CMJ Original Research March 2017, Volume: 39, Number: 1
Cumhuriyet Medical Journal 374-379
http://dx.doi.org/10.7197/cmj.v39i1.5000187135

Evaluation of *BRCA1* and *BRCA2* gene mutations in breast cancer patients

Meme kanserli hastalarda *BRCA1* ve *BRCA2* gen mutasyonlarının değerlendirilmesi

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Received/Accepted: April 26, 2016 / January 21, 2017
Conflict of interest: There is not a conflict of interest.

SUMMARY

Objective: Worldwide, breast cancer is the most common malignancy among women. In Turkey, breast cancer is also the most common cancer among women with the frequency of 25% of all female cancers. Germline mutations in tumor suppressor genes (*BRCA1* and *BRCA2)* cause genetic susceptibility to malignancies and are responsible for 5–10% of all breast and ovarian cancers. Women carrying mutations in *BRCA1* or *BRCA2* genes are at high risk to develop breast cancer, especially before the age of 45. The aim of this study was to determine the frequencies of the most common *BRCA1* and *BRCA2* gene mutations (185delAG and 5382insC in *BRCA1* gene and 6174delT in *BRCA2*) in patients with early-onset breast cancer in a Turkish population.

Method: 50 female early-onset (≤45) breast cancer patient were included in this study. The common *BRCA1* and *BRCA2* gene mutations were determined using conventional DNA sequencing.

Results: The patient's ages ranged from 28 to 45 years with a mean age of 40.08±4.275 years. The 185delAG (rs386833395) and 5382insC (rs397507246) mutations of *BRCA1* gene and 6174delT (rs80359550) mutation of *BRCA2* gene were analyzed in 50 breast cancer patients. These three mutations were not observed any of the breast cancer patients including in our study.

Conclusions: Our results showed that *BRCA1* gene 185delAG and 5382insC mutations and *BRCA2* gene 6174delT mutation are not common in Turkish breast cancer patients. It is believed that there might be other mutations of *BRCA1/2* genes or other genes rather than *BRCA1/2* that might be responsible for breast cancer in Turkish population.
Keywords : Breast cancer; *BRCA1*; *BRCA2*; mutation; sequencing

ÖZET

Amaç: Dünya çapında, meme kanseri kadınlarda en sık görülen kanserdir. Türkiye'de de meme kanseri tüm kadın kanserlerinin %25'i gibi bir sıklıkta kadınlarda en sık görülen kanserdir. Tümör baskılayıcı genlerdeki (*BRCA1* ve *BRCA2*) germline mutasyonlar kanser için genetik yatkınlığa neden olur ve tüm meme ve yumurtalık kanserlerinin %5-10'undan sorumludur. *BRCA1* veya *BRCA2* genlerinde mutasyon taşıyan kadınlar, özellikle 45 yaşından önce meme kanserine yakalanmak için yüksek riske sahiptir. Bu çalışmanın amacı, en yaygın olan *BRCA1* ve *BRCA2* gen mutasyonlarının, Türk populasyonunda erken yaş meme kanserli hastalardaki sıklığını belirlemektir.

Yöntem: Bu çalışmaya, erken yaş (≤45) meme kanserli 50 kadın hasta dahil edilmiştir. Yaygın *BRCA1* ve *BRCA2* gen mutasyonları, geleneksel DNA dizileme tekniği kullanılarak belirlenmiştir.

Bulgular: Yaşları 28 ila 45 yıl arasında değişen hastaların yaş ortalaması 40.08 ± 4.275 olarak belirlenmiştir. 50 meme kanserli hastada, *BRCA1* geni 185delAG (rs386833395) ve 5382insC (rs397507246) mutasyonları ile *BRCA2* geni 6174delT (rs80359550) mutasyonu analiz edilmiştir. Bu çalışmaya dahil edilen meme kanserli hastaların hiçbirinde bu üç mutasyona da rastlanmamıştır.

Sonuç: Sonuçlarımız, *BRCA1* geni 185delAG ve 5382insC mutasyonları ile *BRCA2* geni 6174delT mutasyonunun, Türk meme kanserli hastalarda yaygın olmadığını göstermiştir. Türk populasyonunda, meme kanserinden sorumlu olabilecek başka BRCA1/2 gen mutasyonları veya BRCA1/2 genleri dışında başka genlerin olabileceği düşünülmektedir.
Anahtar Sözcükler: Meme kanseri; *BRCA1*; *BRCA2*; mutasyon; dizileme

INTRODUCTION

Worldwide, breast cancer is the most prevalent cancer among women with one million cases per year[1]. In Turkey, breast cancer is the most common malignancy among women with the frequency 25% of all female cancers and with 17.531 new cases per year[2]. The risk of breast cancer is thought to be modified by lifestyle and environmental exposures possibly in combination with the genetic factors[3]. Germline mutations in tumor suppressor genes cause genetic susceptibility to malignancies and are responsible for 5–10% of breast and ovarian cancers[4]. Breast cancer 1 and 2 *(BRCA1* and *BRCA2*) are tumor supressor genes necessary for accurate repair of double-chain DNA breaks by homolog recombination[5]. Women carrying mutations in *BRCA1* or *BRCA2* genes are at high risk to develop breast cancer, especially before the age of 45[6].

