REVIEW

Editorial Process: Submission:10/31/2023 Acceptance:06/14/2024

A Systematic Review of the Prevalence of Germline *BRCA* mutations in North Asia Breast Cancer Patients

Polina Gervas[1,2]*, Molokov Yu Aleksey[1], Babyshkina N Nataliya[1], Olesya Kollantay[1], Choynzonov L Evgeny[1], Nadezda V Cherdyntseva[1,2]

Abstract

Objective: The *BRCA1/2* mutation status testing is the global standard of care for breast cancer patients with a family history of cancer. *BRCA1/2* mutations are known to be ethno-specific. For some ethnic groups of the Northern Asia (Buryats, Yakuts, Altaians, Tuvans, Khakasses, etc.) the founder mutations in the *BRCA1/2* genes have not been revealed. This systematic review was conducted to assess the prevalence of *BRCA1/2* mutation in breast cancer patients inhabiting Eastern Europe and Northern Asia (or Siberia). **Methods:** A total of 23,561 studies published between 2014 and 2024 were analyzed, of which 55 were included in the review. The literature search was conducted using RusMed, Cyberleninka, Google Scholar, eLibrary, NCBI databases (n=5) and conference papers. **Results:** The founder mutations (c.5266dupC and/or c.181T>G) of *BRCA1* gene that were frequently observed in the Slav peoples were also identified in Chechens, Armenians, Bashkirs, Ukrainians, Mordovians, Mari, Kabardians, Tatars, Uzbeks, Kyrgyz, Ossetians, Khanty indigenous peoples and Adygs. For Chechens, Kabardians, Ingush, Buryats, Khakasses, Sakha, Tuvans and Armenians, rare pathogenic variants of the *BRCA1/2*, *ATM, CHEK2, BRIP1, NBN, PTEN, TP53, PMS1, XPA, LGR4, BRWD1* and *PALB2* genes were found. No data are available about the frequency of pathogenic *BRCA1/2* mutations for ethnic groups, such as the Udmurts, Komi, Tajiks, Tabasarans, and Nogais indigenous people. **Conclusion:** This is the first systematic review that provides the spectrum of BRCA mutations in ethnic groups of breast cancer patients inhabiting Eastern Europe and Northern Asia. It has been shown that the mutations are ethnospecific (varied widely within groups) and not all groups are equally well studied. Further studies on the ethnic specificity of BRCA gene mutations are required.

Keywords: *BRCA*- germline variant- indigenous peoples- ethnic groups- hereditary breast cancer

Asian Pac J Cancer Prev, **25 (6)**, 1891-1902

Introduction

Globally, more than two million cases of breast cancer (BC) are diagnosed annually [1]. Up to 10% of all BC cases are caused by accumulation of *BRCA1/2* mutations, which increase the risk of developing BC to 99% [2]. There are significant differences in the type and frequency of *BRCA1/2* mutations depending on the geographical region and race/ethnicity.

BRCA1 and BRCA2 mutations across race and ethnicity

For some racial/ethnic groups, the founder mutations, such as the Ashkenazi Jews variant *BRCA1* c.5266dup (5382insC), BRCA1 c.68_69del (185delAG) and BRCA2 c.5946del (6174delT); the Icelandic founder variant BRCA2 c.771_775del (999del5); the French Canadian variant BRCA1 c.4327C>T (C4446T), BRCA2 c.8537_8538del (8765delAG); the BRCA1 variant c.181T>G, and c.4034delA in Central-Eastern Europe; the *BRCA1* c.548-4185del in Mexico; the *BRCA2* variant c.9097dup in Hungary and others, were identified. The mutations listed above represent the majority of mutations observed in these populations [3, 4]. Recurrent mutations have been identified in other populations, but they have not been characterized as true founder mutations (Scandinavian, Dutch, French, Italian, Hispanic/Mexican, African-American, Middle Eastern, and Asian populations) [3].

Eight founder variants (*BRCA1* 185delAG, 4153delA, 5382insC, 3819delGTAAA, 3875delGTCT, 300T>G (Cys61Gly), 2080delA, and BRCA2 6174delT) have been found for the Slavic ethnic group (Russian Federation). The *BRCA1* 5382insC variant accounts for up to 90% of all *BRCA1* gene mutations in BC patients regardless of the region of their residence [2]. However, the molecular factors that determine the hereditary BC risk in the

[1]Department of Cancer Research, Cancer Research Institute Tomsk, National Research Medical Center, Russian Academy of Science, Tomsk, Russia. [2]Department of Physical and Colloid Chemistry, National Tomsk State University, Tomsk, Russia. *For Correspondence: gervaspa@oncology.tomsk.ru

indigenous population of Siberia (Northern Asia, Russian Federation) remain poorly understood.

Indigenous peoples in Northern Asia (or Siberia)

BC is the most common malignancy among women in the transcontinental region, spanning Eastern Europe and Northern Asia (or Siberia). According to the 2010 census, more than 80 ethnic groups live in Eastern Europe and Northern Asia (or Siberia). The largest minorities include Tatars, Belarusians, Ukrainians, Bashkirs, Chuvashs, Chechens, and Armenians. The Kazakhs, Yakuts, Buryats, Ingush, Udmurts, Ossetians, etc. make up about 0.5% of the population (Table 1 and Figure 1) [5, 6].

Siberia is a geographical area that includes all of North Asia, from the Ural Mountains in the west to the Pacific Ocean in the east and covers an area of at least 13,100,000 km^2 [7]. Northern Asia is one of the largest regions in Asia, while simultaneously being the least populated region. In 2020, the highest BC incidence was observed in Northern Asia (Siberia) among the Buryats (42.50 cases per 100,000 population), and Khakasses (42.26cases per 100,000), while the lowest among Tuvans (26.49 cases per 100,000), Yakuts (27.84 cases per 100,000) and Altaians (29.61 cases per 100,000). The highest mortality was observed in Buryats (13.18 deaths per 100,000), Khakasses (10.89 deaths per 100,000) and Tuvans (10.06 deaths per 100,000), while the lowest one was observed in Yakuts (6.94 cases per 100,000), and Altaians (7.06 deaths per 100,000 population) [8].

A minority of the current population are descendants mainly of Mongol (Buryats) or Turkic indigenous people (Yakuts, Tuvans, Altaians, Tatars and Khakasses) and northern indigenous people (Samodeic people, Finno-Ugric peoples and others). Historically, the indigenous peoples of Siberia (Buryats, Tuvans, Altaians) live also in Mongolia, China and other countries. For example, Yakuts live also in Kazakhstan, Ukraine, Belarus, Kyrgyzstan, Latvia, Estonia and other countries. The Buryats live in China in the historical region of Barga (Inner Mongolia). The Tuvans live in China in Xinjiang Autonomous Region. The Altai people live in the Mongolia (the Mongolian Altai Mountains), in China (Altai Prefecture, northern Xinjiang) and in Kazakhstan [9–13].

Given recent achievements in the management of patients with *BRCA1/2* mutations in breast cancer (PARPi) it is important that worldwide healthcare providers and decision makers are kept informed about of *BRCA1/2* mutations ethnospecificity. Further research into the ethnic specificity of *BRCA1/2* gene mutations will allow more patients with *BRCA1/2* mutations around the world to receive the correct treatment. In this systematic review, we summarize the data on the spectrum of BC-associated gene mutations in ethnic groups of Siberia or Northern Asia, mainly focusing on mutation testing in different ethnic groups.

Materials and Methods

This systematic review was conducted in accordance with PRISMA guidelines (the Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [14]. A range of electronic databases was searched (N=5), including RusMed, Cyberleninka, Google Scholar, eLIBRARY.RU, and NCBI db PubMed. Searches of conference abstracts were also conducted. Details of resources and strategies used are available in the Supplement (Appendix 1).

