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ORIGINAL ARTICLE

High frequency of *BRCA1* founder mutations in Polish women with nonfamilial breast cancer

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Abstract Possession of a *BRCA1/2* mutation increases risk of contralateral breast and ovarian cancer recurrence and may have an impact on health management decisions, such as imaging screening, preventive surgical interventions and systemic therapies. A hospital-based study was conducted to assess the frequency and spectrum of pathogenic germline *BRCA1* and *BRCA2* mutations in Polish women with familial and nonfamilial breast cancer. Genomic DNA was extracted from 1581 women with breast cancer and from 2225 healthy individuals. For genotyping *BRCA1* (5382insC, T300G, 3819del5, 185delAG, C5370T, 3875del4, 3896delT, 4153delA, 4184del4, 4160delAG, G5332A) mutations and *BRCA2* (G1408T, 5467insT, 6174delT, 6192delAT, 6675 delTA, 8138del5, 9152delT, C9610T, 9630delC) mutations, a Custom TaqMan (Applied Biosystems) PCR-based technology was adopted. A *BRCA1* mutation was found in 26 and 12.5 % of women with familial breast cancer and in 13 and 8.3 % nonfamilial (sporadic) breast cancer, diagnosed before or after 50 years of age, respectively. A much lower frequency of *BRCA2* mutation was observed. The predominance of seven *BRCA1* mutations (5382insC, T300G, 3819del5, 185delAG, C5370T, 3875del4, 4153delA) studied in the Masovian voivodeship population confirmed a strong founder effect for *BRCA1* mutations in the Polish population, and the results of *BRCA2* testing confirmed a high diversity in the studied pathogenic mutations in *BRCA2* gene. We propose offering inexpensive testing for the presence of *BRCA*1 founder mutations to all Polish women at the time of initial breast cancer diagnosis, regardless of the patient's family history or age of disease onset.

Keywords *BRCA1* · *BRCA2* · Mutations · Nonfamilial · Sporadic · Breast · Cancer · Familial

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Introduction

Breast cancer is the most common type of cancer in the Polish population, and is a leading cause of cancer-related morbidity and mortality [1]. Most breast cancers are sporadic and their heritable risk may be explained by a combination of modest effects of inherited common low-penetrance polymorphisms of multiple genes [2, 3]. Highly penetrant hereditary breast cancers result from strong effect size mutations of a single "cancer gene", and their risk can be recognized by family history, even if high-penetrance mutations are not identified [4].

Germline mutations in *BRCA1* and *BRCA2* genes confer a risk of breast cancer up to 30-times higher than the

general population risk, and they account for up to 80 % of breast/ovarian cancer families [5, 6]. The lifetime risk of *BRCA1/2* mutation carriers for developing breast and ovarian cancer is as high as 85 and 64 %, respectively [6]. According to the Breast Information Core (http://research.nhgri.nih.gov/bic/), more than 1700 *BRCA1* mutations, polymorphisms and variants are deposited in the database [7]. The incidence and spectrum of the mutations vary among populations, and the carrier frequency in general populations ranges between 1/40 and 1/800 [8]. Some populations demonstrate a wide spectrum of mutations, while others are characterized by high prevalence of a small number of founder mutations [9]. In Poland, the frequency of *BRCA1* mutations is estimated between 1/240 and 1/360, and the two founder mutations 5382insC and T300G (C61G) account for 70–90 % of the *BRCA1* mutations found in the Polish population [8]. None of the *BRCA1* founder mutations is unique to Poland.

Targeted genetic counseling and testing for the presence of *BRCA1/2* mutations are mostly offered in the context of familial cancer genetics, and focus on high-risk factors, such as young age of diagnosis and the number of relatives affected by breast and/or ovarian cancers. However, since 30–50 % of women with a *BRCA1/2* mutation have no known family history of breast or ovarian cancer [10, 11], and possession of a *BRCA1/2* mutation may have an impact on health management decisions [12–14], other recommendations for testing of *BRCA1/2* mutations are also possible.

In the study presented here, we asked whether the predictive testing guidelines in the Polish population could be readily limited to screening the most frequent *BRCA1/2* mutations, and whether inclusion criteria should be based on the family history and age of screeners. To address this, we compared the incidence of selected *BRCA1* and *BRCA2* mutations screened in Polish women with familial and nonfamilial breast cancer. Selection of the most frequent mutations to be screened was based on the results of previous studies [7, 8, 15–19].

