Genetics and Molecular Research

Mutational analysis of BRCA1/2 gene and pathologic characteristics from Kazakh population with sporadic breast cancer in northwestern China

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Genet. Mol. Res. 14 (4): 13151-13161 (2015)
Received May 31, 2015
Accepted July 14, 2015
Published October 26, 2015
DOI http://dx.doi.org/10.4238/2015.October.26.11

ABSTRACT. Mutations in the BRCA1/2 genes are associated with an increased risk of breast cancer, but no large-scale research have examined the *BRCA1/2* mutations in Chinese Kazakh women. We evaluated the frequency and distributions of BRCA1 and BRCA2 gene mutations in Kazakh sporadic breast cancer patients and healthy women in China. The association between the clinical-pathologic features of Kazakh breast cancer patients and *BRCA1/2* mutations were also investigated. Two unclassified variants (T539M and T1915M) and 16 polymorphisms were detected in this study, 4 of which (G356A, His743, Asn991Asp, Val1269) were detected more frequently in breast cancer patients than in healthy controls. We observed a higher prevalence of *BRCA1/2* common sequence alterations and a large number of Kazakh women carrying multiple co-existing *BRCA1/2* mutations. The prevalence of *BRCA1* mutations was similar to that of *BRCA2* mutations. Although no significant differences were observed, *BRCA1/2* carriers were generally younger at diagnosis

of wild-type breast cancer patients. *BRCA1*-associated Kazakh sporadic breast cancers present with high tumor grade, early stage, negative lymph node status, absence of estrogen receptor expression and progesterone-positive status. Estrogen receptor expression was the only predominant histological type in *BRCA2* carriers. In this study, we determined the BRCA1 and BRCA2 gene mutation status and determined the association with clinical-pathologic characteristics in a Chinese Kazakh population. Larger population-based screening studies screening the entire coding region of *BRCA1/2* are required to evaluate the breast cancer risk induced by the sequence alterations detected in this study.

Key words: Breast cancer; *BRCA1*; *BRCA2*; Kazakh; Mutations

INTRODUCTION

There are currently approximately 18 million Kazakh worldwide; nearly 10% of this population lives in China. China's Kazakh ethnic population is mainly distributed in Xinjiang in the northwest of China. As the third largest ethnic group in Xinjiang, Kazakh has a special background of history, the Asia-Europe descent, customs, and environmental and geographical factors. The breast cancer characteristics of Kazakhs include low incidence, early onset age, later clinical stage, and poor prognosis. To date, few studies examining the spectrum of *BRCA* mutations in China's Kazakh populations have been conducted, and most were performed in Han and Uygur populations (Zhang et al., 2012; Ou et al., 2013; Cao et al., 2014).

Evidence showed that several risk factors are associated with breast cancer (Dumitrescu and Cotarla, 2005; Gram et al., 2005), among which mutations in the BRCA1/BRCA2 genes increase the lifetime breast cancer risk to 85%, as compared to a 12% lifetime risk of breast cancer in women without mutations in *BRCA1* and *BRCA2* (Eeles, 2000; King et al., 2003). More than 1500 *BRCA1* or *BRCA2* mutations including nonsense, missense, frameshift mutations, and large and small deletions have been recorded in the Breast Cancer Information Core database (Easton et al., 2007). Not only are specific *BRCA1/2* mutations associated with certain ethnic populations, but also founder mutations have been identified in several groups. A single *BRCA2* founder mutation, 999delTCAAA, was found in 0.4-0.6% of the Icelandic population (Johannesdottir et al., 1996; Thorlacius et al., 1997). Three founder mutations, 187delAG and 5382insC in *BRCA1* and 6174delT in *BRCA2*, have been well-characterized and have an estimated prevalence of 2.5% in the Ashkennazi Jewish population (Roa et al., 1996; Struewing et al., 1997; Fodor et al., 1998). A few studies on *BRCA1/2* mutations have been reported in familial or early-onset breast cancer patients from China (Zhang et al., 2012; Cao et al., 2014), but little information is available regarding *BRCA1/2* mutations in sporadic breast cancers, particularly in the Kazakh ethnic group in China.