BRCA1 gene contains 22 exons and it maps to human chromosome 17q21[7]. *BRCA2* gene is mapped to chromosome 13q12-q13 and contains 27 exons[8, 9]. Both the *BRCA1* and *BRCA2* genes have a large exon 11, translational start sites in exon 2, and coding sequences that are AT-rich; both span approximately 70 kb of genomic DNA[9]. *BRCA1* plays critical roles in DNA repair, cell cycle checkpoint control, and maintenance of genomic stability by forming several distinct complexes through association with different adaptor proteins[10].

Currently, more than 3500 clinical variations have been identified for *BRCA1* gene and about 2000 clinical variations have been identified for *BRCA2* gene (http://www.ncbi.nlm.nih.gov/clinvar, Accessed on February 26, 2016). Mutations in these genes have been reported in different populations and some of them are unique to each population. 185delAG mutation in exon2 and 5382insC mutation in exon 20 of *BRCA1* gene and 6174delT mutation in exon 11 of *BRCA2* gene are the most common *BRCA* mutations (>%90) in Ashkenazi Jewish population[11].

The present study aimed to investigate the frequencies of 185delAG mutation in exon2 and 5382insC mutation in exon 20 of *BRCA1* gene and 6174delT mutation in exon 11 of *BRCA2* gene in early onset breast cancer patients in a Turkish population.

MATERIAL AND METHODS

Subjects

The study consists of fifty female breast cancer patients under the age of 45 who had taken part in our previous study[12]. All subjects were diagnosed histologically using specimens obtained by surgical resection or biopsy. Clinical data information, including family history of cancer, diagnosis, tumor histology, tumor stage, menarche and menopause age, number of births, duration of breastfeeding, estrogen receptor (ER) and progesterone receptor (PR) status were obtained from patients' medical records. The mean age of the fifty patients was 40.08±4.275 years (between the ages 28-45). The breast cancer patients signed an informed consent form for genetic analysis after receiving information about the study. The study was approved by the Local Ethics Committee of Ondokuz Mayis University, Faculty of Medicine.

Genotyping

Genomic DNA was extracted from the peripheral blood leukocytes of breast cancer patients using a standard salting-out method[13]. All DNA samples were stored at -20^{o}C until further analysis. The gene regions including mutations 185delAG (rs386833395) and 5382insC (rs397507246) in *BRCA1* and 6174delT (rs80359550) in *BRCA2* were amplified by polymerase chain reaction (PCR) assay. The sequences of primers used to amplify gene regions including mutations, hybridization temperature of PCR conditions and PCR product sizes are shown in Table 1. The PCR products were subsequently resolved by electrophoresis on 2% agarose gel and visualized using ethidium bromide. After PCR amplification, conventional DNA sequencing was performed.

Table 1: Sequences of primers used to amplify gene regions including mutations, hybridization temperature of PCR conditions and PCR product sizes

Gene mutations	Primers	Hybridization temperature (ºC)	Product size (bp)
BRCA1			
185delAG	F-5'-GACGTTGTCATTAGTTCTTTGG-3' R-5'-CCAGTTAAGACAAGTAAACG-3'	54	315
5382insC	F-5'-ATATGACGTGTCTGCTCCAC-3' R-5'-ACGTTTCCCCTCACCTTATG-3'	54	232
BRCA2			
6174delT	F-5'-AACGAAAATTATGGCAGGTTGTTAC-3' R-5'-CGAAAGGTGAACGACATGATTTAGG-3'	55	535

RESULTS

Fifty patients with early onset breast cancer (≤45 age) were included in this study. The patient's ages ranged from 28 to 45 years with a mean age of 40.08±4.275 years. The clinical and pathological characteristics of the breast cancer patients (family history of cancer, diagnosis, tumor histology, tumor stage, menarche age, menopause age, number of births, duration of breastfeeding, ER status and PR status) are shown in Table 2. Out of 50 cases, 46% has a family history of breast or other cancers and the remaining had not any related person diagnosed with any type of cancer. Except two cases (4.0%), all of the patients had unilateral breast cancer.