Materials and methods

Study population

A hospital-based study of Polish women with breast cancer was conducted at the Cancer Center-Institute of Oncology. Between 2003 and 2010, blood samples were collected from a total of 1581 women with newly-diagnosed breast cancer, predominately exhibiting early age of onset. Most of 906 cases who represented a family with at least one more breast or ovarian cancer diagnosis in a first- or second-degree relative were recruited at either the Department of Breast Cancer and Reconstructive Surgery or Genetic Counseling Unit when most of 675 cases with negative history for breast and/or ovarian cancer were recruit at the Department of Breast Cancer. The personal and familial cancer history was acquired by in-depth interviews in all patients. Patients from the both groups were treated mostly at the Warsaw Cancer Center. In addition, 2225 healthy individuals (1629 females and 596 males) exhibiting no known history of malignancy, normal results of screening colonoscopy, and normal mammography or PSA levels, were recruited, primarily from the National Colorectal Cancer Screening Program. The median age at diagnosis for women with breast cancer and healthy controls was 45 years (range: 17–85) and 58 years (range: 40–81), respectively. All patients and control subjects were Polish Caucasians recruited from the Masovian voivodeship population.

Mutation analysis

Genomic DNA was extracted from whole blood and treated with EDTA using the QIAamp DNA Mini Kit (Qiagen, Germany), following the manufacturer's protocol. DNA samples that passed quality control were then brought to a final concentration of 50 ng/µl in Tris–EDTA buffer (pH = 8), with concentrations of Tris and EDTA not exceeding limits of 10 and 0.1 mM, respectively. Individual genotyping was carried out using Custom TaqMan SNP Genotyping Assays (Life Technologies, USA), a SensiMix^{TM} II Probe Kit (Bioline Ltd, United Kingdom), and a 7900HT Real-Time PCR system (Life Technologies, USA). Samples with detected mutation were sequenced.

The *BRCA1/2* mutation frequency disproportions between the specific groups of breast cancer cases and the group of control subjects were tested using the Fisher's exact test implemented in PLINK v1.07 software (http://pngu.mgh.harvard.edu/purcell/plink/) [20]. The Bonferroni correction for multiple testing was used.

Results

To analyze the frequency and spectrum of pathogenic germline *BRCA1* and *BRCA2* mutations in Polish women with breast cancer, we selected 11 *BRCA1* mutations (185delAG, T300G, 3819del5, 3875del4, 3896delT, 4153delA, 4160delAG, 4184del4, G5332A, C5370T, 5382insC) and 9 *BRCA2* mutations (G1408T, 5467insT, 6174delT, 6192delAT, 6675delTA, 8138del5, 9152delT, C9610T, 9630delC) based on the results of previously reported research conducted on Polish subpopulations [7, 8, 15–19]. Most of the mutations tested introduce premature stop codons. The proportion of breast cancer patients with or without mutations was calculated for familial and nonfamilial instances and by age of onset.

A total of 266 (16.8 %) *BRCA1* mutations (Table 1) and 14 (0.89 %) *BRCA2* mutations (Table 2) were found among 1581 cancer patients. Of these, the highest prevalence was found for the two Polish founder mutations, 5382insC and T300G, which accounted for 82.3 %, and the four most common mutations (5382insC, T300G, 3819del5, 185delAG) accounted for 91 % of all detected *BRCA1* mutations (Table 1). Five *BRCA1* mutations (5382insC, 3896delT, 185delAG, 4153delA, C5370T) were also detected in nine (0.4 %) of 2225 healthy controls, while no *BRCA2* mutations were found in the control group.

Breast cancers were classified as familial with non-restrictive criteria when a proband represented a family with at least one breast or ovarian cancer diagnosis in a first- or second-degree relative. Information about cancers in relatives was obtained from the patient's interview. As expected, the frequency of *BRCA1* (Table 1) and *BRCA2* (Table 2) mutations was higher in familial than in nonfamilial breast cancer patients. A *BRCA1* and *BRCA2* mutation was detected in 20.8 and 1.3 % patients with familial cancer and in 11.6 and 0.3 % patients with nonfamilial breast cancer, respectively. Notably, the high significance of association obtained for the dominant model of inheritance was particularly well pronounced in the nonfamilial breast cancer cases, and was predominantly constituted by the T300G and 5382insC *BRCA1* gene mutations (Table 1).

Hereditary breast cancers are characterized by an early age of onset. In fact, in the screened breast cancer patients with a family history of breast and/or ovarian cancer, a *BRCA1* mutation was found in 144 (26 %) of 553 and 44 (12.5 %) of 353 cases in which the disease was diagnosed before or after 50 years of age, respectively (Table 1). However, an unexpectedly high number of mutation positive women were also found among nonfamilial breast cancer patients. In this group, a *BRCA1* mutation was detected in 61 (13 %) of 471 and 17 (8.3 %) of 204 patients with the disease onset before or after 50 years of age, respectively (Table 1).

