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ANALYSIS OF THE OCCURRENCE OF GERMLINE MUTATIONS BRCA1\2, PALB2, CHEK2, NBN IN PATIENTS WITH PANCREATIC MALIGNANCIES. SINGLE-CENTER COHORT NON-RANDOMIZED RETROSPECTIVE STUDY

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АНАЛИЗ ВСТРЕЧАЕМОСТИ ГЕРМИНАЛЬНЫХ МУТАЦИЙ BRCA1\2, PALB2, CHEK2, NBN У ПАЦИЕНТОВ СО ЗЛОКАЧЕСТВЕННЫМИ НОВООБРАЗОВАНИЯМИ ПОДЖЕЛУДОЧНОЙ ЖЕЛЕЗЫ: ОДНОЦЕНТРОВОЕ КОГОРТНОЕ НЕРАНДОМИЗИРОВАННОЕ РЕТРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ

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Objective. To analyze the frequency of carriage of BRCA1\2, PALB2, CHEK2, NBN mutations in patients with malignant neoplasms of pancreas.
Materials and methods. The single-center cohort non-randomized retrospective study is based on the data of 82 patients who were examined and treated in Russian Research Center of Radiology and Surgical Technologies named after academician A.M. Granov from 2020 to 2022. Patients with confirmed ductal adenocarcinoma of pancreas were included into the study group. Screening of mutations in exons 2,10, 18, 19 of BRCA1 gene and exon 11 of BRCA2 gene was performed in these patients. In addition, oncological family histories were studied.
Results. Analysis of medical documentation data showed that 18 (22 %) patients with pancreatic cancer had a hereditary oncological history. In this cohort of patients, 5 (28 %) had relatives with pancreatic cancer, 9 (50 %) had a family history of ovarian cancer, 2 (11 %) female relatives of patients in the study group were diagnosed with breast cancer before the age of 50, also 2 (11 %) patients had a history of more than 2 relatives who suffered from breast cancer and / or prostate cancer. When evaluating the results of revealing the mutations in the entire study group (82 patients), BRCA1 (c.5266dupC) was revealed in 8 patients (9.7 %), PALB-2 (c.1592delT) – in 2 patients (2.4 %), mutations CHEK2, NBN and BRCA2 were not diagnosed in any patient. 5 (6 %) patients who were BRCA1 mutation carriers and one patient with an established PALB2 mutation, according to the analysis of case histories, had no oncological history. None of the patients in the study group was a carrier of the BRCA2, CHEK2 and NBN mutations.
Conclusions. Some patients with pancreatic cancer are carriers of germline mutations. Considering our data on the trend of association between germline mutations and pancreatic cancer, we can make an assumption about the prospect of using this indicator as one of the markers for early detection of pancreatic cancer not only in patients with hereditary risk factors for neoplasia, but also in patients without cancer anamnesis. To obtain the results, further observation of patients in the study group and randomized multicenter studies are required.
Keywords. Pancreatic cancer, germline mutations, BRCA1, BRCA2, PALB2.

