes were identified in 169 (3.8%) cases. In the CSHD group, such mutations were revealed in 15.4% of cases. NGS uncovered 33 rare pathogenic *BRCA1* and *BRCA2* gene mutations in 40 out of 290 breast cancer patients (13.8%). It was concluded that among the residents of the Russian Federation, the range of pathogenic variants of *BRCA*-associated breast cancer is wide, and it stretches beyond the mutations considered by the "standard" diagnostic panels. Analysis of the entire coding regions of *BRCA1* and *BRCA2* genes allows increasing efficiency of detection of germline mutations in breast cancer patients at least twofold.

Keywords: *BRCA1* and *BRCA2* mutations, next-generation sequencing, NGS, hereditary breast cancer

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ХАРАКТЕРИСТИКА *BRCA*-АССОЦИИРОВАННОГО РАКА МОЛОЧНОЙ ЖЕЛЕЗЫ В РОССИЙСКОЙ ПОПУЛЯЦИИ

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Использование «стандартных» диагностических панелей, дающих возможность определять лишь несколько наиболее распространенных в популяции мутаций в генах *BRCA1* и *BRCA2*, может приводить к появлению ложноотрицательных результатов из-за наличия других повреждений в кодирующих областях данных генов, что, в свою очередь, может привести к неадекватному выбору тактики лечения у больных раком молочной железы (РМЖ). Целью работы было выявить особенности *BRCA*-ассоциированного рака молочной железы в российской популяции. В исследование вошли пациенты с диагнозом РМЖ (n = 4440). На первом этапе методом ПЦР в реальном времени проведено скрининговое исследование всех пациентов на наличие восьми наиболее распространенных мутаций в генах *BRCA1* и *BRCA2*. Далее при наличии у пациентов клинических признаков наследственного заболевания (КПНЗ) и отсутствии распространенных мутаций (n = 290) проводили исследование всей кодирующей части генов *BRCA1* и *BRCA2* методом секвенирования нового поколения (NGS). В 169 случаях (3,8%) были выявлены «стандартные» мутации в генах *BRCA1* и *BRCA2*. В группе пациентов с КПНЗ частота выявленных «стандартных» мутаций составила 15,4%. Методом NGS у 40 из 290 больных РМЖ (13,8%) были обнаружены 33 редкие патогенные мутации в генах *BRCA1* и *BRCA2*. Сделан вывод, что *BRCA*-ассоциированный РМЖ в российской популяции характеризуется широким спектром патогенных вариантов, который не ограничен мутациями, включенными в «стандартные» клинико-диагностические панели. Анализ всей кодирующей части генов *BRCA1* и *BRCA2* позволяет повысить эффективность выявления герминальных мутаций у больных РМЖ по крайней мере в 2 раза.

Ключевые слова: мутации в генах *BRCA1* и *BRCA2*, секвенирование нового поколения, NGS, наследственный рак молочной железы

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Hormonal status and genetic predisposition are the key factors influencing breast cancer (BC) development [1].

In up to 90–95% of BC patients, the cancer is sporadic, non-hereditary by nature. Its hereditary forms, which are characterized by various mutations in genes *BRCA1*, *BRCA2*, *CHEK2*, *NBN*, ATM, PALB2 etc. [2, 3], are diagnosed in 5–10% of BC patients [2].

The most common hereditary reasons behind BC are *BRCA1* and *BRCA2* gene mutations. These genes encode proteins that enable double-strand DNA break repairs, control

cell cycle, regulate transcription and apoptosis, maintain genomic stability [4]. Damage to these genes increases the likelihood of development of cancer, with the majority of such progressions registered in young patients [5, 6]. The mutations registered in genes *BRCA1* and *BRCA2* largely determine the choice of therapy and preventive measures [7].