BRCA1/2-associated breast cancers generally exhibit as estrogen receptor (ER)-, progesterone receptor (PR)-, and Her-2-negative (triple-negative tumor) in Caucasian women (Parise et al., 2009; Oprea-Ilies et al., 2013). Few studies have reported *BRCA1/2* mutations in Chinese multiple ethnic groups in high-risk breast cancer patients (Li et al., 2008; Zhang et al., 2012). Additionally, few studies have investigated the clinical-pathological characteristics of *BRCA1/2* tumors in the Kazakh ethnic population in China. In this study, we examined *BRCA1/2* gene mutations in Kazakh sporadic breast cancer patients and healthy women with no family

history of breast cancer by screening 4 *BRCA1* and 2 *BRCA2* coding regions and the exon-intron boundaries of the BRCA1/2 gene in 129 Kazakh sporadic breast cancer patients and 105 healthy controls from the Xinjiang region of China. Furthermore, we investigated whether *BRCA1/2*-associated breast cancers had distinct clinical-pathological features.

MATERIAL AND METHODS

Study subjects

The samples included the groups described below.

Sporadic cancer patients

We recruited Kazakh nationality women with pathologically confirmed sporadic breast cancer from January 2004 and October 2014, enrolled from the First Affiliated Hospital and Tumor Affiliated Hospital of Xinjiang Medical University, which are 2 of the largest public hospitals in Xinjiang, China. A total of 129 female breast cancer patients diagnosed at 33-70 years, with a mean age of 48.3 years and median age of 46 years, were recruited for the study during an out-patient visit to the Mammary Surgery Clinic and Medical Oncology clinic, or during a hospital admission. Among the 129 breast cancer patients, clinical-pathological information was acquired by medical record review. The clinical-pathological characteristics such as the age at diagnosis, histological subtype, histological grade, TNM stage, node status, ER, PR, HER-2 expression, and Ki-67 were obtained.

Healthy controls

The control group included 105 healthy Kazakh nationality women unrelated to any of the patients and ranging in age from 28-73 years, with a mean age 48.6 years. Control subjects had no personal history of malignancy at the time of recruitment, and with no family history of breast or ovarian cancer.

The project was approved by the local medical ethical committee (Approval Number: 20110818-7). Written informed consent was obtained from all study subjects. Information regarding family history was obtained through interview, and all subjects were confirmed to not have a family history of affected first-degree or second-degree relatives with breast cancer and/or ovarian cancer.

BRCA1/*BRCA2* mutation detection

Genomic DNA was extracted using a standard procedure from 5 mL peripheral blood with a DNA extraction kit according to the manufacturer instructions (Tiangen, Beijing, China). The coding exons 2, 10, 18, and 20 of *BRCA1* (NM_007300.3/NP_009231.2/NC_000017.11) and exon 10 and 11 of *BRCA2* (NM_000059.3/NP_000050.2/NC_000013.11) and the exon/intron splice junctions were *in vitro*-amplified from genomic DNA. Eighteen reverse and forward primers were used for polymerase chain reaction (PCR). The reactions were performed in a 30-µL volume containing 0.6 µL DNA, 3 µL 10X Pfu PCR buffer, 0.6 µL 10 mM dNTP mix, 0.3 µL 2.5 U/ µL Pfu DNA polymerase (Tiangen), 24.3 µL ddH_2O_2, and 0.6 µL each 10 µM forward and reverse primers. The reaction conditions were as follows: 95°C for 5 min, followed by denaturation at 95°C for 30 s, annealing

at a suitable temperature for each pair of primers for 30 s, and extension at 72°C for 60 s. The PCR was conducted for 40 cycles with final elongation for 5 min (Bio-Rad, Hercules, CA, USA); Pfu DNA polymerase (Tiangen) was used for all PCR amplifications. We amplified 18 overlapping regions of the exons using a set of specific primers. The samples were evaluated by 1% agarose gel electrophoresis at 120 V constant voltage electrophoresis for 30 min, and the results were observed using a gel imager. DNAMAN software 6.0.3.99 (Lynnon BioSoft, Quebec, Canada) was used for comparison and analysis, and CromasPro software 2.33 was used for spectrum analysis. The fragments with the correct band size were then sequenced in an automated ABI 3730 DNA sequencer (Applied Biosystems, Foster City, CA, USA) following the manufacturer instructions. The results were analyzed according to US National Center for Biotechnology Information nucleotide database (*BRCA1* GenBank accession No. NM_007300.3/NP_009231.2/NC_000017.11 and *BRCA2* GenBank accession No. NM_000059.3/NP_000050.2/NC_000013.11).

