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Original scientific paper

THE SPECTRUM OF THE MOST COMMON BRCA1/BRCA2 MUTATIONS IN LITHUANIAN HIGH RISK FAMILIES

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Breast cancer is the neoplasm with the highest incidence and mortality among women in Lithuania. The aim of the study was to determine the mutational incidence in BRCA1 and BRCA2 genes in high-risk breast and/or ovarian cancer families. After written informed consent, 36 participants from Lithuanian health science university hospital provided a blood sample for genetic analysis. Molecular diagnostics was done for 6 BRCA1and BRCA2 mutations. From 36 tested subjects for BRCA1/BRCA2 mutations. Positive test for BRCA1/BRCA2 mutations test was found in 12 (33%) cases. Most common BRCA1 mutation was 5328insC – 6 (50%) cases, other mutations: 185delAG - 1 (8,3%), 300t>6(c61G) - 4 (33,3%), 4153 del A – 1 (8,3%). All mutations were BRCA1, but none of the women were positive for the analyzed BRCA2 mutation. The mean age when the cancer was diagnosed in BRCA1 mutations group was 40.40±3.39 comparing with the group without mutations – 43.29 ±2.52. Rates of BRCA1 and BRCA2 mutation testing are increasing in young women with breast and ovarian cancer. Detected mutations in

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BRCA1 contribute to up to one-third of the families with breast and ovarian cancer in Lithuania.

Key words: BRCA, breast and ovarian cancer, sceening

INTRODUCTION

BRCA1 and *BRCA2* are the most important genes predisposing to inherited breast and ovarian cancers (FOULKES, 2014). Germline mutations in these two highly penetrant genes can increase the lifetime risk of developing these tumors by as much as 80%, and are also associated with an earlier onset of disease. Among women, breast cancer is the most commonly diagnosed cancer after nonmelanoma skin cancer, and it is the second leading cause of cancer deaths after lung cancer (ROSENBERG *et al.,* 2016).

BRCA1 and BRCA2 are human genes that produce tumor suppressor proteins. Like many other tumor suppressors, the proteins produced from the BRCA1 and BRCA2 genes helps prevent cells from growing and dividing too rapidly or in an uncontrolled way. In women who have a BRCA1 or BRCA2 gene mutation there is an increased risk of getting breast cancer (BC) and ovarian cancer (OC) (CECENER *et al.,* 2014). So it is important to ask patients about family history of BC and OC so as to find it on earlier stages (SAITO e*t al.,* 2014).

BRCA1 gene cytogenetic location is 17q21 (KARAMI *et al.,* 2013). In addition to female breast cancer, mutations in the *BRCA1* gene increase the risk of several types of cancer: fallopian tube cancer, male breast cancer, and pancreatic cancer. Many of these mutations change one of the amino acids used to make the BRCA1 protein, resulting in a protein that cannot perform its normal DNA repair function, and cells become proliferate in an uncontrolled way. BRCA1 gene mutation increases risk of BC from 60% to 85%, and fallopian tube cancer from 40% to 60% (FOULKES, 2014).BRCA2 gene cytogenetic location is 13q12.3.Mutations in one copy of the *BRCA2* gene can lead to an increased risk of OC, prostate cancer, pancreatic cancer, fallopian tube cancer, male breast cancer, and an aggressive form of skin cancer called melanoma. The aim of the study was to identify the frequency of BRCA mutations in Lithuanian families with BC /OC and strong family history for cancer.

MATERIALS AND METHODS

Study subjects

36 women attending Lithuanian health science university hospital during 2013-2014 were consecutively enrolled in the study. All enrolled patients underwent pre-test counseling during which they were informed about the significance of molecular screening, provided information about their personal and familial history, and gave written informed consent . The 26 enrolled women had at least one of the following conditions: early-onset breast cancer (BC) (diagnosed at 45 years or earlier); ovarian cancer (OC); 10 woman had positive family history: two and more first or second degree relatives with breast and/or ovarian cancer.

Molecular analysis

Here we describe a simple and rapid method for the simultaneous detection of common mutations: 185delAG and 5382insC in *BRCA1*, and 6174delT in *BRCA2*.