This manuscript includes studies reporting on the prevalence of germline BRCA mutations in BC patients. The prevalence of any mutation was included regardless of whether the mutation was a founder mutation or not. Study inclusion was not limited by language. Only data that were available and reported from 2014 to 2024 were eligible for inclusion. Data from the included studies were extracted, stored, and analyzed. Studies were grouped by

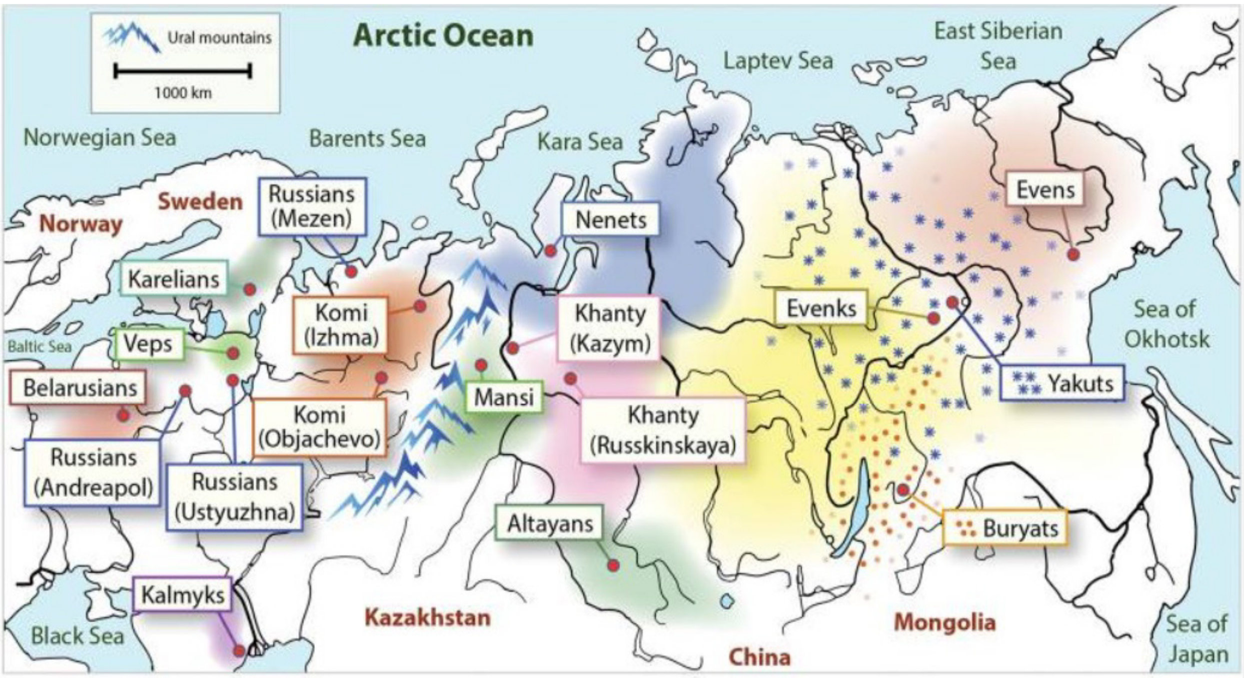

Figure 1. Map of Siberia and Eastern Europe, Genome Res. 2017;27:1-14. [5]

ethnic groups inhabiting Eastern Europe and Northern Asia. Data were highlighted and discussed separately for subgroups of patients that were of particular interest.

Results

Study selection

A total of 23,561 papers and abstracts were retrieved from the literature searches and background papers, and systematic reviews. From these, full papers were obtained for 55 citations. After further review, 13 papers were excluded (Supplement, Appendix 2). A summary of the study selection process is reported in Figure 2.

The spectrum of pathogenic variants in the BC genes in ethnic groups inhabiting Eastern Europe and Northern Asia

The existence of ethno-specific mutations is well established. Here, we report detailed information from some studies (Tables 2 and 3). According to the literature data, the molecular features of BC in 32 ethnic groups inhabiting Eastern Europe and Northern Asia were studied [15–56]. The founder mutations (c.5266dupC and/or c.181T>G) of *BRCA1* gene that were frequently observed in the Slav peoples were also identified in Chechens, Armenians, Bashkirs, Ukrainians, Mordovians, Mari, Kabardians, Tatars, Uzbeks, Kyrgyz, Ossetians, Khanty and Adygs. For Chechens, Kabardians, Ingush, Buryats, Khakasses, Sakha, Tuvans and Armenians, rare pathogenic variants of the *BRCA1/2*, *ATM, CHEK2, BRIP1, NBN, PTEN, TP53, PMS1, XPA, LGR4, BRWD1* and *PALB2* genes were found. No data are available about the frequency of pathogenic *BRCA1/2* mutations for ethnic groups, such as Udmurts, Komi, Tajiks, Tabasarans, Turks, and Nogais indigenous people.

In ethnic groups of Siberia, the founder variants of *BRCA1/2* gene, that were observed in Slav, were identified in Khanty (*BRCA1* 5382insC), Tuvans (*BRCA2* c.3875_3878delGTCT) and Khakasses (*BRCA1* gene c.T40G). For Tuvans rare variant of the *BRCA2* gene (c.8208_8209insAG) was found. No pathogenic *BRCA1/2* mutations were found in Buryats, Altaians, and Yakuts, probably due to the small sample size for the studied groups.

Rare pathogenic mutations of *BRCA2, RAD51D, ATM* genes that were previously found in Asians, were found in the ethnic groups of Siberia. The pathogenic variant of *BRCA2* gene (c.8208_8209insAG, p.Leu2737Serfs*2, rs483353122) was observed in young Tuvan BC patients. The frameshift variant (c.8208_8209insAG, p.Leu2737Serfs*2, rs483353122), which was previously mentioned in the dbSNP, was also identified as germline in the Chinese population of the Hksar geographic origin. The pathogenic variant of *RAD51D* gene (rs137886232) was observed in young Buryat BC patients. The rs137886232 variant was identified as a founder mutation in Chinese population [57]. Loveday C. et al. [58] indicated that RAD51D -deficient tumor cells were found to be sensitive to PARP inhibitors, suggesting a possible therapeutic approach for the anti-cancer treatment of RAD51D variant carriers [58]. The germline pathogenic variant of the *ATM* gene was identified (rs780619951, NC_000011.10:g.108259022C>T) in a Khakass BC patient with a family history of cancer. The pathogenic truncating variant in the *ATM* gene (p. R805* or c.2413C>T) leads to nonfunctional version of the protein. The pathogenic variant of the PTEN gene (rs786201044) was described in a young Buryat BC patient. This mutation affects the protein-tyrosine phosphatase-like domain and is associated with Cowden syndrome [44, 59–61].

The spectrum of germline variants (conflicting or uncertain significance) in the BC-related genes among the ethnic groups inhabiting Eastern Europe and Northern Asia

There are many reports pointing to the need for a more thorough study of the clinical significance of germline variants (conflicting or uncertain significance)

