e-ISSN 2544-1620

Medical Science Pulse 2020 (14) 1

Original papers

Published online: 31 Mar 2020

DOI: 10.5604/01.3001.0014.0779

ORGANIZATIONAL FORMS AND METHODS OF EARLY DIAGNOSIS OF HEREDITARY TUMORS

Aleh Kuzniatsou[1,2 A–F]
• ORCID: 0000-0002-1348-8688
Andrei Shpakou[1 A,B,E,F]
• ORCID: 0000-0003-4340-5211

[1] Yanka Kupala State University of Grodno, Grodno, Belarus
[2] University of Medical Sciences in Bialystok, Bialystok, Poland

A – study design, **B** – data collection, **C** – statistical analysis, **D** – interpretation of data, **E** – manuscript preparation, **F** – literature review, **G** – sourcing of funding

ABSTRACT

Background: With the development of genetic research in oncology, it has become possible to track and identify early and preclinical forms of hereditary oncological diseases, which allows timely and effective preventive and therapeutic measures in relation to relatives at risk.

Aim of the study: Assessment of genetically determined neoplasms in the region and the development of organizational forms and methods for early diagnosis.

Material and methods: 10,727 residents of the Belarus-Poland border region were examined. Clinical and medical history data of 2,054 patients with tumors of the breast (1406), ovaries (239), and colon (409) were analyzed. As a result of the questionnaire, three main observation groups were formed: "high risk of hereditary cancer", "hereditary cancer suspected", and "no risk of hereditary cancer".

Results: Register and hospital screenings were the most informative types of screening. Of the 149 HBC patients who underwent molecular genetic testing, BRCA1 gene mutations were found in 5.37%, 5382insC in all cases. Seven mutations were detected in 77 individuals with a diagnosis of HOC and in 6 cases 5382insC and in 2 – 4145delA. Signs of hereditary ovarian cancer and suspicion of it were found in 1.12%, including people who were found to have a high risk of hereditary ovarian cancer. By their effectiveness, register and hospital screenings significantly exceeded the population, $p<0.01$. 1.67% of women suffering from this disease met the high clinical risk criteria for hereditary ovarian cancer. A high clinical risk of hereditary tumor genesis was established in 0.73% of cases among patients with a diagnosis of colon cancer.

Conclusions: The results of assessing the clinical risk of hereditary cancer according to population screening indicates that approximately 1.2% of the population has an increased clinical risk of developing hereditary breast, ovarian, and colon cancer.

KEYWORDS: oncology, hereditary cancer, clinical risk, screening, risk, mutation, breast cancer, ovary cancer, colon cancer

Background

In connection with the development of genetic research in oncology, it has become possible to track and identify early and preclinical forms of hereditary oncological diseases, allowing timely and effective preventive and therapeutic measures in relation to relatives at risk. About 10% of diagnosed neoplasms are hereditarily determined and in the so-called "cancer families" up to 45% of relatives are affected by various forms of cancer [1–3].

The improper use of medical care for the timely detection and prevention of malignant neoplasms along with the lack of a scientifically based approach in the interaction of oncological and medico-genetic services amongst cancer patients is what led to this study [4,5].

Only half of blood relatives are carriers of mutations of a particular gene. However, the peculiarity of these genes is that they do not manifest themselves in any way before the onset of the tumor. Therefore, it is impossible to know in advance which family member is the carrier of the mutant gene and is predisposed to the development of cancer [6–9]. All members of such families have to be included in the high-risk group and subjected to expensive diagnostic tests. As a result, you may encounter a large number of healthy relatives with carcinophobia. This casts doubt on the need for unnecessary cardinal interventions, such as the currently used

prophylactic removal of the mammary glands in carriers of BRCA1 and BRCA2 [10–14]. At the same time, mammography self-monitoring and other diagnostic methods remain a prerequisite for early detection of cancer in the population [15].

After our experience with this contingent of the population, we recommend raising awareness and providing doctors, of both the oncological profile and the outpatient health department, about the role of the hereditary factor in the development of tumors of different localizations.