Discussion

Specific founder mutations in *BRCA1* are common in several populations. The study on relative contribution of founder and nonfounder *BRCA* mutations in all regions of Poland revealed that >60 % of breast and breast-ovarian cancer families with 3 or more cases of cancer carried *BRCA* mutation; of them 91 % was one of the 3 common founder mutations (5382incC, T300G, 4153delA) [7]. As reported recently, the most frequent mutations in unselected Polish breast and ovarian cancer patients were 5382incC and T300G [11]. The dominance of these two mutations, also found in our study, confirms a strong founder effect for *BRCA1* mutations in the Polish population [15–18].

We found a *BRCA1* mutation in 26 and 12.5 % of women with breast cancer diagnosed before or after 50 years of age, respectively, among whom at least one verified breast or ovarian cancer was also diagnosed in a first- or second-degree relative. In women diagnosed with sporadic breast cancer before or after 50 years of age, a *BRCA1* mutation was found in 13 and 8.3 % patients, respectively (Table 1). Thus, unselected nonfamilial breast cancer patients, especially those who were diagnosed with breast cancer after 50 years of age, revealed unexpectedly high prevalence of the *BRCA1* mutations. In contrast to the high prevalence of *BRCA1* mutations found in both familial and sporadic breast cancers, even with late onset, a much lower frequency of *BRCA2* mutations was observed.

According to roughly similar national guidelines and recommendations, genetic testing is preferentially offered to families with breast and/or ovary cancer history in the context of a familial cancer service [21]. Until now, Genetic Counseling Unit at the Warsaw Cancer Center-Institute of Oncology has offered adequate counseling and testing for the presence of *BRCA1/2* mutations mostly to patients with familial breast and/or ovary cancer and their relatives. However, recently published studies revealed rather limited value of cancer family history for prediction of *BRCA1* mutation presence in Polish breast and ovarian cancer patients [11]. In a consequence, it has been suggested the necessity for targeted genetic testing for T300G mutation in families with a single diagnosis of ovarian cancer [11].

The high frequency of *BRCA1* mutations in nonfamilial breast cancers, as found in our study, may expand the indications for genetic testing of founder mutations to also include women with nonfamilial (sporadic) breast cancer. Such an expanded inclusion criteria would not significantly increase the cost of genetic testing, because testing limited to the sets of founder mutations represents a rather inexpensive and rapid analytical procedure. A cost-effective (internal costs, not including personnel and overhead, are around $20) PCR-based genotyping technology has proven to be adequately reliable in Polish population genetic screening. Unfortunately, a similar inexpensive genetic screening test for *BRCA2* mutations could not be established.

Women affected with *BRCA1/2*-related breast cancer have a higher risk of developing independent, contralateral breast and ovarian cancer [5, 22]. To identify breast cancer at an early stage, an intensified surveillance program should be provided [21]. However, negative result of genetic testing is not informative for assessing the cancer risk. Therefore, genetic testing should not be offered without adequate genetic counseling that considers all biomedical, social and ethical challenges, as well as the implementation costs of surveillance programs offered to probands and their family members. To this end, while genetic testing integrated with breast cancer diagnosis can

Table 1 Frequency of selected BRCA1 mutations in breast cancer cases and case–control association significance