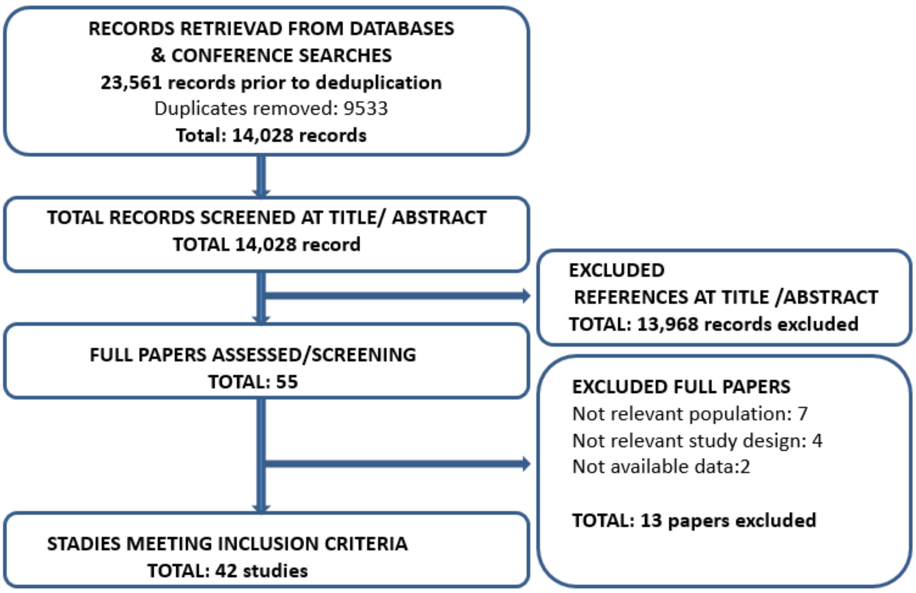

Figure 2. Flow Chart Detailing Literature Searches and Inclusion Screening

Table 1. The Largest Minorities Live in Eastern Europe and Northern Asia

No	Ethnic groups	Number	%
1	Tatars	5,310,649	3.72%
2	Ukrainians	1,927,988	1.35%
3	Bashkir	1,584,554	1.11%
4	Chuvashs	1,435,872	1.01%
5	Chechens	1,431,360	1.00%
6	Armenians	1,182,388	0.83%
7	Avars	912,090	0.64%
8	Mordvins	744,237	0.52%
9	Kazakhs	647,732	0.45%
10	Azerbaijanis	603,070	0.42%
11	Dargins	589,386	0.41%
12	Udmurts	552,299	0.39%
13	Mari	547,605	0.38%
14	Ossetians	528,515	0.37%
15	Belarusians	521,443	0.37%
16	Kabardins	516,826	0.36%
17	Kumyks	503,060	0.35%
18	Yakuts	478,085	0.34%
19	Lezgians	473,722	0.33%
20	Buryats	461,389	0.32%
21	Ingush	444,833	0.31%
22	Germans	394,138	0.28%
23	Uzbeks	289,862	0.20%
24	Tuvans	263,934	0.19%
25	Komi	228,235	0.16%
26	Karachays	218,403	0.15%
27	Roma	204,958	0.14%
28	Tajiks	200,303	0.14%
29	Kalmyks	183,372	0.13%
30	Laks	178,630	0.13%
31	Georgians	157,803	0.11%
32	Jews	156,801	0.11%
33	Moldovans	156,400	0.11%
34	Koreans	153,156	0.11%
35	Tabasarans	146,360	0.10%
36	Adyghe	124,835	0.09%
37	Balkars	112,924	0.08%
38	Turks	105,058	0.07%
39	Nogais	103,660	0.07%
40	Kyrgyz	103,422	0.07%

as risk modifiers for developing BC. They are classified into the following categories: missense, synonymous, nonsense, deletion, insertion, and InDels. The list of the most important germline variants in ethnic groups inhabiting Eastern Europe and Northern Asia introduced in Tables 2 and 3. Some authors have found that germline variants of the genes such as cyclin-dependent kinase 12 and folate cycle gene are involved in the pathogenesis of BC. Bogdanova N et al. [42] revealed the c.1047-2A>G splice acceptor variant of the *CDK12* gene (cyclin-dependent kinase 12) in Tatars with BC incidence of 7.6% [42]. *CDK12* demonstrated to specifically up regulate the expression of genes involved in response to DNA damage [62]. Akilzhanova A., et al. (2008) found that rs1801133 (677C>T) of the *MTHFR* (methylenetetrahydrofolate reductase) gene was involved in the development of hereditary BC in Kazakhs [34]. A reduced activity of MTHFR (methylenetetrahydrofolate reductase) due to C677T variant affects DNA synthesis, repair and methylation and may be involved in BC risk [63].

According to the PubMed ClinVar database, the variants of conflicting significance were found in the ethnic groups of Northern Asia (or Siberia). For example, variants of conflicting significance of the *PALB2* and *TP53* genes were described in the Yakuts and Tuvans, respectively [54, 56]. A never-before-reported variant in the *PALB2* gene (frameshift deletion, NM_024675:exon1:c.47delA:p.K16fs) was described in a young BC Yakut woman with a family history of pancreatic cancer. In accordance with db PubMed ClinVar, a new variant is located in codon of the *PALB2* gene, where the likely pathogenic donor splice site variant (NM_024675.3:c.48+1delG) associated with hereditary cancer-predisposing syndrome has been earlier described. The variant of the *TP53* gene (LRg_321t1: c.80C>T, rs397516438) was found in a young Tuvinian woman with a family history of BC. In accordance with ProteinPaint tool, the lRg_321t1: c.80 C>T mutation is located in codon of the TP53 gene, where the pathogenic mutation associated with Li-Fraumeni syndrome has been earlier described. Conflicting variants of *MUTYH, ATM, RAD51D* genes that were previously found in Chinese populations were found in Buryats, Khakasses and Tuvans [55]. Further research into the genetic variants of BC-associated genes is required to bring us closer to understanding the pathogenesis of hereditary BC in ethnic groups of the Eastern Europe and Northern Asia.

Discussion

Although the mortality rates have declined in developed countries, hereditary reproductive system cancer remains socially significant and requires improved approaches to prevention, early detection, and effective therapy. Mutations in the *BRCA1/2* genes lead to the loss of function of the proteins encoded by these genes, as well as disruption of the major DNA double-strand breakage repair mechanism [2, 4]. Curation technologies based on the data about the presence of *BRCA1/2* gene mutations have currently been developed for BC patients. The presence of *BRCA1/2* mutations makes it possible to assess the BC risk in healthy mutation carriers, as well as improve the existing approaches to prevention (prophylactic mastectomy), early detection of BC and making an accurate diagnosis [64]. The importance of the *BRCA1/2* status has increased manifold with the advent of *PARP* inhibitors, a group of targeted antitumor drugs blocking poly(ADP-ribose) polymerase enzymes (PARP) and participating in the repair of damaged DNA in BC patients. A total of 72.5–73.2% of patients with BC and *BRCA* mutations respond to PARP inhibition therapy [65].

Table 2. Germline variants in *BRCA1/2* and Others Genes that were Found in Ethnic Groups Inhabiting Eastern Europe (excluding Northern Asia or Siberia)