The current approach to diagnosing hereditary forms of BC adopted in the Russian Federation implies using "standard" diagnostic panels that, relying on PCR, make detection of the *BRCA1* and *BRCA2* gene mutations most common in our population quick and relatively inexpensive [8]. However, a number of studies points to other clinically significant mutations that cannot be detected with the "standard" panel but increase the risk of cancer development. Therefore, their presence requires a specialized approach in the treatment and prevention of diseases [9].

This research effort aimed to study the features of *BRCA*-associated breast cancer in the population of the Russian Federation.

METHODS

The study included 4440 patients who underwent examination and treatment at the Russian Scientific Center of Roentgenoradiology from 2010 to 2019. The inclusion criteria were: any age; diagnosed BC. The exclusion criterion was patient's refusal to participate in the study. The age of cancer onset varied from 20 to 90 years (Table 1). Samples of the tumors of all patients were subjected to histological examination and immunohistochemical analysis (IHC). Compiling the patients' medical histories, we paid special attention to the signals of possible hereditary nature of the disease.

Based on the medical histories and following recommendations of the US National Comprehensive Cancer Network (NCCN) [7], we formed a high-risk group exhibiting clinical signs of hereditary disease (CSHD). The group included 1026 breast cancer patients aged 20–90 years. The patient was added to the high-risk group if she had at least one CSHD: disease manifestation at any age under 50, multiple primary tumors (BC and/or ovarian cancer (OC)), cancer in the family history (BC and/or OC in first- and/or second-degree relatives), triple negative molecular subtype of the tumor.

At the first stage of the study, we employed real-time PCR (RT PCR) in search of the *BRCA1* and *BRCA2* mutations most common in the Russian Federation: 185delAG, 4153delA, 5382insC, 3819delGTAAA, 3875delGTCT, 300T>G, 2080delA (*BRCA1*) and 6174delT (*BRCA2*). All 4440 patients participating in the study were examined. For DNA isolation, we used the M-Sorb kits (Syntol; Russia). OncoGenetics BRCA reagent panel (DNA-Technology; Russia), which includes specific primers for detection of the eight studied mutations, was used to carry out RT PCR.

At the second stage, we examined 290 patients from the high-risk BC development group that had no "standard" mutations detected at the first stage of the study. The entire coding regions of their *BRCA1* and *BRCA2* genes were analyzed using next generation sequencing (NGS).

Using QIAamp DNA Blood Mini Kit reagents (Qiagen; Germany) and relying on the protocol suggested by the manufacturer, we isolated genomic DNA from peripheral blood. The minimal acceptable DNA concentration was 10 ng/μL. TruSight Cancer panel (Illumina; USA) and TruSight Rapid Capture reagent kit (Illumina; USA) allowed us to prepare the sequencing libraries. We followed manufacturer's instructions and used the selective DNA region capture method.

The prepared libraries were pair-end sequenced (2 × 151 base pairs) on a MiSeq system (Illumina; USA) using MiSeq Reagent Kits v2 (Illumina; USA). The average coverage of the target DNA regions was 100× and over.

The sequencing data were processed with the help of the standard MiSeq Reporter v2.5 (Illumina; USA) software. In some samples, the regions studied presented genetic abnormalities. To increase accuracy, we excluded poor quality sequencing reads from the analysis. Variant Studio 2.2 (Illumina; USA) software was used to annotate and classify the identified sequence variants.

Assessing the clinical significance of the genetic abnormalities identified, we relied on the sequence variant pathogenicity criteria suggested by the American College of Medical Genetics and Genomics (ACMG) [10] taking into account information published in accessible databases: dbSNP (The Single Nucleotide Polymorphism database), ClinVar (Clinical Variation), HGMD (Human Gene Mutation Database), BIC (Breast Cancer Information Core), OMIM (Online Mendelian Inheritance in Man), ExAC (Exome Aggregation Consortium), 1000G (1000 Genomes Project) and CADD (Combined Annotation Dependent Depletion), PolyPhen (Polymorphism Phenotyping) and Sift (Sorting Intolerant from Tolerant). We did not consider sequence variants that have no clinical significance, as well as those of unknown clinical significance.