Clinical-pathologic characteristics

Histology, grading, TNM stage, and ER, PR, HER-2, Ki-67, and note status of breast cancer patients were extracted from medical records. When the information that cannot be acquired from the medical record, we reused the wax block tissue to make an immunohistochemical analysis to supplement the information. HER-2 status was assessed by fluorescence *in situ* hybridization analysis in ambiguous cases (immunohistochemical score = 2+).

Statistical analysis

Chi-square analysis or Fisher exact test was appropriately used to test the association between qualitative variables. In addition, an independent *t*-test was used to compare the mean age between groups. In all analysis, P values less than 0.05 were considered to be statistically significant. All statistical analyses were performed using SPSS version 17.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

BRCA1/BRCA2 gene mutations in Kazakh sporadic breast cancer patients and healthy controls

A total of 234 Kazakh individuals were screened for germline mutations of *BRCA1* and *BRCA2*, and 292 sequence variants in exons 2, 10, 18, and 20 of *BRCA1* and exon 10 and 11 of *BRCA2* were identified in 129 women with sporadic breast cancer. A total of 214 sequence variants were identified in 105 healthy women (Table 1). We found a prevalence of *BRCA1/2* sequence alterations in 79 of the 129 women (61.2%) with breast cancer and in 71 of the 105 healthy women (57.1%). Mutations in the BRCA1 gene were observed in 30 (23.3%) patients and 24 (22.9%) healthy women, whereas in the BRCA2 gene, mutations were observed in 63 (48.8%) patients and 51 (48.5%) healthy women. Included in the case and control groups were 14 and 15 patients with mutations observed in both the BRCA1 and BRCA2 genes.

BRCA1 and *BRCA2* single-nucleotide polymorphism (SNPs) in Kazakh population

Two unclassified variants of unknown clinical significance were included rs80357374 in

exon 10 of *BRCA1* and rs4987117 at exon 11 of *BRCA2*. rs80357374 was observed in 2 healthy women. rs1987117 was observed in 6 breast cancer patients and 3 healthy women, but there was no significant difference between groups. The other SNPs were all missense mutations. Although deleterious mutations were not detected in either group, with the exception of rs1799950, rs1801499, rs1799944, and rs543304, none of the identified sequence variants exhibited statistically significant differences in allele frequency between the patients and controls. We also observed that 14 of 129 (10.8%) patients and 33 of 105 (31.4%) healthy women carried ≥ 4 co-existing *BRCA1/2* alterations. List of SNPs observed in the BRCA1/2 gene are shown in Table 1.

Table 1. Details and frequency of the variants detected in partial exons of the BRCA1/2 gene in breast cancer and control groups.