Ethnic groups	Pathogenic variants			Non-pathogenic variants			Reference
	Gene	Lokus	dbSNP	Gene	Lokus	dbSNP	
Adygs	*BRCA1*	c.5266dupC	rs80357906	Not found			[15]
Armenians	*BRCA1*	c.1059G>A	rs80356935	*ATM*	c.3371A>T	rs876660498	[16-19]
		c.181T>G	rs28897672		c.7503T>A	rs1591161664	
		c.211A>G	rs80357382	*BRCA1*	c.4589A>G	-	
		c.302-1G>A	rs80358116		c.4680delC	-	
		c.798_799del	rs80357724		c.5191G>A	rs397507244	
		c.1504_1508delTTAAA	rs80357888		c.5360G>A	rs1597801649	
		c.2649_2650insGGCA	rs886038003	*BRCA2*	c.8699A>T	rs398122712	
		c.3436_3439delTGTT	rs397509067	*CHEK2*	c.1312G>T	rs200050883	
		c.3477_3480delAAAG	rs80357781		c.480A>G	rs575910805	
		c.3485delA	rs80357509	*FANCB*	c.1480A>G	rs1601985311	
		c.4065_4068delTCAA	rs80357508	*FANCI*	c.3812C>T	rs202066338	
		c.5153–1G>C	rs80358137	*MC1R*	c.104G>A	rs779504604	
		c.5444G>A	rs80356962	*MLH1*	c.954C>A	rs146777069	
	BRCA2	c.574dupA	rs397507802	*MSH6*	c.3727A>T	rs147453999	
		c.1414C>T	rs80358429	*PALB2*	c.2821A>G	rs778602038	
		c.1528G>T	rs80358438		c.3428T>A	rs62625284	
		c.2095C>T	rs878853559				
		c.2808_2811delACAA	rs80359351				
		c.3847_3848delGT	rs80359405				
		c.4037_4038delCT	rs80359421				
		c.4631dupA	rs80359460				
		c.4548_4549delCA	rs1064793413				
		c.4965C>A	rs80358721				
		c.5006T>G	rs1555284032				
		c.5722_5723delCT	rs80359530				
		c.5845delG	-				
		c.6302delA	rs397507839				
		c.7689delC	rs80359674				
		c.7721G>A	rs80358997				
		c.7879A>T	rs80359014				
		c.8437G>T	rs2137597605				
		c.9027delT	rs80359742				
		c.9097dupA	rs397507419				
		c.9253delA	rs80359752				
	BRIP	c.917dupA	rs1555609121				
	CHEK2	c.409C>T	rs730881701				
	NBN	c.1502G>A	rs1554558472				
	PALB2	c.932_933insC	rs1060502772				
		c.3299_3306dupCTCTCAGC	rs1555458187				
Azerbaijanis	*BRCA1*	c.5266dupC	rs80357906	Not found			[20]
		c.68_69delAG	rs80357914				
		c.4035delA	rs80357711				
	BRCA2	c.5946delT	rs80359550				
Avars	*BRCA1*	c.115T>C	rs80357164	Not found			[21]
		c.5266dupC	rs80357906				
	BRCA2	c.5621_5624delTTAA	rs80359526				
		c.7976G>A	rs80359027				
		c.9895C>T	rs1555289997				
Balkars	*BRCA2*	c.7868A>G	rs80359012				[21]
Bashkirs	*BRCA1*	c.117T>G	rs886040898	Not found			[22-25]
		c.5266dupC	rs80357906				
		c.4035delA	rs80357711				

Table 2. Continued

Ethnic groups	Pathogenic variants			Non-pathogenic variants			Reference
	Gene	Lokus	dbSNP	Gene	Lokus	dbSNP	
Bashkirs	*BRCA1*	c.181T>G	rs28897672				
		c.1918C>T	rs886039981				
		c.3143delG	rs886040100				
		c.3700_3704del	rs80357609				
		c.3743_3752del	-				
		c.3779T>G	rs886038025				
		c.4810C>T	rs80357352				
		c.5161C>T	rs878854957				
		c.5453A>G	rs80357477				
		c.68_69delAG	rs80357914				
		c.814G>T	rs886040321				
		c.1291_1295delTTACT	-				
	BRCA2	c.-39-1_-39del	rs758732038				
		c.2990T>G	rs397507649				
		c.3847_3848delGT	rs80359405				
		c.51_52delAC	rs80359483				
		c.5156A>T	rs1179768667				
		c.8021delA	rs397507952				
		c.8023A>G	rs397507954				
		c.8754+1G>A	rs397508006				
		c.9097delA	rs397507419				
		c.1287delA	-				
		c.728delA	-				
		c.9463_9464insG	-				
Belarusians	*BRCA1*	c.5266dupC	rs80357906	Not found			[26]
		c.4035delA	rs80357711				
Chechens	*ATM*	c.3511C>T	rs876659067	BRCA1	c.3320A>G	rs1597864403	[21;28]
	BRCA1	c.5266dupC	rs80357906.	BRCA2	c.1714G>A	rs587782713	
		c.1338_1339delAG	-.		c.5860A>G	rs1566233345	
		3748delAG	rs80357589.				
		c.5296delA	-				
		c.5153-2A>G	rs786202545				
		c.3629_3630delAG	rs80357589				
		c.9895C>T	rs1555289997				
		c.5296delA	-				
	BRCA2	c.9895C>T	rs1555289997				
		c.5351dupA	rs80359507.				
		c.7408_7409delTT	rs397507915.				
		c.9117G>A	rs28897756				
		c.7407_7408delTT	rs397507915				
Cherkess	*BRCA2*	c.6998dupT	rs754611265	Not found			[21]
Chuvashi	*BRCA1*	c.5266dupC	rs80357906	Not found			[22-23;29]
		c.4035delA	rs80357711				
	BRCA2	c.8754+1G>A	rs397508006				
Crimean Tatars	*BRCA1*	c.5266dupC	rs80357906	Not found			[30]
		c.4035delA	rs80357711				
		c.68_69delAG	rs80357914				
	BRCA2	c.5946delT	rs80359550				
Dargins	*BRCA1*	c.115T>C	rs80357164	Not found			[21]
	BRCA2	c.7806-1G>C	rs81002860				
Ingush	*ATM*	c.1673delG	-	Not found			[21]
	BRCA1	c.5266dupC	rs80357906				
	BRCA2	c.5057T>G	-				

Table 2. Continued

Ethnic groups	Pathogenic variants			Non-pathogenic variants			Reference
	Gene	Lokus	dbSNP	Gene	Lokus	dbSNP	
Ingush	*BRCA2*	c.5351dupA	rs80359507				
		c.7407_7408delTT	rs397507915				
	PALB2	c.2218C>T	rs1555460445				
Kabardini	*ATM*	c.8876_8879delACTG	rs786204726	Not found			[21;31-33]
	BRCA1	c.1961delA	rs80357522				
		c.4035delA	rs80357711				
		c.4205delA	-				
		c.5266dupC	rs80357906				
	BRCA2	c.429delT	rs587781945				
		c.5946delT	rs80359550				
		c.6482_6485delACAA	rs80359598				
		c.7868A>G	rs80359012				
		c.8009C>A	rs80359027				
		c.8437G>T	rs2137597605				
		c.993_994delAA	rs80359777				
Karachays	*BRCA1*	c.2907_2910delTAAA	-	Not found			[21]
	BRCA2	c.6998dupT	rs754611265				
Kazakhs	*BRCA1*	c.5266dupC	rs80357906	*MTHFR*	c.665C>T	rs1801133	[34-36]
		c.5278-2delA	rs878853285				
		c.2T>C	rs80357111				
		c.2498del	-				
	BRCA2	c.9409dupA	-				
		c.9253delA	rs80359752				
	PALB2	c.1034T>G	rs781757934				
		c.18_22del	-				
	TP53	c.154C>T	rs2151042795				
	XPA	c.20del	rs2131411756				
	PMS1	c.1258del	-				
Kumyks	*BRCA2*	c.9895C>T	rs1555289997	Not found			[21]
		c.7806-1G>C	rs81002860				
Kyrgyzi	*BRCA1*	c.5266dupC	rs80357906	*HMMR*	c.1106T>C	rs299290	[37-39]
		c.68_69delAG	rs80357914	*TP53*	c.215C>G	rs104252	
		c.4035delA	rs80357711	*XRCC1*	c.1196A>G	rs25487	
		c.181T>G	rs28897672		c.580C>T	rs1799782	
		c.1954delA	rs80357522	*HMMR*	c.1106T>C	rs299290	
				MDM2	c.14+309T>G	rs2279744	
				PALB2	c.3306T>G	rs45516100	
Laks	*BRCA2*	c.429delT	rs587781945	Not found			[21]
Lezgins	*BRCA1*	c.66dupA	rs80357783	Not found			[21]
Mari	*BRCA1*	c.5266dupC	rs80357906	Not found			[22-23]
Mordva	*BRCA1*	c.5266dupC	rs80357906	Not found			[22-23]
Ossetians	*BRCA1*	c.5266dupC	rs80357906	Not found			[21]
	BRCA2	c.2808_2811delACAA	rs80359351				
		c.6341delC	-				
		c.9895C>T	rs1555289997				
Tatars	*BRCA1*	c.5161C>T	rs878854957	*CDK12*	c.1047-2A>G	-	[22-24]; [40-42]
		c.5266dupC	rs80357906				
		c.181T>G	rs28897672				
		c.915T>A	rs2154485509				
	BRCA2	c.7544C>T	rs28897744				
		c.468dupT	rs1555280955				
	CHEK2	del5395	-				