Цель. Проведение анализа частоты носительства мутаций BRCA1\2, PALB2, CHEK2, NBN у пациентов со злокачественными новообразованиями поджелудочной железы (ЗНО ПЖ).
Материалы и методы. В одноцентровое когортное нерандомизированное ретроспективное исследование включены данные 82 пациентов, прошедших обследование и лечение в ФГБУ РНЦРХТ им акад. А.М. Гранова в период с 2020 по 2022 г. В группу исследования включены пациенты с морфологически подтвержденным диагнозом протоковой аденокарциномы поджелудочной железы. У этих больных проводили скрининг мутаций в экзонах 2, 10, 18, 19 гена BRCA1 и в ключевом регионе 11-го экзона гена BRCA2. Дополнительно проводили изучение семейного онкологического анамнеза.
Результаты. Анализ данных медицинской документации установил, что 18 (22 %) больных ЗНО ПЖ имели наследственный онкологический анамнез. В данной когорте 5 (28 %) человек сообщили о случаях ЗНО ПЖ у родственников, 9 (50 %) имели семейный анамнез рака яичников, у 2 (11 %) родственниц пациентов группы исследования диагностирован рак молочной железы до возраста 50 лет, также у 2 (11 %) пациентов в анамнезе было более 2 родственников, которые страдали раком молочной железы и/или раком простаты. При оценке результатов определения мутаций во всей исследуемой группе (82 человека) BRCA1 (c.5266dupC) выявлена у 8 пациентов (9,7 %), PALB-2 (c.1592delT) – у 2 (2,4 %), мутаций CHEK2, NBN и BRCA2 – не диагностировано ни у одного пациента; 5 (6 %) носителей BRCA1 мутации и один пациент с установленной мутацией PALB2, по данным анализа историй болезни, не имели онкологического анамнеза. Ни один из пациентов группы исследования не являлся носителем BRCA2, CHEK2 и NBN мутации.
Выводы. Некоторые пациенты, страдающие ЗНО ПЖ, являются носителями герминальных мутаций. Учитывая полученные нами данные о тенденции связи герминальных мутаций и рака поджелудочной железы, можно сделать предположение о перспективе использования данного показателя в качестве одного из маркеров раннего выявления рака поджелудочной железы не только у больных с наследственными факторами риска возникновения данной неоплазии, но и у пациентов без онкологического анамнеза. Для получения дальнейших результатов требуется продолжение набора пациентов в группу исследования и проведение рандомизированных мультицентровых исследований.
Ключевые слова. Злокачественные новообразования поджелудочной железы, герминальные мутации, BRCA1, BRCA2, PALB2.

INTRODUCTION

According to the World Cancer Research Fund, malignant neoplasms of pancreas occupy a leading position among all oncological diseases of the gastrointestinal tract in terms of late detection and mortality. Unfavourable medical and statistical indicators of pancreatic cancer are associated with late treatment of patients, as well as with tumour resistance to existing chemotherapy regimens. Due to the absence of screening and detection programs for patients with pancreatic cancer, the disease is represented by a locally advanced or metastatic stage in more than 80 % of cases at the time of primary diagnosis, which significantly worsens the prognosis of the disease and the results of treatment [1; 2]. Given the lack of recognized biomarkers for early detection of pancreatic cancer, as well as the difficulties of instrumental diagnosis of this pathology at early, preclinical stages, the search for "markers" for detecting pancreatic cancer is an urgent problem in modern clinical oncology [3]. One of the possible methods for early detection of pancreatic cancer is genetic testing in risk groups and patients with a family history of pancreatic cancer [4]. During normal cell functioning, genome stability is maintained by a system for recognizing DNA sequence defects by ATM and ATR kinases, CHEK2 and BRCA1 signal conversion molecules, and BRCA2 and RAD51 repair initiation effectors. The system also contains the molecules that coordinate the interaction of recognition and repair, such as PALB2 and BRIP1. It should be noted that it is BRCA2 that plays a more specific role in DNA repair, regulating the RAD51 activity required for homologous recombination. According to a number of authors, it is disorders in this system that play a fundamental role in the development of pancreatic cancer [5]. A multicenter IMPACT study conducted by a group of authors from the USA indicated that out of 76 patients suffering from common forms of prostate cancer 21.5 % had germinal mutations [6]. In general, there is evidence in the literature that the presence of BRCA gene mutations increases the risk of pancreatic cancer, but the effect of these mutations on the clinical course of the disease is insufficiently studied. The cohort studies have shown that patients with pancreatic cancer who carry germinal mutations BRCA1, BRCA2, PALB2, CDKN2A, and ATM are diagnosed with the disease earlier than patients without mutations [7; 8]. However, a study conducted by C. Ferrone et al. in a population of Ashkenazi patients with pancreatic cancer did not reveal significant differences between the presence of BRCA mutations and any clinical and pathological signs of the disease, including the moment of manifestation of pancreatic cancer [9]. The prognostic role of BRCA mutations in pancreatic cancer has not been definitively determined. Study by T. Golan et al., which included patients with pancreatic cancer with different BRCA mutation statuses, revealed that the median overall survival of patients receiving therapy in the presence of BRCA mutations was 14 months, and for patients without established germinal mutations – 12 months. It should be noted that at the time

of publication, the median overall survival in patients with early-stage pancreatic cancer was not achieved at all, since 52 % of patients had been alive for 60 months from the start of the study [10].

