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 (CSDH) 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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Compliance with ethical standards: the study was approved by the ethics committee of the RSCR (minutes #3 of March 27, 2020); all patients included in the study signed a voluntary informed consent.

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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 ненадежному 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, включёнными в "стандартные" клинико-диагностические панели. Анализ всей кодирующей части генов BRCA1 и BRCA2 позволяет повысить эффективность выявления генеральных 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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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 from 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). Oncogentics 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.4698C>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 (%)      | 866 (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.

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-associated (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  | 2080delE                          | 8                                                        | 0.2                   | 8                                                      | 0.8                   |
| BRCA1  | 185delAG                          | 10                                                       | 0.2                   | 9                                                      | 0.9                   |
| BRCA1  | 3819delGTAAA                      | 8                                                        | 0.2                   | 8                                                      | 0.8                   |
| BRCA1  | 3875delKTCT                       | --                                                       | --                    | --                                                     | --                    |
| BRCA2  | 6174delT                          | 1                                                        | 0.02                  | 1                                                      | 0.1                   |
| Total  |                                   | 169                                                      | 3.8                   | 158                                                    | 15.4                  |
Among the rare pathogenic mutations detected with NGS, were described in foreign publications and databases only. We confirmed that in the population of the Russian Federation, BRCA1 and BRCA2 gene mutations c.5224C>T and c.5314C>T were found in the Tatar population in patients with hereditary BC and OC [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 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, (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 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.

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