Peripheral blood was collected in acid citrate dextrose (ACD) tubes to prevent coagulation of blood samples. Genomic DNA was isolated from peripheral blood leukocytes using a commercially available DNA extraction kit (ThermoFisher Scientific Baltics, Lithuania) utilizing

silica-based membrane technology. Allele-specific oligonucleotide primers were used as previously published (CHAN *et al.*, 1999).

For each mutation, three primers (one common, one specific for the mutant, and one specific for the wild-type allele) were used. The competing wild-type and mutant primers were designed to differ by ~20 bp size, allowing detection of the PCR products by standard electrophoresis and ultraviolet illumination after ethidium bromide staining. The wild-type (shortand) mutant (long) primers both contain a mismatched base sequence near the 3′ end. In the early cycles of amplification, the mismatched sequences generate mutagenized PCR products that are refractory to cross-amplification by the competing primer, thereby ensuring specificity of the reaction. The long (mutant) primer also incorporates two additional mismatched bases at two contiguous positions corresponding to the 5′ end of the short (wild-type) primer. The primer sequences and sizes of corresponding amplicons are shown in Table 1.

Table 1. Nucleotide sequences of the primer sets.

Primer	Primer sequence[1]	Size of amplicon
BRCA1 185delAG		
Common forward (P1)	5′-ggttggcagcaatatgtgaa	
Wild-type reverse (P2)	5′-gctgacttaccagatgggactctc	335 bp
Mutant reverse (P3)	5′-cccaaattaatacactcttgtcgtgacttaccagatgggacagta	354 bp
BRCA1 5382insC		
Common reverse (P4)	5′-gacgggaatccaaattacacag	
Wild-type forward (P5)	5′-aaagcgagcaagagaatcgca	271 bp
Mutant forward (P6)	5′-aatcgaagaaaccaccaaagtccttagcgagcaagagaatcacc	295 bp
BRCA2 6174delT		
Common reverse (P7)	5′-agctggtctgaatgttcgttact	
Wild-type forward (P8)	5′-gtgggatttttagcacagctagt	151 bp
Mutant forward (P9)	5′-cagtctcatctgcaaatacttcagggatttttagcacagcatgg	171 bp

PCR amplification was carried out using the GeneAmp® PCR 2400 system from Perkin-Elmer. In each PCR reaction, 25 ng of genomic DNA was added to 10 μL of reaction mixture consisting of 1× PCR reaction buffer (10 mmol/L Tris-HCl, pH 8.3, 50 mmol/L KCl, 0.01 g/L gelatin), 3.25 mmol/L $MgCl_2$, 0.2 mmol/L dNTPs, and 50 kU/L AmpliTaq Gold™ (all from Perkin-Elmer). Allele-specific primers were added at 2.0 μmol/L for P1 and P3; 0.4 μmol/L for P2; 0.12 μmol/L for P4, P5, and P6; 0.31 μmol/L for P7 and P9; and 0.24 μmol/L for P8. Each PCR reaction consisted of an initial 12 min of AmpliTaq Gold activation at 95°C, followed by 35 cycles of 15 s of denaturation at 94°C, 15 s of annealing at 57°C, and 30 s of extension (with an increment of 1 s for each subsequent cycle) at 72°C, and a final extension step of 5 min at 72°C. At the conclusion of the reaction, the PCR product was mixed with 2 μL of loading dye (200 g/L sucrose, 0.05 g/L bromphenol blue) and then separated on precast Clearose BG Mini (9 × 12 cm) Gels (Elchrom Scientific) by routine submerged electrophoresis (120 V, 80 min). The resolved amplicons were then stained with 0.5 mg/L ethidium bromide and viewed under ultraviolet illumination.

RESULTS

From 36 tested subjects for BRCA1/ BRCA2 mutations 26 were patients with breast and/or ovarian cancer and 10 cases with positive family history for hereditary cancers. Positive test for BRCA1/BRCA2 mutations test was found in 12 (33%) cases. Most common BRCA1 mutation was 5328insC – 6 (50%) cases, other mutations: 185delAG - 1 (8.3%), *300T*>G/*C61G*) - 4 (33.3%), 4153 del A – 1 (8.3%) (Table 2).