Exon	Mutation position	Sequence variant	Amino acid variant	Mutation type	Mutation effect	Frequency in the breast cancer group (N = 129), N (%)	Frequency in the control group (N = 105), N (%)	P
BRCA1								
10	rs1799950[a]	c.1067A>G	p.Gln356Arg	M	D	**12 (9.3)***	2 (1.9)	**0.018**
	rs80357374[a]	c.1616C>T	p.Thr539Met	M	UV	0 (0)	2 (1.9)	0.115
	rs4986850[a]	c.2077G>T	p.Asp693Asn	M	P	2 (1.6)	1 (1.0)	0.686
	rs1799949	c.2082C>T	p.Ser694	S	P	13 (10.1)	9 (8.6)	0.695
	rs16940	c.2311T>C	p.Leu771	S	P	15 (11.6)	9 (8.6)	0.443
	rs799917	c.2612C>T	p.Pro871Leu	M	P	18 (14.0)	16 (15.2)	0.782
	rs16941	c.3113A>G	p.Glu1038Gly	M	P	18 (14.0)	16 (15.2)	0.782
	rs16942	c.3548A>G	p.Lys1183Arg	M	P	15 (11.6)	13 (12.4)	0.860
Intron18	rs3092994	c.5215+66G>A	p./	-	P	15 (11.6)	13 (12.4)	0.860
	Intron18-268	c.5215+268G>A	p./	-	P	0 (0)	2 (1.9)	0.115
BRCA2								
10	rs766173	c.865A>G	p.Asn289His	M	P	42 (32.6)	24 (22.9)	0.101
	rs144848	c.1114A>C	p.Asp372His	M	P	12 (9.3)	6 (5.7)	0.306
	rs1801439	c.1365A>G	p.Ser455	S	P	31 (24.0)	21 (20)	0.461
11	rs1801499	c.2229T>C	p.His743	S	D	**36 (27.9)***	15 (14.3)	**0.012**
	rs1799944	c.2971A>G	p.Asn991Asp	M	D	**36 (27.9)***	15 (14.3)	**0.012**
	rs1801406	c.3396A>G	p.Lys1132	S	P	15 (11.6)	18 (17.1)	0.228
	rs543304[a]	c.3807T>G	p.Val1269	S	P	**6 (4.7)***	0 (0)	**0.025**
	rs4987117[a]	c.5744C>T	p.Thr1915Met	M	UV	6 (4.7)	3 (2.9)	0.478
Total mutations						292	185	

*P < 0.05, between cases and controls. [a]P value from Fisher exact test for trend, and other P values without [a]from χ^2 for trend. Sequence variant nomenclature is according to GenBank accession No. NM_007300.3 (*BRCA1*) and NM_000059.3 (*BRCA2*). Amino acid variant nomenclature is according to Protein accession No. NP_009231.2 (*BRCA1*) and NP_000050.2 (*BRCA2*). M = missense; S = synonymous; D = deleterious mutation; UV = unclassified variant; P = polymorphism.

For the BRCA1 gene, we detected 4 exons (exons 2, 10, 18, and 20). As a result, all SNPs were identified in exon 10. A total of 10 distinct mutations were identified, including 1 unclassified variants T539M and 9 polymorphisms (Table 1). The most frequent *BRCA1* mutations were P871L and Glu1038Gly, which were both found in 18 patients (14.0%) and 16 healthy women (15.2%); there were no differences between groups. The polymorphism intron18-268 detected in our study population has not been reported previously in a Chinese population.

In the BRCA2 gene, exons 10 and 11 were detected. Three SNPs were in exon 10 and 5 were in exon 11. The most frequent mutation was A289H in exon 10 (32.6%), with no significant difference observed between the patients and the healthy controls. However, there were significant differences (the second-most prevalent SNPs were His743 and Asn991Asp in exon 11) between groups (27.9 *vs* 14.3%). V1269 was observed in 6 patients, whereas this mutation was not observed in the healthy controls (P = 0.025).

Clinical-pathologic characteristics of Chinese Kazakh breast cancer cases

Clinical characteristics and pathologic features of the 129 Chinese Kazakh breast cancer patients included in this study are presented in Table 2.

Table 2. Clinical-pathologic characteristics of Kazakh breast cancer patients.

Characteristics[a]	N	%
Age at diagnosis		
31-40	22	17.1
41-50	58	45.0
51-60	38	29.5
61-70	11	8.5
BRCA1/2 Mutational status		
BRCA1/2 mutational-positive	79	61.2
BRCA1/2 wild-type	50	38.8
Histology		
IDC	107	82.9
Other	22	17.1
Grading		
1	5	6.2
2	44	54.3
3	32	39.5
Stage		
I	16	20.3
II	33	41.8
III	25	31.6
IV	5	6.3
Lymph node status		
Negative	49	51.6
Positive	46	48.4
ER		
Negative	27	29.0
Positive	66	71.0
PR		
Negative	42	46.2
Positive	49	53.8
HER-2		
Negative	30	38.0
Positive	49	62.0
Ki-67		
Low	11	15.3
High	61	84.7