The identified nucleotide sequence changes were verified with the help of the Sanger sequencing method. The analysis was enabled by the ABI PRISM 3100 automated capillary electrophoresis system (Applied Biosystems; USA).

RESULTS

Out of the total sample of RT PCR-diagnosed BC patients (n = 4440), 169 people (3.8%) had *BRCA1* and *BRCA2* gene mutations detectable with the "standard" diagnostic panels (Table 2). In the CSHD group, the share of patients with such "standard" gene mutations was 4 times higher: the analysis put it at 15.4%. The most common mutation was 5382insC in the *BRCA1* gene. In the overall sample, this variant was detected in 2.9% of patients, while for the high-risk CSHD group this figure was 11.5%, i.e., every 9th patient had the said mutation. Among the identified "standard" mutations, the 5382insC variant was found in 75% of cases. The remaining genetic variants included in the "standard" diagnostic panel were detected at least an order of magnitude less frequently (Table 2).

Next generation sequencing of the entire coding regions, as well as the *BRCA1* and *BRCA2* splicing regions, revealed 33 clinically significant variants in 40 out of 290 (13.8%) BC patients from the high-risk group. In 18 cases, the abnormalities were in the *BRCA1* gene: nine variants of nonsense mutations, three variants of frameshift deletions, and two abnormalities in splice sites. *BRCA2* pathogenic sequence variants were found in 22 patients; there were seven nonsense mutations, eight variants of frameshift deletions and insertions, and two splice site abnormalities (Table 3).

Among the identified genetic disorders, the most common abnormal nucleotide sequence change was the c.3607C>T mutation in *BRCA1* (7.5% of cases, three patients). The following pathogenic mutations were detected in approximately 5% of cases: c.4689C>G and c.5224C>T in *BRCA1*, c.1301_1304delAAAG, c.9089_9090insA and c.3283C>T in *BRCA2*.

With the exception of mutation 5382insC in *BRCA1*, the frequency of occurrence of each pathogenic variant detected through NGS is comparable to the frequency of "standard"

Table 1. Clinical characteristics of the examined BC patients group

Characteristic	BC patients (n = 4440)
Age	
Average age of disease manifestation, years	52 (20–90)
Under 50 y.o., people (%)	1332 (30)
51 y.o. and older, people (%)	3108 (70)
Family cancer history	
Yes, people (%)	533 (12)
No, people (%)	3907 (88)
Diagnosis	
PMMN (BC/BC or BC/OC), people (%)	313 (7)
BC, people (%)	4127 (93)
Molecular subtype of tumor	
ER(+) and/or PR(+)Her2(-), people (%)	2930 (66)
ER(+) and/or PR(+)Her2(+), people (%)	888 (20)
ER(-)PR(-)Her2(+), people (%)	222 (5)
ER(-)PR(-)Her2(-), people (%)	400 (9)
Histological type of tumor	
Infiltrating ductal carcinoma, people (%)	3330 (75)
Invasive lobular carcinoma, people (%)	577 (13)
Other, people (%)	533 (12)

Note: PMMN — primary multiple malignant neoplasms.

BRCA1 and *BRCA2* gene mutations, with the difference insignificant ($p > 0.05$).

Taking into account the available information on the features of *BRCA*-associated breast cancer, we analyzed some clinical characteristics of the patients that carried *BRCA1* and *BRCA2* gene mutations, and studied morphological features of their tumor samples (Table 4). In 94% of patients with *BRCA1*-associated breast cancer and in all patients with *BRCA2*-associated breast cancer, we detected at least one hereditary disease sign (age under 50, cancer in family history, primary multiple tumors, triple negative molecular subtype of the tumor). Six percent of the patients exhibited no clinical signs of a hereditary disease.

Comparison of the groups of patients with identified *BRCA1* and *BRCA2* gene mutations showed that in the *BRCA1*-associated BC group, the average disease manifestation age was 42 years (20–82 years), and in the *BRCA2*-associated BC group the onset of the disease was registered at 44, on average (25–79 years old). Moreover, 87% of the *BRCA2*-associated BC group patients had the cancer diagnosed when they were under 50, and in the *BRCA1*-associated BC group this figure was 81%.