As we expand our knowledge about the problems of hereditary cancer, the medical community and health authorities are convinced of the need to introduce molecular genetic methods, into clinical practice. In particular for diagnosing hereditary predisposition to certain types of cancer and other forms of malignant neoplasms associated with the pathological BRCA1/2 genotype through the creation of hereditary tumor diagnostic centers. The main tasks are:

- hospital, population, and "register" screenings: compiling and studying pedigrees and identifying clinical signs of the presence of hereditary tumors among the population of the region;
- creation of a database for storing pedigrees obtained during population and hospital screenings and their analysis in order to calculate the risk of possible development of tumors in relatives of patients with cancer;
- dispensary registration: the organization and conduct of dispensary registration of relatives of cancer patients (first degree of kinship) for whom a high risk of tumors has been calculated (high risk group for the development of tumors);
- laboratory diagnostics: carrying out molecular genetic, immunological, and immunohistochemical studies in the case of a high probability of a hereditary predisposition;
- instrumental diagnostics: for the early diagnosis of tumors in groups of relatives with an increased oncological risk;
- educational and methodical work: with the aim of promoting knowledge and prevention.

Early detection of tumors is a very real goal, the achievement of which is seen in the screening of relatives of patients and "active monitoring" of patients with identified hereditary mutations. Patients who meet the criteria for hereditary cancer must be examined for mutations in the genes for the repair of tumor DNA [16–21].

Alternative methods of instrumental research can be magnetic resonance and computed spiral tomography for tumors of the mammary gland and ovaries and autofluorescence endoscopy and photodynamic diagnosis in combination with magnetic resonance imaging (MRI) for hereditary forms of colorectal cancer. Molecular genetic, immunological, and immunohistochemical methods are of great interest in the search for reliable criteria for the early diagnosis of cancer and its hereditary forms.

Aim of the study

The assessment of genetically determined neoplasms in the region and the development of organizational forms and methods for their early diagnosis.

Material and methods

Participants

A survey of 10,727 residents of the Belarus-Poland border region was conducted. The clinical and medical history of 2,054 patients with breast (1,406), ovarian (239 cases), and colon (409 cases) tumors was analyzed.

Study design

The study was conducted while the patient was seeking medical help in the clinic, during the treatment period in the hospital, or during preventive examinations. The survey contained questions to clarify the presence of cases of oncological pathology in the patient's family and the degree of kinship in the family [22]. As a result of the questionnaire, three main observation groups were formed: the group "at high risk of hereditary cancer", "hereditary cancer suspected", and "no risk of hereditary cancer". The distribution of probands was carried out according to three nosological forms of hereditary cancer tumors: breast (HBC), ovary (HOC), and colorectal cancer (HCC) (Tab. 1).

The main advantage of the system was its adaptability to the cancer register with the possibility of using register databases. The basis for identifying hereditary forms of oncological diseases is the screening method for examining the population; the results of which can be represented as:

- hospital screening: the study of the pedigree and the identification of clinical signs of the presence of hereditary tumors in people who seek medical help;
- screening of the register: based on the analysis of the data of the oncological register of patients whose tumors are highly likely to be associated with a hereditary predisposition, and surveys of their family members and relatives of the first and second level of kinship;
- population screening: questionnaire and genealogy of randomly selected individuals (visits to the clinic, to local doctors, home calls, etc.)

Statistical methods

The data obtained was analyzed statistically using Statistica v.10 software (Chi-squared test, Kruskal-Wallis test). The assumed level of significance was $p<0.05$.

Results

Of the 10,727 questionnaires, 762 individuals were selected based on the clinical risk of hereditary cancer. 47 respondents (0.44 ± 0.06%) had signs of high risk of

hereditary cancer and 715 (6.67 ± 0.24%) were assigned to the group "hereditary cancer suspected" (Tab. 2).

In 226 patients, 149 with a diagnosis of HBC and 77 with a diagnosis of HOC, venous blood was taken for molecular genetic (PCR method) studies for the presence of BRCA1 gene mutations (Exon 5382insC and 4145delA) [22].

The distribution of probands depending on the clinical risk of cancer and the type of screening study are presented in Tab. 3.

Table 1. Surveillance Groups ("high risk", "hereditary cancer suspected").