The age of patients at first diagnosis ranged from 33-70 years, with a mean age of 48.3 ± 9.3 years. Seventy-nine patients (61.2%) carried *BRCA1/2* mutations. Most tumors were invasive ductal carcinoma (82.9%). Approximately 54.3% of breast cancer patients were G2 and the minority (6.2%) was G1. Approximately 41.8% of patients presented with stage II disease, followed by stage III (31.6%). Lymph node status was negative in nearly half of the patients. Most tumors were ER+ (71.0%), PR+ (53.8%), and HER-2 positive (62.0%), and 84.7% of tumors showed high proliferative activity (Ki-67 high).

Association between clinical-pathologic characteristics and *BRCA1/2* status

The median age at the time of diagnosis of patients with *BRCA1* mutations was younger than that of the patients without mutation, but the difference between groups was not significant. There was also no difference in histology between the women diagnosed with breast cancer with or

without *BRCA1* mutations. Furthermore, patients with *BRCA1* mutations had higher-grade tumors (83.3% with grade 3, P = 0.022), lower TNM stage (81.8% with stage I-II, P = 0.024), and negative lymph node status (78.6%, P = 0.001).

The *BRCA1* mutation group included more ER-negative cases (60.0%, P = 0.001) and PR-positive cases (75.0%, P = 0.002) than the group without *BRCA1* mutations. However, there was no significant difference in the proportion of patients regarding HER-2 and Ki-67 status.

Similarly to the *BRCA1* status, although no significant differences were observed for at diagnosis, the *BRCA2* mutation group had a younger median age than the wild-type group at diagnosis. In contrast to the status of *BRCA1*, ER-positive breast cancer was observed more often in the *BRCA2* mutation group than in the wild-type group. There were no other significant differences between patients with or without *BRCA2* mutation (Table 3).

Table 3. Association between clinical-pathologic characteristics and *BRCA1/2* in breast cancer patients of Kazakh minority in Xinjiang.

Characteristics [a]	Status of BRCA1		P	Status of BRCA2		P
	WT N (%)	Mutation N (%)		*WT* N (%)	Mutation	N (%)
Age at diagnosis (years)*	49.1 (±1.6)	46.8 (±2.3)	0.385	49.4 (±2.1)	47.6 (±1.7)	0.096
Histology						
IDC	80 (80.8)	27 (0.90)	58 (84.1)	49 (81.7)		
Other	19 (19.2)	3 (0.10)	0.241	11 (15.9)	11 (18.3)	0.719
Grading						
1-2	48 (64.0)	1 (16.7)	33 (54.1)	16 (53.3)		
3	27 (36.0)	5 (83.3)	0.022	28 (45.9)	14 (46.7)	0.945
Stage						
I-II	31 (54.4)	18 (81.8)	23 (63.9)	26 (60.5)		
III-IV	26 (45.6)	4 (18.2)	0.024	13 (36.1)	17 (39.5)	0.755
Node status						
Negative	27 (40.3)	22 (78.6)	16 (0.40)	32 (59.3)		
Positive	40 (59.7)	6 (21.4)	0.001	24 (0.60)	22 (40.7)	0.065
ER						
Negative	15 (20.5)	12 (60.0)	19 (43.2)	8 (16.3)		
Positive	58 (79.5)	8 (40.0)	0.001	25 (56.8)	41 (83.7)	0.004
PR						
Negative	38 (50.7)	4 (25.0)	22 (46.8)	20 (45.5)		
Positive	37 (49.3)	12 (75.0)	0.002	25 (53.2)	24 (54.5)	0.897
HER-2						
Negative	24 (40.7)	6 (30.0)	11 (40.7)	19 (35.8)		
Positive	35 (59.3)	14 (70.0)	0.395	16 (59.3)	34 (64.2)	0.669
Ki-67						
Low	9 (16.7)	2 (11.1)	6 (13.6)	5 (17.9)		
High	45 (83.3)	16 (88.9)	0.570	38 (86.4)	23 (82.1)	0.627

*Mean age (± standard error). ER = estrogen receptor; PR = progesterone receptor; IDC = invasive ductal carcinoma. [a]Some data for each parameter are not available. [b]P value from Fisher exact test or c^2 for trend, as appropriate. Statistically significant values (P ≤ 0.05) are indicated in bold.