Table 2. Continued

Ethnic groups	Pathogenic variants			Non-pathogenic variants			Reference
	Gene	Lokus	dbSNP	Gene	Lokus	dbSNP	
Ukrainians	*BRCA1*	c.5266dupC	rs80357906	Not found			[22-23]
		c.403delA	rs80357711				
	CHEK2	c.1100delC	rs555607708				
		c.444+1G>A	rs121908698				
		del5395	-				
		c.470T>C	rs17879961				
		c.433C>T	rs137853007				
Uzbeki	*BRCA1*	c.5266dupC	rs80357906	Not found			[43]

Table 3. Germline Variants in *BRCA1/2* and Other Genes that were Found in Ethnic Groups of Nothern Asian (or Siberia)

Ethnic groups	Pathogenic variants			Non-pathogenic variants			Reference
	Gene	Lokus	dbSNP	Gene	Lokus	dbSNP	
Altaians	*RAD54L*	c.1018del	-	Not found			[44-45;46]
Buryats	*RAD51D*	c.421C>T	rs137886232	*MUTYH*	c.1034C>T	rs35352891	[44;48]
	PTEN	c.406T>C	rs786201044				
Khakasses	*ATM*	c.2413C>T	rs780619951	Not found			[49]
Khanty	*BRCA1*	c.5266dupC	rs80357906	Not found			[50]
Sakha (Yakutian)	Not found			*MUTYH*	c.796C>T	rs199840380	[51-54]
					c.C817T	-	
				PALB2	c.47delA	-	
Tuvans	*BRCA1*	c.3756_3759delGTCT	rs80357868	*ATM*	c.737A>G	rs781023264	[46; 55-56]
	BRCA2	c.8208_8209insAG	rs483353122	*MUTYH*	c.796C>T	rs199840380	
	BRWD1	c.5573A>T	rs147211854	*RAD51D*	c.992T>A	rs145309168	
	LGR4	c.2531A>G	rs34804482	*TP53*	c.80C>T	rs1555526933	

Over the recent decades, BC has been the most common malignancy in the Eastern Europe and Northern Asia. The population is primarily descended from newcomers (Slavs) and indigenous population (Asian peoples). More than 13.8 million women inhabit these regions. More than 45 ethnic groups live in Northern Asia (Buryats, Evenks, Altaians, Tuvans, and Khakasses). The incidence of BC among the newcomers is significantly higher than that among the indigenous peoples. The indigenous population has an earlier age of disease onset, and the peak incidence occurs almost 10 years earlier than that for the newcomers. Previous studies have shown that the indigenous peoples of Siberia have short stature, the brachymorphic body type, a high degree of muscle and bone components with a slight development of adipose tissue, a later onset of biological maturity and an early onset of menopause. Moreover, body mass index (grade I-II obesity are classified as a risk for the BC) is significantly lower among the indigenous women (25.6 ± 0.4 kg/m^2) than among newcomers ($p = 0.015$) [66]. For the indigenous population of Eastern Europe and Northern Asia, molecular factors determining the risk of developing hereditary BC remain poorly understood.

BC-associated mutation testing in the ethnic groups all over the world is challenging: 1) in some medical centers collecting information on race and ethnicity during *BRCA1/2* mutation testing is forbidden; 2) populations of non-white ancestry are still underrepresented in studies of genes associated with BC; 3) genetic testing in the developing countries remains insufficient [3]. For the ethnic groups of Siberia, the problems of testing for mutations in genes involved in BC pathogenesis are presented below.

First, *BRCA1/2* mutation testing is carried out without taking into account the origin of BC patients. In order to identify the molecular abnormalities responsible for the genetic predisposition to BC in various ethnic groups, it is necessary at least to take into account the challenges, such as the ethnic diversity (more than 200 ethnic groups), demographic situation and special climatic and geographic conditions.

Second, for Asian ethnic groups the determination of eight Slavic mutations (by RT-PCR) is inappropriate because of the significant difference in the spectrum of mutations between the newcomers (Slavs) and the indigenous population (being of the Asian origin). In Siberia, the frequency of the 5382insC variant of the *BRCA1* among newcomers with Slavic ancestry is 3.5%; no mutations in the *BRCA1/2* genes have been identified among indigenous people [67]. The search for ethno-specific molecular genetic disorders by high-throughput sequencing is needed for the ethnic groups. Moreover, studying the genome of ethnic patients with BC during mass screening does not reveal their inherent genetic features, since they are lost in the mass of the NGS data from patients not selected according to the ethnicity parameter.

Third, the enormous amount of data obtained during high-throughput sequencing requires detailed and extensive annotation to identify clinically significant changes in genes. This problem has been widely discussed all over the world. Special attention should be paid to reclassifying the new mutations, as well as the variants of uncertain and conflicting significance to determine the clinical (pathogenic) significance. In poorly studied populations the proportion of variants of uncertain significance is up to 30–50%. The presence of these variants makes it difficult to make an accurate diagnosis and, therefore, prescribe the adequate therapy [68]. To reclassify variants of an unknown significance, it is necessary to use available tools, for example, PolyPhen2, Mutation Taster, SIFT or ActiveDriverDB and ProteinPaint tool. Open-source database https://www.ActiveDriverDB.org (Ontario Institute for Cancer Research), which annotates mutations through the prism of post-translational modification sites (PTMs). It was reported that up to 30% of mutations in post-translational modification sites were considered as benign by PolyPhen2, SIFT and others [69]. ProteinPaint tool was created to expand an existing cancer genome portal and provide a comprehensive and intuitive view of cancer genomic data with advanced visualization features (https://pecan.stjude.cloud/proteinpaint) [70].

Fourth, the BRCA databases obtained using the data mainly from the Caucasians are used as reference materials for the diagnosis, treatment and prevention of BC all over the world. In the CIMBA study, which collected data on *BRCA* mutations of about 50 countries across six continents, there were very few data on these mutations among the non-Caucasians. Therefore, a disproportionately large transfer of genomic data of the Caucasian population to the poorly studied ethnic minorities around the world is currently observed. Open-access databases (ClinVar, the BIC, ENIGMA and other) that used widely for the interpretation of VUS are not suitable for variants found in Asian ancestry populations. The caution also should be exercised when analyzing data of Asian populations sush as Chinese, Koreans, Japanese. For example, the use of ExAC EAS (East Asian), which is mainly composed of Chinese and Japanese, led to misleadingly in assessing the frequency of variants found among Koreans. It became apparent when an extended own control group consisting of Korean population was used [71].

Finally, very little is known about the penetrance of *BRCA1* and BRCA2 mutations in the development of BC in ethnic minorities due to short follow-up duration and smaller cohort sizes. For example, in Korea, the BC penetrance for *BRCA1* and *BRCA2* carriers to age 70 years was 49 and 35%, respectively [72].

Therefore, because of the aforementioned challenges, there exist neither risk assessment models for *BRCA1/2* mutation carriers nor guidelines for prevention and surveillance strategies in BC patients belonging to ethnic minorities. In order to meet these challenges, genomic research specialists believe that it is essential to facilitate the exchange of experience, technology and information between countries of all income levels and all the major populations of the world, as well as to create a registry of rare mutations or genetic variants found in BC patients belonging to ethnic minorities [72].

This is the first systematic review that provides the spectrum of *BRCA* mutations in ethnic groups of BC patients inhabiting Eastern Europe and Northern Asia. Our study had some limitations arising due to the fact that some ethnic groups were studied in more details (Tatars, Armenians, Kazakhs, Tuvans) while others remained poorly studied (Mari, Mordovians, Uzbeks) or not studied (Komi, Tajiks, Tabasarans, Nogais). The studies also varied in methods (from PCR to high-throughput sequencing) and sample sizes, which made data analysis difficult. In addition, a significant part of the studies were excluded due to the fact that they studied the prevalence of mutations in any territory or region without taking into account the ethnic composition. In addition, there was no data on the frequency of mutations depending on the clinical and morphological characteristics of the tumor (triple negative cancer, hormonal status, etc.) and the anamnestic data of patients (family history of cancer, age of breast cancer manifestation, etc.).