Over half of gene mutation carriers (63% with abnormal BRCA1 and 74% with mutations in *BRCA2*) mentioned having blood relatives with BC/OC. In both *BRCA1*-associated and *BRCA2*-associated BC groups the frequency of detection of primary multiple malignant neoplasms was rather high (22% and 30% of cases, respectively) (Table 4).

The examination revealed that the majority of both *BRCA1*- (91%) and *BRCA2*-associated tumors (61%) were infiltrating ductal carcinomas (Table 4). However, upon comparison of the groups it was found that the carriers of *BRCA1* gene mutations had the said type of cancer in 91% of cases, while those with mutations in *BRCA2* — only in 61% (p = 0.0003). For *BRCA2*-associated tumors, on the contrary, there was a predominance of invasive lobular breast cancer (30%) compared with *BRCA1*-associated tumors (5%) (p = 0.0005).

The current classification of molecular subtypes of BC relies on the IHC-enabled detection of expression levels of estrogen (ER), progesterone (PR) and epidermal growth factor (Her2) receptors. These indicators, scored in points, allow classifying the cancer as one of the molecular subtypes, which, in turn, largely determines the disease therapy and prognosis. In the context of this study, we detected triple negative breast cancer

Table 2. Frequency of occurrence of *BRCA1* and *BRCA2* gene mutations most common in the population (BC patients)

Gene	Mutation name (BIC classification)	Number of mutation carriers in the examined group, people	Mutation frequency, %	Number of mutation carriers in the CSHD group, people	Mutation frequency, %
BRCA1	5382insC	127	2.9	118	11.5
BRCA1	4153delA	5	0.1	4	0.4
BRCA1	300T>G	10	0.2	10	1.0
BRCA1	2080delA	8	0.2	8	0.8
BRCA1	185delAG	10	0.2	9	0.9
BRCA1	3819delGTAAA	8	0.2	8	0.8
BRCA1	3875delGTCT	–	–	–	–
BRCA2	6174delT	1	0.02	1	0.1
Total		169	3.8	158	15.4

Table 3. Characteristics and frequency of rare pathogenic *BRCA1* and *BRCA2* sequence variants, CSHD BC patients group