Clinical Risk Group	HBC or HOC	HCC
High Risk	– Three or more first-degree relatives suffer from HBC and/or HOC; – History of breast cancer in men present in the family; – HBC or HOC at any age in Ashkenazi Jewish women (Jewish, European)	– HCC or its associated tumors were diagnosed in 3 or more relatives of the 1st degree of kinship; – At least one relative under the age of 50 years
Hereditary Cancer Suspected	– HBC or HOC developed in a patient under the age of 40; – Two first-degree relatives suffer from HBC and/or HOC; – HBC or HOC in one patient present in family history; – A single case of HOC in a family history if the patient is from the genus Ashkenazi Jewish	– The presence of synchronous or metachronal colorectal cancer and associated tumors at any age; – The presence of pathological signs of high microsatellite instability (lymphocyte infiltration, Crohn's-like lymphocytic reaction, molecular growth pattern), established at 60 years of age; – HCC and associated tumors (cancer of the endometrium, stomach, ovaries, pancreas, etc.) diagnosed in at least one relative of the 1st degree of kinship under 50 years of age; – HCC or associated tumors diagnosed at any age in two relatives of 1st or 2nd degree of affinity

Table 2. Results of screening studies to identify among the population persons with clinical signs of hereditary forms of malignant neoplasms.

Clinical Risk Group	Nosological Form of Hereditary Cancer						Total	
	HBC		HOC		HCC			
	n	%	n	%	n	%	n	%
High Risk	32	0.30	7	0.065	8	0.07	47	0.44
Hereditary Cancer Suspected	461	4.60	113	1.05	141	1.31	715	6.67
Combination of Two Target Groups	493	4.60	120	1.12	149	1.39	762	7.10
No Risk of these Forms of Cancer	10,190	95.0	9,219	88.06	9446	88.06	9965	92.90
Total	10,727		10,727		10,727		10,727	

Table 3. Clinical risk assessment of hereditary breast cancer (HBC), hereditary ovarian cancer (HOC) and hereditary colorectal cancer (HCC) according to screening studies.

Clinical Risk Group	Type of Cancer	Type of Screening Study							
		Register		Hospital		Population		Total	
		n	%	n	%	n	%	n	%
High Risk	HBC	9	0.64±0.21	10	4.59±1.42	13	0.14±0.04	32	0.3±0.05
	HOC	4	1.67±0.83	3	3.13±1.78	0	0	7	0.07±0.03
	HCC	3	0.73±0.42	2	2.41±1.48	3	0.033±0.02	8	0.08±0.03
Hereditary Cancer Suspected	HBC	347	24.68±1.15	65	29.81±3.1	49	0.54±0.08	461	4.3±0.2
	HOC	82	34.31±3.07	24	25.0±4.42	7	0.077±0.03	113	1.05±0.1
	HCC	103	25.19±2.15	20	24.1±4.7	18	0.2±0.05	141	1.47±0.12
Combination of Two Target Groups	HBC	356	25.32±1.16	75	34.4±3.22	62	0.68±0.09	493	4.6±0.2
	HOC	86	36.0±3.1	27	28.13±4.59	7	0.077±0.03	120	1.12±0.1
	HCC	106	25.92±2.17	22	26.51±4.84	21	0.23±0.05	149	1.55±0.13
No Risk	HBC	1050	74.68±1.16	143	65.6±3.22	8997*	98.83±0.11	10190	95.0±0.21
	HOC	153	64.02±3.1	69	71.87±4.59	8997**	98.83±0.11	9219	85.9±0.34
	HCC	303	74.08±2.17	61	73.49±4.84	9082***	99.77±0.05	9446	98.4±0.13
Total	HBC	1406	100	218	100	9103*	100	10727	100
	HOC	239	100	96	100	9103**	100	10727	100
	HCC	409	100	83	100	9103***	100	9595	100

Note:
* included 36 cases of hereditary forms of cancer of a different localization and eight cases of "family congestion" which is classified as five or more episodes of cancer of different localization in three generations of the same family
** included 91 cases of hereditary forms of cancer of a different localization and eight cases of "family congestion"
*** included 36 cases of hereditary forms of cancer of a different localization and eight cases of "family congestion"

The most informative types of screening were register screening (25.32±1.16% of probands showed a high risk of HBC or suspected hereditary breast cancer) and hospital (34.4±3.22% of probands). In the population screening, only 0.68±0.11% of the respondents had a high risk of a hereditary breast tumor and/or suspicion of its development.