In conclusion, this is the first systematic review that provides the spectrum of *BRCA* mutations in ethnic groups of BC patients inhabiting Eastern Europe and Northern Asia. It has been shown that the mutations are ethnospecific (varied widely within groups) and not all groups are equally well studied. Further studies on the ethnic specificity of *BRCA* gene mutations are required.

Author Contribution Statement

All authors contributed equally to the concept, literature search, writing manuscript, critical revision, and finalizing the manuscript.

Acknowledgements

General
Work was carried out on equipment of Tomsk regional common use center and The Core Facility «Medical genomics», Tomsk NRMC.

Funding Statement
The reported study was funded by Russian Science Foundation according to research project 24-25-00287.

Conflict of Interest
The authors declare no potential conflict of interest

Abbreviation list

1. *BRCA1/2* - Breast cancer type 1 susceptibility protein
2. *ATM* - ataxia telangiectasia mutated
3. *PALB2*- Partner and localizer of *BRCA2*
4. *CHEK2*- checkpoint kinase 2
5. *APC* - adenomatous polyposis coli
6. *MUTYH* - mutY DNA glycosylase

7. *BRIP1* - *BRCA1*-interacting protein
8. *NBN*- Nibrin
9. *PARP* - poly(ADP-ribose) polymerase enzymes
10. *PTEN* - phosphatase and tensin homolog
11. InDels - insertion-deletion
12. *CDK12* - cyclin-dependent kinase 12
13. *MTHFR*- methylenetetrahydrofolate reductase
14. *NGS* - Next-Generation Sequencing
15. CIMBA - Consortium of Investigators of Modifiers of *BRCA1/2*
16. the BIC - Breast Cancer Information Core
17. ENIGMA - Evidence-based Network for the Interpretation of Germline Mutant Alleles
18. VUS - Variant of uncertain significance
19. *HMMR*- Hyaluronan-mediated motility receptor
20. MDM2- Mouse double minute 2
21. SIFT- Sorting Intolerant From Tolerant
22. *TP53*- tumor protein
23. *PMS1*- postmeiotic segregation increased 1
24. XPA- Xeroderma pigmentosum complementation group A
25. *LGR4*- Leucine Rich Repeat Containing G Protein-Coupled Receptor 4
26. *BRWD1*- Bromodomain and WD repeat-containing protein 1
27. *PRISMA* - the Preferred Reporting Items for Systematic Reviews and Meta-Analyses
28. db SNP - The Single Nucleotide Polymorphism Database
29. *RT-PCR* – real time -polymerase chain reaction

References

1. Cancer Today - Global Cancer Observatory. [Internet]; 2022. Available from: https://gco.iarc.fr/today/online 2022Dec12
2. Rempel E, Kluck K, Beck S, Ourailidis I, Kazdal D, Neumann O, et al. Pan-cancer analysis of genomic scar patterns caused by homologous repair deficiency (hrd). NPJ Precis Oncol. 2022;6(1):36. https://doi.org/10.1038/s41698-022-00276-6.
3. Rebbeck TR, Friebel TM, Friedman E, Hamann U, Huo D, Kwong A, et al. Mutational spectrum in a worldwide study of 29,700 families with brca1 or brca2 mutations. Hum Mutat. 2018;39(5):593-620. https://doi.org/10.1002/humu.23406.
4. Karami F, Mehdipour P. A comprehensive focus on global spectrum of brca1 and brca2 mutations in breast cancer. Biomed Res Int. 2013;2013:928562. https://doi.org/10.1155/2013/928562.
5. Wong EH, Khrunin A, Nichols L, Pushkarev D, Khokhrin D, Verbenko D, et al. Reconstructing genetic history of siberian and northeastern european populations. Genome Res. 2017;27(1):1-14. https://doi.org/10.1101/gr.202945.115.
6. RosInfoStat. RosInfoStat.ru [Internet]. 2022 Dec12. Available from: https://rosinfostat.ru/natsionalnyj-sostav
7. Wikipedia. en.wikipedia.org [internet]. Wikimedia Foundation, Inc. c2024 [2024Apr11]. Available from: https://en.wikipedia.org/wiki/Siberia.
8. Kaprin AD, Starinskiy VV, Shakhzodova AO. Malignant neoplasms in Russia in 2020 (morbidity and mortality) Moscow: MNIOI im. PA Gertsena− filial FGBU «NMITs radiologii» Minzdrava Rossii. 2021;252.
9. Khar'kov VN, Stepanov VA, Medvedev OF, Spiridonova MG, Maksimova NR, Nogovitsyna AN, et al. The origin of yakuts: Analysis of y-chromosome haplotypes. Mol Biol (Mosk). 2008;42(2):226-37.
10. Kharkov VN, Khamina KV, Medvedeva OF, Simonova KV, Khitrinskaya IY, Stepanov VA. Gene-pool structure of tuvinians inferred from y-chromosome marker data. Genetika. 2013;49(12):1416-25. https://doi.org/10.7868/s0016675813120035.
11. Har'kov VN, Hamina KV, Medvedeva OF, Simonova KV, Eremina ER, Stepanov VA. Gene pool of buryats: Clinal variability and territorial subdivision based on data of y-chromosome markers. Genetika. 2014;50(2):203-13.
12. Khar'kov VN, Khamina KV, Medvedeva OF, Shtygasheva OV, Stepanov VA. Genetic diversity of khakassian gene pool: Subethnic differensiation and the structure of y-chromosome haplogroups. Mol Biol (Mosk). 2011;45(3):446-58.
13. Khar'kov VN, Stepanov VA, Medvedeva OF, Spiridonova MG, Voevoda MI, Tadinova VN, et al. Gene pool differences between northern and southern altaians inferred from the data on y-chromosomal haplogroups. Genetika. 2007;43(5):675-87.
14. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The prisma statement. PLoS Med. 2009;6(7):e1000097. https://doi.org/10.1371/journal.pmed.1000097.
15. Anohina EN. Polymorphisms of pro- and anti-inflammatory cytokine genes, *BRCA* 1/2 gene mutations in malignant neoplasms of female reproductive organs. PhD. Maykop. 2015. (in Russia.)
16. Atshemyan S, Chavushyan A, Berberian N, Sahakyan A, Zakharyan R, Arakelyan A. Characterization of brca1/2 mutations in patients with family history of breast cancer in armenia. F1000Res. 2017;6:29. https://doi.org/10.12688/f1000research.10434.1.
17. Moradian MM, Babikyan DT, Markarian S, Petrosyan JG, Avanesian N, Arutunyan T, et al. Germline mutational spectrum in armenian breast cancer patients suspected of hereditary breast and ovarian cancer. Hum Genome Var. 2021;8(1):9. https://doi.org/10.1038/s41439-021-00140-2.
18. Vodolazhskij DI, Shatova JuS, Komova EA, Dvadnenko KV. *BRCA* mutations among the patients with clinically hereditary breast cancer in the South Federal State. Modern Problems of Science and Education. 2015;3:49. (in Russia.)
19. Belysheva Y, Bakaeva E, Venina A, Romanko A, Raskin G, Sokolenko A, et al. Brca1/2 mutation spectrum in armenian patients with breast and ovarian cancers. Sib J Oncol. 2024;22:83-91. https://doi.org/10.21294/1814-4861-2023-22-6-83-91.
20. Aliyev JA, melikova LA, mansurov EB, aliyeva FK, bagirova EE, mexdizade SQ, et al. Activating point muation of brca1/2 genes in azerbaijan population. 2019;v17:2.39-43. Https://doi.Org/10.29296/24999490-2019-02-05.
21. Sokolenko AP, Bakaeva EK, Venina AR, Kuligina ES, Romanko AA, Aleksakhina SN, et al. Ethnicity-specific brca1, brca2, palb2, and atm pathogenic alleles in breast and ovarian cancer patients from the north caucasus. Breast Cancer Res Treat. 2024;203(2):307-15. https://doi.org/10.1007/s10549-023-07135-3.
22. Bermisheva MA, zinnatullina GF, gilyazova IR, et al. Prevalence of brca1 c.5161c>t mutation in cancer patients from bashkortostan. Adv Mol Oncol. 2021;8(4):84-93. (in russ.). Https://doi.Org/10.17650/2313-805x-2021-8-4-84-93.
23. Bermisheva MA, takhirova ZR, bogdanova N, khusnutdinova EK. Frequency of chek2 gene mutations in breast cancer patients from republic of bashkortostan. Mol Biol. 2014;48:55-61. (in russ.). Https://doi.Org/10.7868/s0026898414010029.
24. Valova YV, bogdanova NV, mingazheva ET, prokofieva DS, khusnutdinova EK, karimov DO, kutlina TG. Screening of patients with hereditary ovarian cancer from the republic