The data obtained by the authors indicate that patients with pancreatic cancer and detected BRCA mutations may have a significantly better prognosis than the general population of patients with pancreatic cancer. More recent case-control studies conducted by Blair et al. showed that the overall survival and relapse-free period after surgery in patients with pancreatic cancer and BRCA1 and BRCA2 mutations was significantly lower compared to the control group without mutations. Another case-control study comparing patients with early-stage pancreatic cancer with a BRCA mutation who underwent surgical resection and a control group with BRCA-wild type did not reveal statistically significant differences in the median overall survival in the groups, thus, the authors concluded that BRCA mutations did not have prognostic significance in the early stages of pancreatic cancer [11]. Most of the reported cases of pancreatic cancer are considered sporadic, however, approximately 5 to 10 % are related to a family history of the disease, which is defined as presence of two or more first-degree relatives or three or more relatives of any degree with a diagnosis of pancreatic cancer [12]. Nevertheless, the research in different populations, including patients with pancreatic cancer, confirmed the absence of a clear connection between the presence of BRCA mutations and family history [13; 14]. Taken together, obtained literary data convincingly confirm the extension of indications for genetic testing for patients at risk of pancreatic cancer without a family history. Thus, a clinical study of BRCA1\2 mutations can be of great practical importance in detecting and predicting pancreatic cancer, including in patients without a family history of malignant neoplasms and hereditary syndromes.

The objective of the study: to analyze the incidence rate of BRCA1\2, PALB2, CHEK2, and NBN germinal mutations in patients with malignant neoplasms of pancreas.

MATERIALS AND METHODS

The single-center cohort non-randomized retrospective study is based on the data of 82 patients who were examined and treated in Russian Research Center of Radiology and Surgical Technologies named after academician A.M. Granov from 2020 to 2022. Analysis was performed by new generation sequencing by screening in BRCA1 (538insC, 415delA, 185delAG, T300G, c. 2080insA, c. 208delA, 3875delGTCT, 3819delGTAA, c. 5251C>T, c. 4675G<A, c. 5177 5180delGAAA), BRCA2 (6174delT, c. 3749dupA, c. 961 962ins AA), CHEK2 (c.1100delC, c.444+1G>A, c.839 897del, c.470T>), PLAB2 (c. 1592delT), NBN (657del15). Screening of mutations in exons 2, 10, 18, and 19 of the BRCA1 gene and in the key region of exon 11 of the BRCA 2 gene was performed. Additionally, family history of cancer was investigated. The NCCN 2023 criteria were used as genetic risk factors for pancreatic cancer.

RESULTS AND DISCUSSION

In the study group, the age of patients ranged from 51 to 79 years; the median age was 64.3 years. The number of men – 46 (57 %), women – 36 (43 %) (Table).

Analysis of medical records showed that 18 (22 %) patients had a hereditary history of cancer. Herewith, 5 (28 %) patients reported cases of pancreatic cancer in relatives, 9 (50 %) patients had a family history of ovarian cancer, 2 (11 %) relatives of patients in the study group were diagnosed with breast cancer before the age of 50, while 2 (11 %) patients had a history of more than 2 relatives who suffered from breast cancer and/or prostate cancer.

It should be noted that none of the patients in the study group identified themselves with the Ashkenazi ethnic group. In the group of patients with a history of pancreatic cancer, germinal mutations were detected in 3 patients (two patients were carriers of the BRCA1 mutation (p. 5266dupC), another patient had the PALB2 mutation (p.1592delT)). The mother of one BRCA1 carrier was diagnosed with breast cancer before the age of 50, and the father of the second BRCA1 carrier had pancreatic cancer. Notably, the latter patient's maternal grandmother suffered from breast cancer, and his paternal cousin died of colon cancer. The CECK2 mutation was diagnosed in a patient whose grandmother and grandfather suffered from breast cancer and prostate cancer, respectively.

5 (6 %) patients who carried the BRCA1 mutation and one patient with the determined PALB 2 mutation did not have a history of cancer according to the analysis of medical records. It should be mentioned that one of the carriers of the BRCA1 mutation was diagnosed with advanced prostate cancer during the examination. None of the patients in the study group were carriers of the BRCA2, CHEK2, and NBN mutations.