DISCUSSION

This is the first and largest study to investigate the frequency and the form of sequence alterations as well as the clinical-pathological features of the BRCA1 and BRCA2 genes in Kazakh breast cancer patients in Xinjiang of China. Most studies on BRCA gene mutations have focused on western populations with a family history, ovarian cancer, or high cancer risks (Cherbal et al., 2012; Noh et al., 2014), and few studies have examined the role of the BRCA genes in Asian sporadic breast cancer populations (De Leon Matsuda et al., 2002).

In our study, a total of 129 Kazakh breast cancer cases and 105 healthy women, including 79 *BRCA1/2* mutation carriers in the case group and 71 *BRCA1/2* mutation carriers in the control group, were examined for their clinical-pathologic characteristics from 2 of the largest hospitals admitting patients from different areas of Xinjiang. Despite differences in the method of collecting data, the study populations and the distributions of clinical-pathologic variables considered in our study were fundamentally consistently between the 2 hospitals. The prevalence of germline mutations in *BRCA1/2* varied by ethnicity (De Leon Matsuda et al., 2002; Cherbal et al., 2012; de Juan Jiménez et al., 2012; Stadler et al., 2012; Kim and Choi, 2013; Tariq et al., 2013; Hernández et al., 2014). We observed a higher prevalence of *BRCA1/2* common polymorphisms in breast cancer cases and the control group and also found that a large number of Kazakh women carried ≥ 4 co-existing *BRCA1/2* alterations, which is consistent with the previously reported findings for Kazakhstan (Akilzhanova et al., 2011) and Asian and European populations (Han et al., 2006; Song et al., 2006; Loizidou et al., 2007). We hypothesize that the Kazakh people in Xinjiang region of China were likely relatively stable, retaining most of the Kazakh genetic properties because of geographical location, religious beliefs, social culture, and lifestyle.

A previous study suggested that *BRCA1/2* germ line mutations occur in sporadic breast cancers (de Juan Jiménez et al., 2012), but whether common polymorphisms play an important role in cancer risk is not well-understood. In our study, we found 2 unclassified variants, rs80357374 (*BRCA1* T539M) and rs4987117 (*BRCA2* T1915M), one of which had not been found elsewhere in China (*BRCA1* T539M) and was only detected in 2 healthy women. However, the missense mutations rs1799950 (G356A), rs1801499 (His743), rs1799944 (Asn991Asp), and rs543304 (Val1269) were detected more frequently in breast cancer patients than in healthy controls, and the presence of 4 mutations designated as significantly statistically different between case and control groups indicates that these mutations may be reclassified as deleterious. Janezic et al. (1999) previously reported that the Q356R polymorphism was significantly associated with familial ovarian cancer, suggesting that the risk of ovarian cancer development is increased by this sequence variant. In contrast, Arg356 had a higher genotype distribution in healthy controls than in breast cancer patients, it and may play a protective role against breast cancer (Dunning et al., 1997; Akilzhanova et al., 2011). The missense mutation Asn991Asp has been identified in previous studies and has been classified as a variant with no clinical significance in the Breast Cancer Information Core Database (Easton et al., 2007). Although the other 2 mutations (His743, Val1269) in our series did not cause changes in the amino acids and were silent substitutions, they were still closely related to breast cancer. Thus, previous studies have examined the function of these 2 sites (Karimian Fathi et al., 2014; Samel et al., 2014). Currently, only 2 deleterious mutations have been found in the Kazakh population in China (Ou et al., 2013). *BRCA1/BRCA2* deleterious mutations were not detected in our study, which may be because the subjects were not high-risk patients, such as some patients are with family history or of the triple-negative type. Additionally, we only studied approximately 60% of the *BRCA1/2* exon region.