of bashkortostan on mutations in brca1/brca2 genes. Occupational medicine and human ecology. 2019;3:68-71. (in russ.). Https://doi.Org/10.24411/2411-3794-2019-10040.
25. Minniakhmetov I, kagirova E, mashkov O, khusainova R. Search for pathogenic changes in brca1/2 genes in patients with breast and ovarian cancer using mass parallel sequencing technology. Questions of oncology. 2022;v68.1.48-54. (in russ.) https://doi.Org/10.37469/0507-3758-2022-68-1.
26. Savanevich A, Vasilkevich M, Abdrashitov V, Stepuro T. Brca1 and brca2 genes mutations among women with clinical signs of hereditary breast cancer in western belarus. The Journal of V N Karazin Kharkiv National University, series "Medicine". 2021(42). https://doi.org/10.26565/2313-6693-2021-42-08.
27. Bisultanova ZI, bisultanova ZR, dzhambetova PM. Analysis of the occurrence of 5382insc brca1 mutations in the chechen population. Materials of international caucasian ecological forum. Russia. Grozny. 2015:154-56. (in russ.).
28. Sokolenko AP, sultanova LV, stepanov IA, romanko AA, venina AR, sokolova TN, et al. Strong founder effect for brca1 c.3629_3630delag pathogenic variant in chechen patients with breast or ovarian cancer. Cancer Med. 2022. Https://doi.Org/10.1002/cam4.5159.
29. Onco*BRCA*. https://oncobrca.ru [internet]. Available from: https://oncobrca.ru/stats. 2019-2024 © oncobrca.ru
30. Oleksenko VV, Aliev KA, Malyi KD. *BRCA* genes mutations of hereditary breast cancer in Crimea. Questions of Oncology. 2020;66:5.507-13.
31. Pardilova SA, zhantueva LA, kancaliev AL, pirmagomedov ASH, daurova LV, bogotova ZI, et al. Analysis of hereditary breast cancers, four mutations of the gene brca1 in the kabardino-balkar republic. Modern problems of science and education. 2016;3:169. (in russ.).
32. Bittueva MM, bogotova ZI, daurova LV, gidova JEM, paritov AJU, handohov TH, et al. Hereditary predisposition clinical and morphological features of breast cancer from residents of kabardino-balkaria. Modern problems of science and education. 2014;6:1364. (in russ.).
33. Zhantueva LA, pardilova CA, kancaliev AL, pirmagomedov ASH, bogotova ZI, bittueva MM, et al. Research frequency heritable mutation in patients with diseases of the female reproductive system in the kabardino-balkaria. Modern problems of science and education. 2016;3:168. (in russ.).
34. Akilzhanova A, Nurkina Z, Momynaliev K, Ramanculov E, Zhumadilov Z, Rakhypbekov T, et al. Genetic profile and determinants of homocysteine levels in kazakhstan patients with breast cancer. Anticancer Res. 2013;33(9):4049-59.
35. Zhunussova G, Omarbayeva N, Kaidarova D, Abdikerim S, Mit N, Kisselev I, et al. Determination of genetic predisposition to early breast cancer in women of kazakh ethnicity. Oncotarget. 2023;14:860-77. https://doi.org/10.18632/oncotarget.28518.
36. Svyatova G, Berezina G, Urazbayeva G, Murtazaliyeva A. Frequencies of diagnostically significant polymorphisms of hereditary breast cancer forms in brca1 and brca2 genes in the kazakh population. Asian Pac J Cancer Prev. 2023;24(11):3899-907. https://doi.org/10.31557/apjcp.2023.24.11.3899.
37. Makieva KB, golovachev SV, sultangazieva BB, bukuyev NM. Results of a preliminary analysis of the pattern of hereditary breast cancer in the women of a kyrgyz population. Tumors Female Reprod Syst. 2013;3(4):41-4. (in russ).
38. Makieva KB, golovachev SV, aldashev AA, sultangazieva BB. Analysis of polymorphism in the brca1 and brca2 genes in women with breast cancer in the kyrgyz republic using the method of biological microchips. Actual issues of modern medicine. Materials of the scientific-practical conference with international participation. Russia, yekaterinburg. 2014:163-64. (in russ).
39. Isakova JT, Vinnikov D, Kipen VN, Talaibekova ET, Aldashev AA, Aldasheva NM, et al. Gene-to-gene interactions and the association of tp53, xrcc1, tnfα, hmmr, mdm2 and palb2 with breast cancer in kyrgyz females. Breast Cancer. 2020;27(5):938-46. https://doi.org/10.1007/s12282-020-01092-1.
40. Aliev KA, maly KD. The assessment of brca1/2 gene mutation prevalence in patients with breast cancer in crimea region. Proceedings of the iii scientific conference of the faculty, graduate students, students and young scientists «days of science of the v.I. Vernadsky crimean federal university». Simferopol. 2017;27-30. (in russ).
41. Shagimardanova E, Shigapova L, Gusev O, Nikitin A, Druzhkov M, Enikeev R, et al. Germline brca screening in breast cancer patients in tatar women population. Ann Oncol. 2016;27:vi51. https://doi.org/10.1093/annonc/mdw364.26.
42. Bogdanova NV, Schürmann P, Valova Y, Dubrowinskaja N, Turmanov N, Yugay T, et al. A splice site variant of cdk12 and breast cancer in three eurasian populations. Front Oncol. 2019;9:493. https://doi.org/10.3389/fonc.2019.00493.
43. Abdikhakimov A, Tukhtaboeva M, Adilov B, Turdikulova S. The potential contribution of brca mutations to early onset and familial breast cancer in uzbekistan. Cent Asian J Glob Health. 2016;5(1):228. https://doi.org/10.5195/cajgh.2016.228.
44. Cherdyntseva NV, Pisareva LF, Ivanova AA, Panferova YV, Malinovskaya EA, Odintsova IN, et al. Ethnic aspects of hereditary breast cancer in the region of siberia. Vestn Ross Akad Med Nauk. 2014(11-12):72-9. https://doi.org/10.15690/vramn.v69i11-12.1186.
45. Cherdyntseva N, Gervas P, Voropaeva E, Denisov E, Pisareva L, Malinovskaya E, et al. New variants in the brca1 gene in buryat mongol breast cancer patients: Report from two families. Cancer Biomark. 2017;18(3):291-6. https://doi.org/10.3233/cbm-161649.
46. Gervas PA, Molokov A, Zarubin AA, Shivit-ool N, Babyshkina N, Shefer E, et al. Exome sequencing: The search for mutations associated with hereditary breast and ovarian cancer in the tuvan ethnic group (pilot study). https://doi.org/10.47056/0365-9615-2023-176-12-779-784.
47. Gervas P, Klyuch B, Denisov E, Kiselev A, Molokov A, Pisareva L, et al. New germline brca2 gene variant in the tuvinian mongol breast cancer patients. Mol Biol Rep. 2019;46(5):5537-41. https://doi.org/10.1007/s11033-019-04928-y.
48. Gervas P, Molokov A, Schegoleva A, Kiselev A, Babyshkina N, Pisareva L, et al. New germline mutations in non-brca genes among breast cancer women of mongoloid origin. Mol Biol Rep. 2020;47(7):5315-21. https://doi.org/10.1007/s11033-020-05612-2.
49. Gervas P, Molokov A, Zarubin A, Topolnitskiy E, Shefer N, Pisareva L, et al. Germline variants associated with breast cancer in khakass women of north asia. Mol Biol Rep. 2023;50(3):2335-41. https://doi.org/10.1007/s11033-022-08215-1.
50. Zaharova NA, donnikov MV, filimonov AV. Analysis of brca1/2 and chek2 genes mutations using biological microarray method as a part of the breast cancer screening program in the khanty-mansiysky autonomous okrug – ugra. J Med Technol. 2011;18:67-9. (in russ.).
51. Farahutdinova AR, fedorova SA, nikolaeva TI, Ivanov PM, bermisheva MA, doerk T, et al. Analysis of mutations in the brca1, chek2, nbs1 genes in patients with breast cancer from republic of sakha (yakutia). Yakut Med J. 2009;2:91-