185delAG mutation in exon2 and 5382insC mutation in exon 20 of *BRCA1* gene and 6174delT mutation in exon 11 of *BRCA2* has not been detected in any of the 50 early onset breast cancer patients in our study.

Table 2: Clinical and pathological characteristics of breast cancer patients

Characteristics	n (%)
Family history of cancer (n=50)	
Breast cancer	9 (18.0)
Other cancer	19 (38.0)
None	22 (44.0)
Diagnosis type (n=50)	
Bilateral breast cancer	2 (4.0)
Left breast cancer	25 (50.0)
Right breast cancer	23 (46.0)
Tumor histology (n=49)	
Ductal carcinoma	41 (83.7)
Lobular carcinoma	4 (8.2)
Other	4 (8.2)
Tumor stage (n=44)	
Stage I	8 (18.2)
Stage II	15 (34.1)
Stage III	19 (43.2)
Stage IV	2 (4.5)
Menarche age (n=43)	
<15 years	37 (86.0)
≥15 years	6 (14.0)
Menopause age (n=48)	
Menstruation continue	42 (87.5)
<40 years	1 (2.1)
≥40 years	5 (10.4)
Number of births (n=49)	
None	7 (14.3)
1	5 (10.2)
≥2	37 (75.5)
Duration of breastfeeding (n=50)	
None	8 (16.0)
<6 months	11 (22.0)
≥6 months	31 (62.0)
ER status (n=36)	
Positive	21 (58.3)
Negative	15 (41.7)
PR status (n=27)	
Positive	15 (55.6)
Negative	12 (44.4)

ER: estrogen receptor, PR: progesterone receptor.

DISCUSSION

In the current study, *BRCA1* and *BRCA2* mutations were investigated in Turkish breast cancer patients using conventional DNA sequencing analysis. Any of the 5382insC and the 185delAG mutations in *BRCA1* and the 6174delT mutation in *BRCA2* was not observed in fifty cases with early-onset breast cancer.

The 5382insC and the 185delAG mutations in *BRCA1* and the 6174delT mutation in *BRCA2* are the most common BRCA mutations (>%90) in Ashkenazi Jewish population [11]. These gene mutations also have been studied in other populations in several studies [14-16]. In previous studies, the *BRCA1* 5382insC mutation has been detected in breast/ovarian cancer patients from Turkish population [15, 17-24]. However, we couldn't detect this mutation any of our early-onset breast cancer patients. The *BRCA1* 5382insC mutation is mostly seen in Eastern European [25-29] and the patients who were found to be carrying 5382insC mutation in Turkish population are mostly from Western Turkey, near the Eastern European [15, 19, 21, 23, 24]. Also in these studies, the patients that were investigated were mainly breast/ovarian cancer patients. In our study, we only included breast cancer patient. 185delAG mutation in *BRCA1* was detected in only one patient with hereditary breast ovarian cancer syndrome from Turkish population [30]. Like our results, 6174delT mutation in *BRCA2* gene were not detected in any of the studies investigating the frequencies of common *BRCA1* and *BRCA2* gene mutations in breast/ovarian cancer patients in Turkish population [15, 17-24, 30].

In previous studies, approximately 500 Turkish breast/ovarian cancer patient have been reported to be screened for germline *BRCA1* and *BRCA2* mutations. Different patient selection criteria and different mutation detection methods were applied, no predominant mutation was observed in Turkish population [15, 17-24, 30-34].

185delAG mutation in exon2 and 5382insC mutation in exon 20 of *BRCA1* gene and 6174delT mutation in exon 11 of *BRCA2* gene are observed commonly in Ashkenazi Jewish breast cancer patients and it can be suggested that mutations in the BRCA genes among the Turkish breast cancer patients might be different from that of other populations.

Both *BRCA1* and *BRCA2* gene mutations are mainly observed in hereditary breast cancer cases [35]. The proportion of these gene mutations among breast cancer patients increase when the age of diagnosis of breast cancer is under 36 [36]. In our study, 185delAG mutation in exon2 and 5382insC mutation in exon 20 of *BRCA1* gene and 6174delT mutation in exon 11 of *BRCA2* gene were not detected any of the 50 early-onset breast cancer patients. The results of the current and the other studies showed that, these germline *BRCA1/2* gene mutations are not common in Turkish breast cancer patients.

CONCLUSION

In conclusion, our results showed that there might be other mutations of *BRCA1/2* genes or other genes rather than *BRCA1/2* that might be responsible for breast cancer in Turkish population.

Acknowledgement

This study was supported by Gaziosmanpasa University (Project No. 2013/17).

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