Evaluation of the indication of BRCA1/2 genetic tests in Iranian women and acceptance rate of risk-reducing surgeries in BRCA mutation carriers

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Abstract

Background: A higher risk for breast and ovarian cancer has been reported in BRCA carriers and prophylactic surgeries are proposed to reduce this risk. This retrospective cohort study has evaluated the indication of BRCA1/2 genetic tests in Iranian women and the rate of women’s acceptance of prophylactic surgeries recommended by the surgeon.

Methods: Medical records of 147 high-risk women according to NCCN clinical practice guidelines who referred for BRCA mutations testing were assessed. Individual information, indications for BRCA1/2 genetic testing and their results, physician recommendations, and type of accepted surgery were registered. To evaluate the current status of women an active visit follow-up every six months was conducted.

Results: The mean age of women was 43.40 ± 10.94 and the median follow-up time was 1.92 years. Genetic test results showed 49(33.3%) women were positive for either BRCA1/2 mutations. Although the occurrence of breast cancer younger than 40 was the most common indication for genetic tests (26.5%), positive breast cancer history in first-degree relatives and two relatives younger than 50 was the most common indications with positive results. The rate of acceptance...
of prophylactic mastectomy and bilateral salpingo-oophorectomy was (14.3% and 34.7%) in BRCA mutation carriers.

**Conclusion:** If the onset of breast cancer at a young age (less than 40) will be the only indication for a BRCA analysis, the rate of a positive result (12.8%) is very low. Further studies are warranted to evaluate the age limit for genetic testing in our country. Prophylactic mastectomy acceptance is very low in BRCA1/2 carriers in our centers.

**KEYWORDS**

BRCA1, BRCA2, breast cancer, genes, prophylactic surgical procedures

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1 | **INTRODUCTION**

Breast cancer is the most frequently diagnosed cancer in women in most regions of the world (Ferlay et al., 2019). Evidence shows that breast cancer affects Iranian women at least one decade younger than their counterparts in developed countries (Harirchi et al., 2004; Jazayeri et al., 2015). The age-standardized rate of breast cancer in Iranian women was reported as 27.4 (95% CI: 22.5–35.9) and the mean age and incidence of breast cancer are the lowest in the Middle East (Jazayeri et al., 2015).

Approximately 5–10% of all breast cancers and 25–40% of breast cancers affecting women younger than 35 years of age are attributable to hereditary causes (Anders et al.). BRCA1 (OMIM: 113705) and BRCA2 (OMIM: 600185) are two common genes that are associated with an inherited susceptibility to breast and ovarian cancers and about 3–8% of all women with breast cancer may carry a mutation in one of these genes (Rosman et al., 2007).

In high-risk women with positive test results, the risk of breast cancer by age 70 years is estimated as 66% for BRCA1 and 61% for BRCA2 and the risk of ovarian cancer is about 49% for BRCA1 and 21% for BRCA2 (Nelson et al., 2013).

There are still some controversies about the prognosis of breast cancer with BRCA mutation gene compared with a non-carrier gene. It seems breast cancer in patients who are BRCA mutation carriers is associated with higher grade and poor prognosis and these patients have poor overall survival compared to non-carriers (Zhu et al., 2016). However, some studies reported similar outcomes in BRCA carriers compared with non-carriers (El-Tamer et al., 2004; Veronesi et al., 2005).

Another controversy is about the effect of risk-reducing strategies on breast cancer risk of BRCA1/2 mutation carriers. In practice, BRCA carriers undergo vigorous cancer screening and may offer risk-reducing surgeries like mastectomy and also oophorectomy, when their childbearing is completed (Salhab et al., 2010). The risk-reducing strategies are associated with a gain in life expectancy in BRCA1/2 carriers and depending on the prophylactic interventions, their life expectancy extends from a few months to a few years ultimately (Grann et al., 1998; Roosmalen et al., 2002; Schrag et al., 1997). Although salpingo-oophorectomy will reduce the risk of future ovarian cancer, little impact on the risk reduction of subsequent breast cancer especially in BRCA1 carriers had been reported (Kotsopoulos et al., 2019; Mavaddat et al., 2020). A meta-analysis in 2016 concluded prophylactic bilateral salpingo-oophorectomy and mastectomy in BRCA1/2 mutation carriers with or without breast cancer are associated with significantly lower-all cause mortality rate (Li et al., 2016).