3. (in russ.).
52. Molokov a, gervas p, zarubin a, tihonov d, cherdyntseva n. Germinal mutation of the mutyh gene in young patients of the yakut ethnic group diagnosed with breast cancer. Uspekhi molekulyarnoy onkologii. Materials of the 7th all-russian conference on molecular oncology. Russia. Moscow. 2022;9:23. (in russ.).
53. Gervas p, molokov a, tihonov d, cherdyntseva n. Genotypes of predisposition to breast cancer in the indigenous population of the far north. Uspekhi molekulyarnoy onkologii. Materials of the 7th all-russian conference on molecular oncology. Russia. Moscow. 2022;9:63. (in russ.).
54. Polina G, Molokov A, Zarubin A, Ivanova A, Tikhonov D, Kipriyanova N, et al. A novel germline mutation of the palb gene in a young yakut breast cancer woman. Sib J Oncol 2022;21:72-9. https://doi.org/10.21294/1814-4861-2022-21-4-72-79.
55. Gervas P, Molokov A, Ivanova A, Panferova Y, Kiselev A, Chernyshova A, et al. New germline mutations in brca1, atm, mutyh, and rad51d genes in tuvans early-onset breast cancer patients. Exp Oncol. 2021;43:52-5. https://doi.org/10.32471/exp-oncology.2312-8852.vol-43-no-1.15587.
56. Gervas PA, molokov AYU, zarubin AA, ponomareva AA, babyshkina NN, belyavskaya VA, et al. New mutation of the tp53 gene associated with the hereditary breast cancer in a young tuvinian woman. Sib J Oncol. 2021;20:164-70. Https://doi.Org/10.21294/1814-4861-2021-20-6-164-170.
57. Sun J, Meng H, Yao L, Lv M, Bai J, Zhang J, et al. Germline mutations in cancer susceptibility genes in a large series of unselected breast cancer patients. Clin Cancer Res. 2017;23(20):6113-9. https://doi.org/10.1158/1078-0432.Ccr-16-3227.
58. Loveday C, Turnbull C, Ramsay E, Hughes D, Ruark E, Frankum JR, et al. Germline mutations in rad51d confer susceptibility to ovarian cancer. Nat Genet. 2011;43(9):879-82. https://doi.org/10.1038/ng.893.
59. Paparo L, Rossi GB, Delrio P, Rega D, Duraturo F, Liccardo R, et al. Differential expression of pten gene correlates with phenotypic heterogeneity in three cases of patients showing clinical manifestations of pten hamartoma tumour syndrome. Hered Cancer Clin Pract. 2013;11(1):8. https://doi.org/10.1186/1897-4287-11-8.
60. He X, Arrotta N, Radhakrishnan D, Wang Y, Romigh T, Eng C. Cowden syndrome-related mutations in pten associate with enhanced proteasome activity. Cancer Res. 2013;73(10):3029-40. https://doi.org/10.1158/0008-5472.Can-12-3811.
61. Galatola M, Paparo L, Duraturo F, Turano M, Rossi GB, Izzo P, et al. Beta catenin and cytokine pathway dysregulation in patients with manifestations of the “pten hamartoma tumor syndrome”. BMC Med Genet. 2012;13:28. https://doi.org/10.1186/1471-2350-13-28.
62. Venturini G, Moulin AP, Deprez M, Uffer S, Bottani A, Zografos L, et al. Clinicopathologic and molecular analysis of a choroidal pigmented schwannoma in the context of a pten hamartoma tumor syndrome. Ophthalmology. 2012;119(4):857-64. https://doi.org/10.1016/j.ophtha.2011.09.057.
63. Lui GYL, Grandori C, Kemp CJ. Cdk12: An emerging therapeutic target for cancer. J Clin Pathol. 2018;71(11):957-62. https://doi.org/10.1136/jclinpath-2018-205356.
64. Macis D, Maisonneuve P, Johansson H, Bonanni B, Botteri E, Iodice S, et al. Methylenetetrahydrofolate reductase (mthfr) and breast cancer risk: A nested-case-control study and a pooled meta-analysis. Breast Cancer Res Treat. 2007;106(2):263-71. https://doi.org/10.1007/s10549-006-9491-6.
65. Dykhno yua, chernenko on. Analysis of risk factors for breast cancer in women of the republic of khakassia. Siberian Oncol J. 2012;6:47. (in russ.).
66. Dolgasheva DS, pevzner AM, ibragimova MK, litvyakov NV, tsyganov MM. Parp1 inhibitors in breast cancer therapy. Mechanism of action and clinical use. Tumors Female Reprod Syst. 2020;16:55-64. Https://doi.Org/10.17650/1994-4098-2020-16-1-55-64.
67. Pisareva LF, odintsova IN, ananina OA, malinovskaya YEA, stukanov SL, panferova YEV, et al. The morbidity of mammary gland cancer in indigenous and outsider population of siberia and far east. Zdravookhranenie rossiiskoi federatsii. 2012;4:37-41. (in russ.).
68. Hoffman-Andrews L. The known unknown: The challenges of genetic variants of uncertain significance in clinical practice. J Law Biosci. 2017;4(3):648-57. https://doi.org/10.1093/jlb/lsx038.
69. Krassowski M, Paczkowska M, Cullion K, Huang T, Dzneladze I, Ouellette BFF, et al. Activedriverdb: Human disease mutations and genome variation in post-translational modification sites of proteins. Nucleic Acids Res. 2018;46(D1):D901-d10. https://doi.org/10.1093/nar/gkx973.
70. Zhou X, Edmonson MN, Wilkinson MR, Patel A, Wu G, Liu Y, et al. Exploring genomic alteration in pediatric cancer using proteinpaint. Nat Genet. 2016;48(1):4-6. https://doi.org/10.1038/ng.3466.
71. Eccles DM, Mitchell G, Monteiro AN, Schmutzler R, Couch FJ, Spurdle AB, et al. Brca1 and brca2 genetic testing-pitfalls and recommendations for managing variants of uncertain clinical significance. Ann Oncol. 2015;26(10):2057-65. https://doi.org/10.1093/annonc/mdv278.
72. Nakamura S, Kwong A, Kim S-W, Iau P, Patmasiriwat P, Dofitas R, et al. Current status of the management of hereditary breast and ovarian cancer in asia: First report by the asian brca consortium. Public Health Genomics. 2015;19. https://doi.org/10.1159/000441714.