Of the 149 HBC patients who underwent molecular genetic testing, BRCA1 gene mutations were found in eight (5.37%), 5382insC in all cases. Among 77 examined with a diagnosis of HOC, mutations were detected in 7 people (9.09%), in 6 cases 5382insC, and in 2 - 4145delA (in 1 patient both mutations were found).

Out of 10,727 probands, signs of hereditary ovarian cancer and suspicion of it were found in only 120 people (1.12±0.1%), including 7 people who were found to have a high risk of hereditary ovarian cancer. By their effectiveness, register screening and hospital screening significantly ($p<0.01$) exceeded the population screening. 1.67% of women suffering from this disease met the high clinical risk criteria for hereditary ovarian cancer in the region's population. Among patients with a diagnosis of colon cancer, a high clinical risk of hereditary tumor genesis was established in 0.73% of cases.

When analyzing the relationship between the mutation frequency and the clinical risk group for hereditary cancer, it was found that, patients with a high risk of HBC and/or HOC, BRCA1 mutations were detected with the same frequency as in individuals with no clinical risk (Tab. 4).

Table 4. The results of molecular genetic analysis of patients with different clinical risks of hereditary ovarian and/or breast cancer.

Clinical Risk Group	Studies	Identified Patients with Mutations	%
High risk of hereditary breast cancer and/or ovarian cancer	28	2	7.14
Suspected hereditary breast cancer and/or ovarian cancer	90	5	5.55
No risk of hereditary breast cancer or ovarian cancer	108	8	7.41
Total	226	15	6.76

A low mutation rate was observed in the group with suspected hereditary HBC and/or HOC.

Discussion

The lack of a scientifically based approach in the interaction of oncological and medico-genetic services along with the lack of scientific work in this direction led to this study [4,5].

With the development of genetic research in oncology, it has become possible to track and identify early and preclinical forms of hereditary oncological diseases, which allows timely and effective preventive and therapeutic measures in relation to relatives at risk [1,2]. In "cancer families" up to 45% of relatives are affected by various forms of cancer [3]. 10% of diagnosed neoplasms are hereditarily determined.

Only half of blood relatives are carriers of mutations of a particular gene and the peculiarity of these genes is that they do not manifest themselves in any way before the onset of the tumor [6–8]. All members of such families have to be included in the high-risk group and subjected to expensive diagnostic tests. As a result, you may encounter a large number of healthy relatives with carcinophobia [9]. This casts doubt on the need for unnecessarily cardinal interventions, such as the currently used prophylactic removal of the mammary glands in carriers of BRCA1 and BRCA2 [10–14].

The expansion of knowledge about the problem of hereditary cancer convinces the medical community and health authorities of the need to introduce molecular genetic methods for diagnosing hereditary predisposition to certain types of cancer and other forms of malignant neoplasms associated with the pathological BRCA1/2 genotype through the creation of hereditary tumor diagnostic centers into clinical practice.

Early detection of tumors is a very real goal. This achievement is seen in the screening of relatives of patients and "active monitoring" of patients with identified hereditary mutations. Patients who meet the criteria for hereditary cancer must be examined for mutations in the genes for the repair of tumor DNA [16–21].

As a result of the studies, three main observation groups were formed: "at high risk of hereditary cancer" – "high risk", "hereditary cancer suspected", and "no risk of hereditary cancer". The distribution of probands was carried out according to three nosological forms of hereditary cancer tumors: breast (HBC), ovarian (HOC), and colorectal cancer (HCC).

The ability to obtain objective information about each proband and its family members from existing information databases and systems (a cancer registry, if available in the region), is crucial in identifying hereditary forms of the tumor, along with knowledge of the combination of the clinical and morphological characteristics of this syndrome and the information system of hereditary tumors (Patent of National Center for Intellectual Property of Belarus) [23].

In general, the results obtained are consistent with the data of European researchers, who established during hospital screening that 1.7% of patients diagnosed with breast cancer and 3.7% with a diagnosis of ovarian cancer meet the criteria for being assigned to the high clinical risk group as inherited breast cancer [2,24]. The frequency of hereditary colorectal cancer is 0.8% among the respondents while the suspicion of it is 1.47%. These results coincide quite accurately with the frequency of detection of mutations of the BRCA1 gene in cancer patients in Latvia, 3.7% for breast cancer and 10.7% for ovarian cancer [25]. With these results, it makes sense to propose the creation of special registers of hereditary tumors. This is possible both within the framework of territorial or hospital cancer registries with the introduction of the appropriate graphs, and within the framework of centers for the diagnosis of hereditary forms of cancer [26].