	Age at diagnosis (years)															
	Total				<40				40–49				>50			
	Familial (N = 906)		Nonfamilial (N = 675)		Familial (N = 213)		Nonfamilial (N = 273)		Familial (N = 340)		Nonfamilial (N = 198)		Familial (N = 353)		Nonfamilial (N = 204)	
Mutation	Carriers	P	Carriers	P	Carriers	P	Carriers	P	Carriers	P	Carriers	P	Carriers	P	Carriers	P
185delAG	8 (0.9 %)	1	3 (0.4 %)	9.37E-01	3 (1.4 %)	1	1 (0.4 %)	1	4 (1.2 %)	1	0 (0.0 %)	1	1 (0.3 %)	1	2 (1.0 %)	4.03E-01
T300G	38 (4.2 %)	1	16 (2.4 %)	1.13E-08	15 (7.0 %)	5.08E-01	8 (2.9 %)	1.96E-06	16 (4.7 %)	1	5 (2.5 %)	1.81E-04	7 (2.0 %)	1	3 (1.5 %)	1.59E-02
3819del5	11 (1.2 %)	1	1 (0.1 %)	1	6 (2.8 %)	1	0 (0.0 %)	1	3 (0.9 %)	1	1 (0.5 %)	1	2 (0.6 %)	1	0 (0.0 %)	1
3875del4	4 (0.4 %)	1	2 (0.3 %)	1	0 (0.0 %)	1	1 (0.4 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	4 (1.1 %)	1	1 (0.5 %)	1
3896delT	2 (0.2 %)	1	0 (0.0 %)	1	1 (0.5 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	1 (0.3 %)	1	0 (0.0 %)	1
4153delA	2 (0.2 %)	1	2 (0.3 %)	1	1 (0.5 %)	1	1 (0.4 %)	1	1 (0.3 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	1 (0.5 %)	1
4160delAG	1 (0.1 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	1 (0.3 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1
4184del4	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1
G5332A	0 (0.0 %)	1	1 (0.1 %)	1	0 (0.0 %)	1	1 (0.4 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1	0 (0.0 %)	1
C5370T	8 (0.9 %)	1	2 (0.3 %)	1	1 (0.5 %)	1	1 (0.4 %)	1	3 (0.9 %)	1	0 (0.0 %)	1	4 (1.1 %)	1	1 (0.5 %)	1
5382insC	114 (12.6 %)	1.69E-01	51 (7.6 %)	3.83E-25	36 (16.9 %)	2.09E-02	16 (5.9 %)	6.60E-12	53 (15.6 %)	4.97E-02	26 (13.1 %)	1.44E-23	25 (7.1 %)	1	9 (4.4 %)	2.89E-07
Total	188 (20.8 %)	1.59E-03	78 (11.6 %)	1.47E-36	63 (29.6 %)	1.85E-05	29 (10.6 %)	5.84E-20	81 (23.8 %)	2.58E-04	32 (16.2 %)	1.46E-26	44 (12.5 %)	2.01E-01	17 (8.3 %)	2.45E-12

Table 2 Frequency of selected BRCA2 mutations in breast cancer cases and case–control association significance

	Age at diagnosis (years)															
	Total				<40				40–49				>50			
	Familial (N = 906)		Nonfamilial (N = 675)		Familial (N = 213)		Nonfamilial (N = 273)		Familial (N = 340)		Nonfamilial (N = 198)		Familial (N = 352)		Nonfamilial (N = 204)	
Mutation	Carriers	*P*	Carriers	*P*	Carriers	*P*	Carriers	*P*	Carriers	*P*	Carriers	*P*	Carriers	*P*	Carriers	*P*
G1408T	1	1	0	1	1	1	0	1	0	1	0	1	0	1	0	1
	(0.1 %)		(0.0 %)		(0.5 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)	
5467insT	4	1	2	5.12E-01	2	1	0	1	1	1	1	7.60E-01	1	1	1	7.81E-01
	(0.4 %)		(0.3 %)		(0.9 %)		(0.0 %)		(0.3 %)		(0.5 %)		(0.3 %)		(0.5 %)	
6174delT	4	1	0	1	2	1	0	1	0	1	0	1	2	1	0	1
	(0.4 %)		(0.0 %)		(0.9 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.6 %)		(0.0 %)	
6192delAT	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
	(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)	
6675delTA	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
	(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)	
8138del5	2	1	0	1	0	1	0	1	0	1	0	1	2	1	0	1
	(0.2 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.6 %)		(0.0 %)	
9152delT	1	1	0	1	0	1	0	1	0	1	0	1	1	1	0	1
	(0.1 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.3 %)		(0.0 %)	
C9610T	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
	(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)	
9630delC	0	1	0	1	0	1	0	1	0	1	0	1	0	1	0	1
	(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)		(0.0 %)	
Total	12	1	2	5.17E-01	5	1	0	1	1	1	1	7.62E-01	6	1	1	7.83E-01
	(1.3 %)		(0.3 %)		(2.3 %)		(0.0 %)		(0.3 %)		(0.5 %)		(1.7 %)		(0.5 %)	

have an impact on prophylactic and therapeutic decisions [10, 22], it may not be universally accepted.

In summary, inexpensive testing for the presence of *BRCA*1 founder mutations should be offered to all Polish women at the time of initial breast cancer diagnosis, regardless of a patient's family history or the age of disease onset.

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Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The study was approved by the local ethics committee (Medical Center for Postgraduate Education and Cancer Center, Warsaw, Poland), and all the participants provided appropriate consent. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki.

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