Most of the reported cases of pancreatic cancer are considered sporadic, however, approximately 5 to 10 % are related to a family history of the disease, while the risk of developing pancreatic cancer during life in the presence of this disease in the family history increases 2.3–3.2 times, depending on the number of sick relatives [12]. In our study, 22 % of patients had a hereditary history of cancer. According to the analysis, most often – in 9 (50 %) and 5 (28 %) patients – blood kin suffered from pancreatic cancer and ovarian cancer, respectively. In the study of M. Cote et al., which included

Distribution of patients with a family history of cancer by hereditary risk factor (NCCN criteria, 2023)

Hereditary factor	Breast cancer in at least one relative under the age of 50	Pancreatic cancer in a first-degree relative at any age	Ovarian cancer in a first-degree relative at any age	Breast and/or prostate cancer in more than two relatives at any age
Number of patients, abs. (%)	2 (11)	5 (28)	9 (50)	2 (11)

more than 350 patients with pancreatic cancer, relatives most often suffered from pancreatic cancer and ovarian cancer as well [16]. According to the authors, the connection between ovarian cancer and prostate cancer is based on the presence of BRCA2 mutations. In the study of M. Roberts et al. It was found that in 14 % of the population of patients with prostate cancer, mutations are detected in the genes responsible for BRCA 2 DNA repair [12]. However, in our study, no BRCA2-mutation was detected in any patient. The obtained data can probably be explained by the fact that BRCA2 mutations are relatively rare in Russia, and their spectrum is not limited to repeated injuries [17].

The literature describes hereditary syndromes and diseases that are associated with an increased risk of developing pancreatic ductal adenocarcinoma (PDAC), including: familial atypical multiple mole melanoma syndrome (FAMMM-syndrome), Peutz–Jeghers syndrome, and Lynch syndrome [18]. In our study, the above-mentioned hereditary syndromes were not registered in any patient. This may be due to the fact that these syndromes are relatively rare in the population – less than 5 % [19].

In recent times, recommendations for genetic testing of inherited pancreatic cancer have been increasingly criticized by various researchers, as annually updated data appear indicating that existing screening algorithms based on family history are ineffective, which leads to late detection of these neoplasms. In 2007, a study of patients with BRCA1/2 mutations conducted by a group of authors from Norway revealed that 50 % of patients with BRCA germ line mutations do not have a family history of cancer associated with BRCA gene mutations [13; 20]. In our study, more than a half of patients with determined germinal mutations did not have a family history of cancer.

Special attention should be paid to the statistical data of the Ashkenazi ethnic group, since in this group the occurrence of germinal mutations, especially BRCA2 (6174delT), is extremely high, and therefore should be considered separately [20]. In our study, none of the patients associated themselves with this ethnic group. It should be noted that there are some references in the literature about the results of direct genetic testing, according to which 20 % of carriers of Ashkenazi genes do not identify themselves as descendants of this ethnic group and, therefore, may potentially be excluded from the screening criteria of existing programs that include Ashkenazi origin as one of the fundamental risk factor for developing hereditary forms of cancer, prostate cancer in particular. Moreover, in this study, the authors found that out of 393 carriers of BRCA1\2 gene mutations with available family history of cancer, 44 % did not have a family history of BRCA-related cancer [21].

Conclusion

Thus, a number of patients suffering from pancreatic cancer are carriers of germinal mutations. If we take into account our data on the trending association between germinal mutations and pancreatic cancer, we can make an assumption about the prospects of using this indicator as one of the markers for detecting pancreatic cancer in patients at risk. Consider-

ing the fact that only a third of patients with pancreatic cancer had a history of cancer, it is advisable to determine germinal mutations for early detection of pancreatic neoplasia in patients without a history of cancer as well. It seems promising to identify "risk groups" for the development of pancreatic cancer, based not only on data on hereditary risks of pancreatic cancer, but followed by an analysis of germinal mutations as one of the factors for the development of pancreatic cancer. Our study is characterized by a small sample of patients, which certainly may limit the obtained results. Continuing to recruit patients to the study group, as well as conducting multicenter, randomized prospective studies, will help to obtain further results for determining the place of germinal mutations in the diagnosis of pancreatic cancer in patients at risk of developing this type of neoplasia.

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Moiseenko V.E. – information collection, statistical data processing, interpretation of work results, writing the text.

Kardanova I.G. – data processing, writing the article text, preparing the article for publication.

Pavlovsky A.V. – writing the text and critical review of its content.

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