Gene	Genetic variant name (HGVS classification)	Identification number (dbSNP)	Variant characteristic	Number of patients, people
BRCA1	c.4327C>T (p.Arg1443Ter)	rs41293455	nonsense mutation	1
BRCA1	c.4689C>G (p.Tyr1563Ter)	rs80357433	nonsense mutation	2
BRCA1	c.5531-1G>A	rs80358048	splicing site mutation	1
BRCA1	c.3607C>T (p.Arg1203Ter)	rs62625308	nonsense mutation	3
BRCA1	c.5224C>T (p.Gln1721Ter)	rs878854957	nonsense mutation	2
BRCA1	c.4258C>T (p.Gln1420Ter)	rs80357305	nonsense mutation	1
BRCA1	c.1687C>T (p.Gln563Ter)	rs80356898	nonsense mutation	1
BRCA1	c.4165_4166delAG (p.Ser1389Terfs)	rs80357572	frameshift deletion	1
BRCA1	c.3257T>G (p.Leu1086Ter)	rs80357006	nonsense mutation	1
BRCA1	c.5152+1G>T	rs80358094	splicing site mutation	1
BRCA1	c.1510delC (p.Arg504Valfs)	rs80357908	frameshift deletion	1
BRCA1	c.83_84delTG (p.Leu28Argfs)	rs80357728	frameshift deletion	1
BRCA1	c.5314C>T (p.Arg1772Ter)	rs80357123	nonsense mutation	1
BRCA1	c.763G>T (p.Glu255Ter)	rs80357009	nonsense mutation	1
BRCA2	8002A>T (p.Arg2668Ter)	rs276174900	nonsense mutation	1
BRCA2	6070C>T (p.Gln2024Ter)	rs80358844	nonsense mutation	1
BRCA2	c.6997_6998insT (p.Pro2334Thrfs)	rs754611265	frameshift deletion	1
BRCA2	c.3748_3749insA (p.Thr1251Asnfs)	rs397507683	frameshift deletion	1
BRCA2	c.5718_5719delCT (p.Leu1908Argfs)	rs80359530	frameshift deletion	1
BRCA2	c.1301_1304delAAAG (p.Lys437Ilefs)	rs80359277	frameshift deletion	2
BRCA2	c.9117G>A (p.Pro3039=)	rs28897756	splicing site mutation	1
BRCA2	c.9089_9090insA (p.Thr3033Asnfs)	rs397507419	frameshift deletion	2
BRCA2	c.632-1G>A	rs81002820	splicing site mutation	1
BRCA2	c.4111C>T (p.Gln1371Ter)	rs80358659	nonsense mutation	1
BRCA2	c.7254_7255delAG (p.Arg2418Serfs)	rs80359644	frameshift deletion	1
BRCA2	c.3881T>A (p.Leu1294Ter)	rs80358632	nonsense mutation	1
BRCA2	c.8909G>A (p.Trp2970Ter)	–	nonsense mutation	1
BRCA2	c.8168A>G (p.Asp2723Gly)	rs41293513	nonsense mutation	1
BRCA2	c.5633delA (p.Asn1878ThrfsTer31)	–	frameshift deletion	1
BRCA2	c.7007G>A (p.Arg2336His)	rs28897743	missense mutation	1
BRCA2	c.658_659delGT (p.Val220Ilefs)	rs80359604	frameshift deletion	1
BRCA2	c.3283C>T (p.Gln1095Ter)	rs397507662	nonsense mutation	2
BRCA2	c.8437G>T (p.Gly2813Ter)	–	nonsense mutation	1

(TNBC) in 29% of cases (54 patients) in the *BRCA1*-associated BC group, while for the *BRCA2*-associated BC group the same figure was only 4% (1 patient). We have also established that almost all *BRCA2*-associated tumors (96%) were of the luminal subtype and were characterized by the expression of estrogen (ER) and progesterone (PR) receptors (Table 4).

DISCUSSION

The results of this study are consistent with the data of previously published works. We confirmed that in the population of the Russian Federation, *BRCA1* and *BRCA2* gene mutations are rather frequent, with the most common of them being 5382insC in *BRCA1*, which is found an order of magnitude more often than other mutations in these genes [2, 3, 8]. This fact confirms the assumption that this sequence variant is of Slavic origin [2].

Among the rare pathogenic mutations detected with NGS, the most common sequence variant was the c.3607C>T mutation in the *BRCA1* gene. This genetic variant was described previously; it is associated with a high risk of development of both BC and OC [11, 12].

The analysis of international and Russian publications and databases showed that only a few of the identified rare sequence variants were covered in the Russian studies. The c.3607C>T mutation in the *BRCA1* gene was described in a BC patient from St. Petersburg whose family history included cancer patients [13]. The *BRCA1* gene mutations c.5224C>T and c.5314C>T were found in the Tatar population in patients with hereditary BC and OC [14]. Mutations c.4689C>G, c.5152+1G>T in *BRCA1* and mutations c.6997_6998insT, c.7254_7255delAG and c.658_659delGT in *BRCA2* were detected in residents of Siberia and the Far East with hereditary BC and OC [15]. The remaining variants, detected with the help of NGS, were described in foreign publications and databases only.