The extent to which BRCA1/2 carriers undergo these risk-reducing surgeries is varied in different countries and it has not been studied in Iran, yet. Also, genetic testing criteria may differ between countries according to their mutation prevalence.

The National Comprehensive Cancer Network (NCCN) as a professional organization develops guidelines that include guidance for determining genetic testing eligibility depending on clinical criteria. Because genetic testing requires specialists for genetic counseling and it is known as a high cost-consuming procedure, the necessity of genetic testing considering NCCN guidelines should be investigated in each population for the best recommendations.

The aim of this study was to assess the indication of BRCA1/2 genetic tests in Iranian women as well as the rate of women’s acceptance of prophylactic surgeries. Meanwhile, the occurrence of new breast or ovarian cancer in BRCA positive patients was evaluated during the follow-up time.

2 | **MATERIALS AND METHODS**

2.1 | **Ethical compliance**

This study was approved by the Ethics Committee of Tehran University of Medical Sciences (Code: IR.TUMS.VCR.REC.1397.390).
2.2 | Study design and sample collection

This retrospective cohort study was conducted in two private breast clinics in Tehran, Iran, between 2016 to 2019. Patients’ medical chart reviews of women who assessed for BRCA1/2 genetic tests were evaluated. Basic and clinical information, indications for BRCA1/2 genetic testing and their results, and characteristics of breast cancer in affected patients (tumor size (T), nodal status (N), and immunohistochemistry (IHC)) were extracted. The genetic high-risk assessment was conducted according to NCCN clinical practice guidelines (Network N.C.C, 2018). Physician recommendations were recorded if available. The final decision and the type of surgical treatment were registered. Records of every six-month active follow-up visit were reviewed and new cases of breast and ovarian carcinoma during this period were registered as well.

2.3 | Mutation analysis and variant classification

All these genetic tests were performed according to the same protocol in Cancer Institute that was previously described in another paper (Ebrahimii et al., 2019a). Briefly, DNA extracted from blood samples according to the manufacture’s instruction using Gentra Puregene Blood Kit (Qiagen). All coding sequence and intron-exon boundaries of BRCA1 (NM_007294.3) and BRCA2 (NM_000059.3) were amplified using WaferGen SmartChip Technology (WaferGen Inc). DNA sequencing was conducted at 2 × 250 cycles using an Illumina MiSeq sequencer and read using Burrow-Wheeler Aligner. Genetic variants including SNP or insertion-deletion were identified by the Unified Genotyper module of the GATK package. To determine the pathogenicity of identified mutations ClinVar, HGMD, and BRCA Exchange databases were used. Deleterious mutations were confirmed by Sanger Sequencing.

2.4 | Statistical analysis

SPSS software (version 20, SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Continues variables were reported by the mean and standard deviation (SD) and the frequency of categorical variables are shown with numbers and percentages.

3 | RESULTS

In this study, we reviewed the medical charts of 159 high-risk patients who performed genetic tests and the results of the 147 available genetic tests were evaluated. General characteristics and medical condition of women at the time of genetic testing were shown in Table 1. One hundred twelve women had breast cancer at the time of requesting the genetic test, and 35 women were in a high-risk group according to NCCN guidelines (Table 1). The mean age of women was 43.40 ± 10.94 and the median follow-up time was 1.92 years.

The results of the genetic test showed 49 (33.3%) women were positive either for BRCA1/2 mutations [including 29 (59.2%) BRCA1, 15 (30.6%) BRCA2; and 5 (10.2%) BRCA1&BRCA2].

Genetic test indication and the results were summarized in Table 2. The most common indications for a genetic test in our sample were a personal history of breast cancer in women younger than 40 (26.5%) followed by histories of breast cancer in two relatives with at least one patient younger than 50 (14.3%). Table 2 indicates 71.4% of women who had a first-degree relative with positive tests and 57.1% of women who had two relatives with a history of breast cancer at least one younger than 50 are BRCA1/2 carriers. In women with more than one indication to assess genetic tests, due to the low number of women in each category, the exact conclusion was not possible. However, it seems the personal history of two primary breast cancers followed by Triple-negative cancer younger than 60 was accompanied with the highest rate of a positive test.