Table 2. Distribution of detected mutations

Gene	Mutation	Cases	Health condition
BRCA1	185delAG	1	Family history (3 cases) of BC
	300T>G/*C61G*)	4	BC
			OC
			Family history (3 cases) of BC
			Family history (2 cases) of BC
	2080delA	0	
	415delA	1	BC
	5382insC	6	BC
			OC
			Family history (3 cases) of BC
			Family history (4 cases) of BC
			Family history (3 cases) of OC
			Family history (2 cases) of OC
BRCA2	6174delT	0	

BC Breast Cancer, OC ovarian cancer

All mutations were BRCA1, but none of the women were positive for the analyzed BRCA2 mutation.

Nineteen percent of the women with breast or ovarian cancer carried one of the analyzed BRCA1 gene mutation: two mutations 5328insC, two mutations *300T*>G/*C61G*) and one 4153 del A (Table 3).

Table 3. Clinical characteristics of BC and OC patients with detected mutations.

Case number	Mutation	Cancer localization	Individual age at diagnosis
1	*300T*>G/*C61G*)	BC	38
2	*300T*>G/*C61G*)	OC	39
3	415delA	BC bilateral	44
4	5382insC	BC bilateral	42
5	5382insC	OC	40

BC Breast Cancer, OC ovarian cancer

The mean age when the cancer was diagnosed in BRCA1 mutations group was 40.60±3.39 comparing with the group without mutations – 43.29 ±2.52.

Every second patient with family history (two or more family members) for BC or OC had BRCA1 or BRCA2 mutation.

DISCUSION

The identification of *BRCA1* and *BRCA2* mutation carriers and individualized risk assessment is an important procedure growing in clinical importance, since management protocols for mutation carriers become well established and proven life-saving, risk-reducing preventive medical interventions exist. Currently, in most countries clinical *BRCA1/2* testing is offered after genetic counseling by geneticist when mutation finding probability exceeds 10%, or even 20% (FOULKES, 2014). Although genetic linkage analysis suggest that the prevalence of *BRCA* gene mutation in familial BC and/or OC is about 45-90 % (FOULKES, 2014). the frequency of *BRCA1* mutation in familial breast cancer varies from 1 to 35 % worldwide (STRUEWING *et al.*, 1995). In our study *BRCA1* mutations were identified in 33 % (12/36) of cases with familial BC and OC patients. This is in contrast 10.3 % of French hereditary BC and/or OC families exhibiting a *BRCA1* mutation and Serbian high risk families that had 12.77% frequency of frameshift mutations (DOBRIČIĆ *et al.,* 2013). The frequency of *BRCA1* mutations among Algerian families was 36.4 % (4/11) (UHRHAMMER *et al.,* 2008). The prevalence of *BRCA1* mutations reported in Tunisian families varies between 15.6 % -37.5 % depending on region and inclusion criteria (TROUDI *et al.,* 2007). Frequency of BRCA mutations is much higher than rare mutations of monogenous diseases (such as Stargardt disease) (SERAPINAS *et al.,* 2013). It is alike to MTHFR mutation that in European population in homozygous state is found up to 20 % cases (DAUGELAITE *et al.,* 2015). Penetrance of *BRCA* mutations may be modified by other risk or protective genes or environmental factors, most notably reproductive history and diet. The effect of lifestyle on this penetrance is significant, as studies of western populations show that carriers born after 1940 have much higher BC incidence and earlier onset than carriers born before 1940 (KING *et al.,* 2003). Our data from local hospital is similar to previously published data from Lithuania (ELSAKOV *et al.,* 2010), that showed 4153delA , 5382insC or C61G mutations to be the most frequent in BC and OC patients. But in Poland 3 most common mutations are different (c.5266dupC, c.181T>G and c.4035delA) that accounted for 91% mutations detected in *BRCA1 gene.*