Conclusions

The results of assessing the clinical risk of hereditary cancer according to population screening indicate that approximately 1.2% of the population has an increased clinical risk of developing hereditary breast, ovarian, and colon cancer. During hospital screenings of patients whose diseases were first detected over the past two years, signs of a high clinical risk of hereditary cancer were detected in 4.5%.

Suspicion of the hereditary nature of cancer with the highest frequency (more than a third of the examined) was determined in the group of people with established ovarian cancer. Among those suffering from breast cancer and colorectal cancer, a quarter of the patients met the criteria for this clinical risk group.

The lack of a relationship between the degree of clinical risk determined by genealogy and the frequency of mutations of Exon 20 and Exon 11 of the BRCA1 gene most likely indicates that there are other genetic defects that play an etiological role in the development of HBC and/or HOC in the analyzed population. In order to identify these breakdowns, it seems appropriate to complete the sequencing of the BRCA1 gene in individuals with a high clinical risk of developing breast and/or ovarian cancer.

References

1. Aarnio M, Mecklin JP, Aaltonen LA, Nyström-Lahti M, Järvinen HJ. Life-time risk of different cancers in hereditary non-polyposis colorectal cancer (HNPCC) syndrome. Int J Cancer 1995 Dec 20; 64(6): 430–433.
2. Knerr S, West KM, Angelo FA. Organizational readiness to implement population-based screening and genetic service delivery for hereditary cancer prevention and control. J Genet Couns 2020 Jan 22. [Epub ahead of print].
3. Flaum N, Crosbie EJ, Edmondson RJ, Smith MJ, Evans DG. Epithelial ovarian cancer risk: a review of the current genetic landscape. Clin Genet 2020 Jan; 97(1): 54–63.
4. Kuznetcov OE, Gorchakova OV, Kuznetcova AA, Ianchevskii PN. Gruppy riska razvitiia nasledstvennykh opukholei tolstogo kishechnika. Materialy respublikanskoi s mezhdunarodnym uchastiem nauchno-prakticheskoi konferentcii, posviashchennoi 60-letiiu Grodnenskogo gosudarstvennogo meditcinskogo universiteta. Grodno: GrGMU; 2018: 451–454. (In Russian).
5. Thompson D, Easton DF, Breast Cancer Linkage Consortium. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002 Sep 18; 94(18): 1358–1365.
6. Narod SA, Feunteun J, Lynch HT, Watson P, Conway T, Lynch J, et al. Familial breast-ovarian cancer locus on chromosome 17q12-q23. Lancet 1991 Jul 13; 338(8759): 82–83.
7. Yamauchi H, Takei J. Management of hereditary breast and ovarian cancer. Int J Clin Oncol 2018 Feb; 23(1): 45–51.
8. Zheng G, Yu H, Kanerva A, Försti A, Sundquist K, Hemminki K. Familial ovarian cancer clusters with other cancers. Sci Rep 2018 Aug 1; 8(1): 11561.
9. Gori S, Barberis M, Bella MA, Buttitta F, Capoluongo E, Carrera P, et al. Recommendations for the implementation of BRCA testing in ovarian cancer patients and their relatives. Crit Rev Oncol Hematol 2019 Aug; 140: 67–72.
10. Bit-Sava EM, Belogurova MB. Hereditary breast cancer. Siberian journal of oncology 2013; 1(55): 75–81.
11. Mitelman F, Mertens F, Johansson B. A breakpoint map of recurrent chromosomal rearrangements in human neoplasia. Nat Genet 1997 Apr; 15 Spec No: 417–474.
12. Campacci N, de Campos Reis Galvão H, Garcia LF, Ribeiro PC, Grasel RS, Goldim JR, et al. Genetic cancer risk assessment: a screenshot of the psychosocial profile of women at risk for hereditary breast and ovarian cancer syndrome. Psychooncology 2020 Jan 26. [Epub ahead of print].
13. Pinsky PF. Recommendations related to genetic testing for breast cancer. JAMA. 2020 Jan 14; 323(2): 187–188.
14. Karamysheva TV, Matveeva VG, Shorina AR, Rubtsov NB. Clinical and molecular-cytogenetic analyses of a rare case of mosaicism for partial monosomy 3p and partial trisomy 10q in Man, Genetika (Moscow), 2001; 37(6): 811–816.
15. Burke W, Daly M, Garber J, Botkin J, Kahn MJ, Lynch P, et al. Recommendations for follow-up care of individuals with an inherited predisposition to cancer. II. BRCA1 and BRCA2. Cancer Genetics Studies Consortium. JAMA 1997 Mar 26; 277(12): 997–1003.
16. Yang S, Axilbund JE, O'leary E, Michalski ST, Evans R, Lincoln SE, et al. Underdiagnosis of hereditary breast and ovarian cancer in medicare patients: genetic testing criteria miss the mark. Ann Surg Oncol 2018 Oct; 25(10): 2925–2931.
17. Abul-Husn NS, Soper ER, Odgis JA, Cullina S, Bobo D, Moscati A, et al. Exome sequencing reveals a high prevalence of BRCA1 and BRCA2 founder variants in a diverse population-based biobank. Genome Med 2019 Dec 31; 12(1): 2.
18. Lynch HT, Smyrk T, Lynch JF. Molecular genetics and clinical-pathological features of hereditary nonpolyposis colorectal carcinoma (Lynch syndrome): historical journey from pedigree anecdote to molecular genetic confirmation. Oncology 1998 Mar-Apr; 55(2): 103–108.
19. Narod SA, Ford D, Devilee P, Barkardottir RB, Lynch HT, Smith SA, et al. An evaluation of genetic heterogeneity in 145 breast-ovarian cancer families. Breast Cancer Linkage Consortium. Am J Hum Genet 1995 Jan; 56(1): 254–264.
20. Olsen JH, Seersholm N, Boice JD, Krüger Kjær S, Fraumeni Jr JF. Cancer risk in close relatives of women with early-onset breast cancer – a population-based incidence study. Br J Cancer 1999 Feb; 79(3–4): 673–679.
21. Sachidanandam R, Weissman D, Schmidt SC, Kakol JM, Stein LD, Marth G, et al. A map of human genome sequence variation containing 1.42 million single nucleotide polymorphisms. Nature 2001 Feb 15; 409(6822): 928–933.
22. Struewing JP, Hartge P, Wacholder S, Baker SM, Berlin M, McAdams M, et al. The risk of cancer associated with specific mutations of BRCA1 and BRCA2 among Ashkenazi Jews. N Engl J Med 1997 May 15; 336(20): 1401–1408.
23. Informatcionnaia sistema ucheta i monitoringa onkologicheskikh zabolevanii: pat. No 675 Resp. Belarus O.E. Kuznetcov; zaiavitel Kuznetcov O.E. – S20140041; opubl.