Table 3 shows 50% of non-cancerous high-risk patients had positive test results. However, 60% of bilateral breast cancers were BRCA1/2 carriers. In unilateral breast cancer
patients, triple-negative subtype is the most common subtype along with BRCA1/2 positive results (50%).

Although prophylactic mastectomy was recommended to BRCA carriers, only 14.3% (7 out of 49) underwent bilateral mastectomy and reconstruction. The acceptance of prophylactic mastectomy was 11.8% (4 out of 34) in BRCA1 positive patients and 15% (3 out of 20) in BRCA2 positives. However, in BRCA negative high-risk breast cancer patients, the rate of prophylactic mastectomy was 3.1% (3 out of 98).

In a median follow-up time of 1.92 years, new breast cancer was diagnosed in 5.4% (8 out of 147) of high-risk women. Five (10.2%) BRCA carriers’ women (four BRCA1 positives, one BRCA2 positive) and 3 (3.1%) women with BRCA negative tests developed new breast cancer. The occurrence of new breast cancer in young (less than 40 years) BRCA carriers was higher (17.6%).

New breast cancers in BRCA positive women mainly occurred in someone who turned down prophylactic mastectomy. Only one BRCA positive patient who had undergone bilateral prophylactic mastectomy was diagnosed with new breast cancer one year after her surgery. It occurred in the tail of a breast in less than one-centimeter mastectomy flap over her implant.

Conducting bilateral salpingo-oophorectomy was proposed to all BRCA carriers whenever their childbearing was complete. During the follow-up time, we found the rate of acceptance of this prophylactic surgery was 34.7% (n = 17) in BRCA positive patients. Three cases of new ovarian cancer were recognized including two cases in BRCA2 carriers (10%) and one case in BRCA1 carriers (2.9%).

### DISCUSSION

In the present study, although the most common indication (26.5%) for genetic testing in our population was a
Breast cancer patients younger than 40 years old constitute 20% of the entire breast cancer population in Iran (Jazayeri et al., 2015). Therefore evaluation of a large number of patients is needed to find a BRCA mutation and if other risk factors do not exist, the probability of negative results will be high. Also, BRCA analysis has a huge impact on the patients, both financially and emotionally. Further studies are required to design a cost-benefit algorithm to better recognize high-risk patients needing further evaluation for a genetic mutation, in our country.

Of the 112 patients with identified breast cancers, at the start of the study, 77 patients were BRCA negative and 35 patients were BRCA positive. Triple-negative breast cancer (i.e., those with negative estrogen receptor, progesterone receptor, and HER-2/neu status) was diagnosed in 31.4% of the BRCA-positive patients, and 14.3% of the BRCA-negative patients. The most prevalent subtype of breast cancer in BRCA carriers was triple-negative, similar to the results of several similar studies (Sønderstrup et al., 2019). In a study in Denmark, 425 BRCA germline-mutated breast cancer patients were analyzed. In that study, 20%, 28%, 6%, and 46% of breast cancers were of luminal A-like, luminal B-like, HER2 positive and basallike subtype, respectively (Chiba et al., 2016). Their results were close to our results. We found the HER-2 positive subtype to be the least frequent subtype of breast cancer in BRCA mutated patients.