A BRCA1 and BRCA2 genes mutation typically increases the risk of breast and ovarian cancer about 80-90%. The BRCA1 and BRCA2 genes provide instructions for making a protein that is directly involved in repairing damaged DNA. In the nucleus of many types of normal cells, the BRCA1 and BRCA2 proteins interacts with several other proteins, including the proteins produced from the BRAC51 gene, to mend breaks in DNA. As a result, cells are more likely to develop additional genetic alterations that can lead to cancer (PARADISO *et al.,* 2011, OKTAY *et al.,* 2010). Single cases are not generally accepted for genetic testing for hereditary BC genes without a strong implication of hereditary factors, such as young age at diagnosis (< 45 years), multifocal or bilateral tumors, and/or medullar histology. In most western populations such testing is not cost-effective, with only 2.6 % of 2-case families in Finland being positive for a *BRCA* mutation (VAHTERISTO *et al.,* 2001), and very few sporadic cases being positive in the US. Other studies, however, suggest that testing of 2-case families or single cases before the age of 36 can be efficient in certain populations (PETO *et al.,* 1999) The findings of a large international prospective study suggest for the first time that women with *BRCA1* mutations should have preventive ovarian surgery (prophylactic oophorectomy) by age 35, as waiting until a later age appears to increase the risk of ovarian cancer before or at the time of the preventive surgery (LOKICH *et al.,* 2013). Women

with BRCA2, however, do not appear to be at an increased risk of cancer by 35 years, so the prophylactic oophorectomy may be delayed to later age (Mac Bride, 2013). But during lifetime various egzogenous and endogenous (hormonal state, inflammation, smoking) factors may break homeostasis and have influence for carcinogenesis (FOULKES, 2014; SERAPINAS *et al.*, 2011). Moreover, women with *BRCA1* and *BRCA2* mutations who had this surgery experienced a 77 percent reduction in their overall risk of death by age 70 (VALACHIS *et al.*, 2014). Also patient with BRCA1 or BRCA2 mutations must have routine screening for breast cancer (self-exams, mammograms, doctor visits) like all women who are older than 50 years old (SYNOWIEC, 2014). The results have implications for the cost-effectiveness of wider implementation of BRCA1 and BRCA2 mutation analysis. Only a proportion of cases with early-onset breast cancer carry a mutation in one or the other gene, and only a small proportion of the familial risk of breast cancer is attributable to these genes. However, a substantial proportion (50% in our data) of young patients with two or more affected relatives is mutation carriers, and perhaps such women should be offered the opportunity of a test for mutations in BRCA1 and BRCA2 genes. Our study had several limitations; the major one is that not all mutations were screened but only most frequent due to the methodological possibilities. Also the population that we screened is not so big and we hope to investigate bigger population and with expended spectrum of mutations in the future.

CONCLUSIONS

More than 20% of the analyzed patients, including positive family history, carried a causative mutation. We point the importance if there are cases of cancer in family, there is need for genetic test of BRCA1 or BRCA2 genes mutation, especially if 2 or more family members have BC or OC. Given that knowledge and concern about genetic risk influence surgical decisions and may affect systemic therapy trial eligibility, all young women with BC and OC should be counseled and offered genetic testing.

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SPEKTAR NAJČEŠĆIH MUTACIJA BRCA1/BRCA2 KOD VISOKORIZIČNIH FAMILIJA U LITVANIJI

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Izvod

Kancer dojke je neoplazma sa najvećom učestalošću i smrtnošću kod žena u Litvaniji. Cilj istraživanja bio je da se utvrdi istovremena pojava BRCA1 i BRCA2 u genima kod visoko rizičnih familija za kancer dojke i/ili jajnika. Posle pisanog pristanka 36 učesnika, Litvanska zdravstvena i naučna univerzitetska bolnica, obezbedila je uzorke krvi za genetičke analize. Molekularna dijagnostika urađena je za 6 BRCA1 i BRCA2 mutacija. Od 36 testiranih individua test je bio pozitivan u 12 (33%) slučajeva. Najčešća BRCA1mutacija bila je 5328insC – 6 (50%), ostale mutacije bile su 185delAG - 1 (8,3%), 300t>6(c61G) - 4 (33,3%), 4153 del A – 1 (8,3%). Sve mutacije bile su za BRCA1, ali ni jedna žena nije bila pozitivna na ispitivanu BRCA2 mutaciju. Prosečna starost žena kod kojih je utvrđena BRCA1 mutacija, bila je 40.40±3.39, u odnosu na prosečnu starost grupe 43.29 ±2.52 bez mutacija. Odnos BRCA1 i BRCA2 mutacija se povećavao kod mladih žena sa kancerom dojke i jajnika. Detektovane mutacije u BRCA1 činile su do jedne trećine familija sa kancerom dojke i jajnika u Litvaniji.

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