20.06.2014 Afitcyiny biul. Natc. tcentr intelektual. Ulasnastci. (In Russian).
24. Rojas K, Stuckey A. Breast cancer epidemiology and risk factors. Clin Obstet Gynecol 2016 Dec; 59(4): 651–672.
25. Gardovski A. Clinical and molecular features of hereditary breast and ovarian cancer in Latvia. Riga: P. Stradin University; 2008.
26. Rodriguez-Bigas MA, Boland CR, Hamilton SR, Henson DE, Jass JR, Khan PM, et al. A national cancer institute workshop on hereditary nonpolyposis colorectal cancer syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997 Dec 3; 89(23): 1758–1762.

Word count: 2740 • Tables: 4 • Figures: – • References: 26

Sources of funding:
The research was funded by the authors.

Conflicts of interests:
The authors report that there were no conflicts of interest.

Cite this article as:
Kuzniatsou A, Shpakou A.
Organizational forms and methods of early diagnosis of hereditary tumors.
MSP 2020; 14, 1: 15–20. Published online: 31 Mar 2020.

Correspondence address:
Andrei Shpakou PhD, MD
Yanka Kupala State University of Grodno
Belarus, Grodno, 230023, 22 Ozheshko str.
E-mail: shpakofff@tut.by

Received: 20.03.2020
Reviewed: 26.03.2020
Accepted: 26.03.2020