The results of this study confirm that BC patients with mutations in the *BRCA1* and *BRCA2* genes often exhibit CSHD, including: disease manifestation at any age under 50,

Table 4. Comparison of *BRCA1*- and *BRCA2*-associated BC, main clinical and morphological characteristics

Characteristic	*BRCA1*-associated BC (*n* = 187)	*BRCA2*-associated BC (*n* = 23)
Age		
Average age of disease manifestation, years	42 (20–82)	44 (25–79)
Under 50 y.o., people (%)	152 (81)	20 (87)
51 y.o. and older, people (%)	35 (19)	3 (13)
Family cancer history		
Yes, people (%)	118 (63)	17 (74)
No, people (%)	69 (37)	6 (26)
Diagnosis		
PMMN (BC/BC or BC/OC), people (%)	41 (22)	7 (30)
BC, people (%)	146 (78)	16 (70)
Molecular subtype of tumor		
ER(+) and/or PR(+)Her2(-), people (%)	122 (65)	22 (96)*
ER(+) and/or PR(+)Her2(+), people (%)	9 (5)	0
ER(-)PR(-)Her2(+), people (%)	2 (1)	0
ER(-)PR(-)Her2(-), people (%)	54 (29)	1 (4)*
Histological type of tumor		
Infiltrating ductal carcinoma, people (%)	171 (91)	14 (61)*
Invasive lobular carcinoma, people (%)	9 (5)	7 (30)*
Other, people (%)	7 (4)	2 (9)
Presence of clinical signs of hereditary BC		
With clinical signs of the disease, people (%)	176 (94)	23 (100)
Without clinical signs of the disease, people (%)	11 (6)	0

Note: * — significant differences with the *BRCA1*-associated BC group ($p < 0.05$); PMMN — primary multiple malignant neoplasms.

multiple primary tumors (BC and/or OC), cancer in the family history (BC and/or OC in first- and/or second-degree relatives), triple negative molecular subtype of the tumor. The absence of CSHD in 6% of patients with mutations in the *BRCA1* may be associated with their unawareness of cancer cases in the family history or development of such mutations *de novo*.

In conformity with the previously published papers, we found that the average age of cancer onset in the *BRCA2*-associated BC group is 44, which is older than the average onset age registered in the *BRCA1*-associated BC group (42). According to the results of the combined study that merged the analysis of pathomorphological characteristics of tumors and clinical data of 3797 carriers *BRCA1* gene mutations and 2392 patients with abnormal *BRCA2* genes, the median age of disease manifestation for the *BRCA1*-associated BC group was 40, for the *BRCA2*-associated BC group — 43 [16].

The data obtained in this study confirm that the majority of *BRCA*-associated tumors are infiltrating ductal carcinomas, but among the *BRCA2*-associated tumors, invasive lobular breast cancer predominates, compared with *BRCA1*-associated tumors [16].

We have shown that in carriers of the *BRCA1* gene mutations (compared to BC patients with this gene undamaged), the tumor is most often characterized by the absence of expression of the estrogen (ER), progesterone (PR) and epidermal growth factor (Her2) receptors, which makes it TNBC [16, 17]. Overall, TNBC was diagnosed in 29% of cases in the *BRCA1*-associated BC group, which is significantly different from the frequency of TNBC recorded in the *BRCA2*-associated BC group. In context of this study, almost all *BRCA2*-associated tumors (96%) belonged to the luminal subtype and were characterized by expression of estrogen (ER) and progesterone (PR) receptors, which is also characteristic of sporadic BC [18].

CONCLUSION

Thus, among the residents of the Russian Federation, the range of pathogenic variants of *BRCA*-associated breast cancer is wide, and it stretches beyond the mutations considered by the "standard" diagnostic panels designed for primary screening. The results of this study highlight the need for analysis of the entire coding regions of *BRCA1* and *BRCA2* genes, which would allow increasing efficiency of detection of germline mutations in BC patients at least twofold. Due to the certain clinical and morphological features of *BRCA*-associated breast cancer, such analysis should be prescribed, first of all, for patients in whom the disease manifested at the age under 50 years, whose blood relatives have tumors in their histories (BC and OC), and who have primary multiple malignant neoplasms (BC and BC and/or OC) and triple negative molecular subtype of the tumor.

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