The prevalence of *BRCA1* mutations was similar to that of *BRCA2* mutations (48.8 *vs* 46.6%). However, the frequency of *BRCA2* mutations was much higher than that of *BRCA1* in Chinese women (Zhang et al., 2012) and other Asian populations (Han et al., 2006). In contrast, *BRCA1* mutation is more common than *BRCA2* mutation in Caucasian populations (Hall et al., 2009). Notably, most Kazakh breast cancer patients carried *BRCA1/2* mutations. A previous study of women in Kazakhstan reported that 71.1% of sporadic breast cancer patients had *BRCA1* mutations (Akilzhanova et al., 2011). Most of these missense mutations were observed

in the Kazakh population both in China and Kazakhstan. Compared with other ethnic groups in China (Zhang et al., 2012; Ou et al., 2013), we examined Kazakh breast cancer characteristics, including low incidence, early onset age, high stage, and poor prognosis. Differences in the clinical pathological characteristics of breast cancer between Kazakh and other ethnicities mainly involve race, economic condition, extent of understanding of diseases, medical and health conditions, and many other factors. Overall, Kazakh sporadic breast cancers in China mainly included invasive ductal carcinomas, G2-3, stage II-III disease, high Ki-67 status, and ER and HER-2 expression.

The average age at diagnosis of breast cancer among *BRCA1* carriers (46.8 years) and *BRCA2* (47.6 years) was lower than that of wild-type patients separately, but the differences were not significant. However, *BRCA1/2* carriers were generally younger at diagnosis compared to wild-type breast cancer patients. The average age of onset of *BRCA1* and *BRCA2* carriers in our study was similar to that in Chinese and Caucasian populations (Yip et al., 2009; Zhang et al., 2012), indicating that *BRCA1/2* mutations may contribute to the early onset of breast cancer development in Kazakh women. Invasive ductal carcinoma is the most common histological subtype found among Kazakh breast cancer patients, but it was not the predominant histological tumor type in *BRCA1/2* carriers in our cohort, which differed from the results observed in a Chinese Han population (de Juan Jiménez et al., 2012).

In our study, patients with *BRCA1/2* mutations showed decreased nodal metastasis and early stage status compared to those without *BRCA1/2* alterations; furthermore, patients with *BRCA1* mutations had a statistically significantly higher prevalence of negative nodal metastasis and early stage than those without mutations. However, there is conflicting evidence regarding the association between *BRCA* status and nodal involvement. *BRCA* mutations are not predictive factors of nodal metastasis (Noori et al., 2014). There were no significant differences between women diagnosed with breast cancer with or without *BRCA1/2* polymorphisms in terms of the age at diagnosis or histology and HER-2 and Ki-67 status. In particular, *BRCA1*-associated Kazakh sporadic breast cancers presented with high tumor grade, early stage, negative lymph node status, the absence of ER expression, and PR-positive status. In addition, the expression of ER was the only predominant histological type in *BRCA2* carriers in our cohort, which was similar to Korean multicenter data (Yu et al., 2014).

Large population-based gene screening studies involving the entire coding region of *BRCA1/2* are also required to precisely establish the penetrance, frequency, and significance of the broad spectrum of variations in the BRCA1/2 genes in China's Kazakh ethnic population. Additionally, the power of our findings may have been limited by missing data for molecular markers. Thus, we are currently collecting more breast cancer cases as well as their epidemiological and molecular features.

In conclusion, *BRCA1* mutation-positive Kazakh breast cancer patients in China have unique clinical and pathological features, such as younger age at diagnosis, higher proportion of invasive ductal proportion, higher tumor grade, high Ki-67 status, and ER and HER-2 expression. Kazakh sporadic breast cancer involving *BRCA2* mutations also more frequently showed ER-positive status. It is generally accepted that after treatment with standard therapy, the prognosis of *BRCA*-mutated breast cancer patients is equal to that of patients with sporadic breast cancer, so *BRCA* mutational screening has become increasingly important in clinical application. BRCA gene mutation screening may enable earlier detection and more targeted therapy. Moreover, further studies are required to investigate the impact of *BRCA* mutations on the unique clinical and pathologic characteristics of Kazakh breast cancer patients in China.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

Research supported by Xinjiang Uygur Autonomous Regional Natural Science Foundation of China (Grant #2011211A084).

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