For eleven patients (22.4%) of BRCA positive breast cancer patients, Breast-Conserving Surgery (BCS) was applied. This large number was mainly due to the patient’s preferences. Furthermore, since the results of the patients’ BRCA testing frequently takes considerable time to be prepared (about 6–12 weeks), there is no other choice, rather than to start the treatment based on the available data, especially when neoadjuvant chemotherapy was not the preferred modality of treatment. The delay was mostly because of the shortage in materials and instruments in the Iranian labs according to the US sanctions upon Iran. In these situations, sending and analyzing the blood samples for genetic tests in other countries prolong the time. When the patient operates by breast-conserving surgery before the availability of the BRCA test result, the acceptance of unilateral mastectomy or prophylactic bilateral mastectomy will be decreased. In a study by Chiba et al, the rates of bilateral mastectomy were higher for the patients with BRCA mutation known before surgery. In that study, if BRCA mutation was identified after surgery, it frequently led to subsequent breast surgery (Chiba et al., 2016). The rates of prophylactic mastectomy in BRCA mutated patients, reported in our study (14.3%) were lower than the rates reported in several studies (Kram et al., 2006; Metcalfe et al., 2008). On the other hand, prophylactic mastectomy and immediate breast reconstruction are personal history of breast cancer younger than 40 without any other risk factors, we found only 12.8% of them to carry BRCA mutations. If we consider women with a personal history of breast cancer younger than 40 with other risk criteria, 10 out of 53 (18.9%) women carried BRCA1/2 mutations, in our study population. As we expected, positive breast cancer history in first-degree relatives and two relatives younger than 50 was the common indications with history of breast cancer younger than 40 with other risk mutation prevalence was higher in cases diagnosed before 35 years of age up to 12.4% (4.7–25%) and it was decreased to 1.7%(0.9–2.8%) in women aged 45 to 54 years old (Anglian Breast Cancer Study Group, 2000). The rate of carrying BRCA1/2 mutation in patients younger than 40 in De Sanjose's study (11.6%) and in the Korean population (11/60: 18.3%) are very similar to our study (Choi et al., 2004; Sanjose et al., 2003). However, in another study from our country, none of the 107 breast cancer patients with only less than 40 years of age at onset of disease criterion had a pathogen mutation (Ebrahimih et al., 2019b). This finding is also confirmed by another study in breast cancer patients younger than 35 years and they suggested that early onset alone was not a good indicator of the presence of BRCA1/2 mutations, but the combination of this criterion with other criteria such as family history and bilateral breast cancer will increase the prevalence of BRCA1/2 carriers (Keshavarzi et al., 2012).
not covered by the public and most private insurance. This may be another reason for a low tendency of the patients toward prophylactic mastectomy in this study.

There is no randomized controlled trial that directly compares BCS with mastectomy for BRCA mutation carriers. In addition, a patient's preference is one important factor in surgical decision making, when it comes to breast surgery. Like mastectomy, BCS is the gold standard surgical treatment in sporadic breast cancer patients; however, the oncologic safety of BCS in BRCA mutation carriers remains controversial. A systematic review of eighteen studies has conducted in Hong Kong to evaluate the safety of BCS in BRCA mutated breast cancer patients. Pooled analysis of overall survival (OS) at 5-, 10- and 15-year were comparable between BCS and mastectomy [88.7%, 89.0% and 83.6% in BCS, compared to 83%, 86.0% and 83.2%, in mastectomy. However, the pooled ipsilateral breast cancer recurrence rates at 5-, 10- and 15-year were higher in the BCS group at 8.2%, 15.5%, and 23%, compared to that of mastectomy at 3.4%, 4.9%, and 6.4% (Co et al., 2020).

More than 20% (11/49) of BRCA carriers were treated by a BCS without an increased rate of local recurrence in 2 years follow-up in this study. BRCA carriers accepted prophylactic oophorectomy (34.7%) more than prophylactic mastectomy (14.3%). This finding was confirmed in previous studies, too (Kram et al., 2006; Metcalfe et al., 2008). An association between BRCA positivity and new ovarian cancer in our study was similar to other studies (Janezic et al., 1999) and the occurrence of a new ovarian cancer was common in BRCA2 mutation.

There were some limitations in this study, including short-term follow-up, a small number of BRCA positive patients, and the retrospective design of this study.

We have shown that if breast cancer at a young age less than 40 years old will be the only indication for a BRCA analysis, the rate of a negative test results is high. Meanwhile, new breast cancer was more common in this group of patients during our follow-up. Further investigations with larger sample size and longer follow-up in patients whose only indication for the BRCA analysis is breast cancer below 40 years of age are suggested to evaluate the benefits of BRCA analysis. In the present study, prophylactic mastectomy was turned down in BRCA mutated patients significantly, while a high rate of BRCA carrier breast cancer patients underwent a BCS. The safety of BCS in BRCA carriers should be evaluated in another prospective study.

In order to increase the rate of prophylactic surgeries in Iranian women who are BRCA carriers, increasing the public knowledge and culture, availability of laboratory instruments and materials, and coverage of the cost of these surgeries by public insurances are needed. The present study data can assist health system legislators, media groups, and stakeholders in taking action to increase the acceptance rate of prophylactic surgeries and reducing the risk of cancer occurrence in women.

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CONFLICT OF INTEREST
The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT
The Data is available from the corresponding author upon reasonable request.

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