Epidemiological and pathological characteristics of post-surgical cases of invasive breast cancer among ethnicities of Iran in 2018: A single center cross-sectional study

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SUMMARY

Background: *Present study aimed to investigate immunohistochemical parameters in post-surgical cases of invasive breast cancer.* **Methods:** *In this single center cross-sectional study we investigated ethnicity, familial history, type of cancer, stage of cancer, lymph node positivity, bilateral involvement, metastasis and immunohistochemical parameters (estrogen and progesterone receptor, human epidermal growth factor receptor 2, as well as frequency of triple positive and triple negative patients merely based on immunohistochemical parameters).* **Results:** *Frequency of positive familial history was 27.42% (16.31-38.52%). Lymph node involvement was detected in 55.93% (43.26-68.60%) of the cases. Frequency of positive HER2 was 38.60% (25.96-51.23%). There were 17.54% (7.67-27.42%) of triple positive and 7.02% (0.39-13.65%) of triple negative cases. The most common stage at the time of diagnosis was stage 3 with 43.33% (30.79-55.87%) frequency. In Lur/Lak population higher frequency of positive HER2 cases was detected whereas in Mazani population frequency of positive HER2 cases was low (p=0.0291).* **Conclusions:** *These results could contribute to understanding of breast cancer patterns among different ethnicities. In order to draw clear conclusion future investigations have to be done in several health centers, for longer time periods and with larger number of patients.*

Keywords: *Breast cancer, estrogen receptor, HER2, triple negative, pathology, Iran*

INTRODUCTION

Background

Breast cancer is the most common solid malignancy in women in Iran. Reported incidence in 2009 was 24 per 100000 (1). The data obtained from National cancer registry of Iran in 2015 reported incidence of 22.1-23.1 per 100000 for 10-year period. This type of cancer covers 24.6% of all female cancers in Iran. In the national cancer registry report there was no information on staging or immunohistochemical (IHC) results of breast cancer patients (2). One of breast cancer studies in Iran suggested that different provinces have different relative risks and therefore therapy, education and screening should rely on different policies (3). A data mining study performed on 3010 breast cancer patients from 1998 to 2014 indicated that typical Iranian breast cancer patient was a 40-50 year old married women with two children, mostly diagnosed at stage 2 of the disease (4). Akbari et al. investigated 313 Iranian patients with early or late recurrence of breast cancer. This study indicated that the most common site of recurrence was bone (27.4%) followed by local recurrence (21.4%). Increased hazard ratio of recurrence was observed in cases when patients were <40 years old, with stage 3 of the disease, and positive lymphovascular invasion and lymph node involvement. However, human epidermal growth factor receptor 2 (HER2) positivity was not associated with risk of recurrence (5).

Breast cancer screening and early detection can reduce mortality and recurrence rate (6). The screening and early detection methods are self-examination, clinical examination and mammography. Studies showed that early detection methods were not common among Iranian women, and therefore education has been suggested (7, 8). One of the most common complications and cause of morbidity in breast cancer patients was lymphedema. Education and training of patients has been suggested to increase quality of life (9, 10).

Pathology wise, most common breast cancers are ductal or lobular carcinomas. Breast sarcoma and lymphoma are rare types of breast malignancies (11). Evaluation of the most common immunohistochemical markers like estrogen receptor (ER), progesterone receptor (PR) and HER2 has opened a door for personalized medicine in breast cancer (12).

Objectives

In the registry-based articles on epidemiology of breast cancer in Iran some clinical and pathological characteristics such as IHC results have not been included. Therefore, the present study aimed to investigate these parameters from post-surgical cases of invasive breast cancers among different ethnicities of Iran during year 2018 using data from referral Firoozgar Clinical Research Development Center (FCRDC). The investigated parameters were ethnicity, familial history of breast cancer, type of cancer, stage of cancer, lymph node positivity, bilateral involvement, metastasis and IHC results, as well as frequency of triple positive and triple negative patients based on IHC.

MATERIAL AND METHODS

Study design and samples

The present research is a single center cross-sectional study. The samples were from invasive breast cancer patients who referred to Firoozgar Clinical Research Development Center (FCRDC) for post-surgical follow up during 2018.

Items and definitions

The investigated items were ethnicity (Fars, Arab, Gilak, Lur/Lak, Mazani, Sistanei, Turk/Azeri, etc.), familial history of breast cancer (in first or second degree relatives), type of cancer (invasive ductal carcinoma or invasive lobular carcinoma), stage of cancer (stages 1-4, based on TNM

staging), lymph node positivity (involvement of at least one lymph node like sentinel lymph node in permanent slide), bilateral involvement (at the same time or recurrence, and both should be invasive), metastasis (based on bone scan or magnetic resonance imaging, MRI) and IHC positivity (ER and PR with any percentage, HER2 with 1, 2 or 3 plus positivity) as well as frequency of triple positive (ER+, PR+ and HER2+) and triple negative patients (ER-, PR- and HER2-), based on IHC.

Ethical considerations

Informed consent was obtained from the participants. This study has been approved by Iran University of Medical Sciences Ethics Committee, code No. IR.IUMS.REC.1397.983.

Statistical methods

For each item, number of positive cases, number of negative cases and number of cases with missing information were reported. The percentage of each frequency was reported excluding missing information. Confidence interval (CI) for each frequency was calculated as $1.96 \times \sqrt{(pq/n)}$ where p and q where based on the current frequency (not reference frequency). All calculations were performed using Excel, Microsoft Office 2013 (Microsoft, USA). Fisher's exact test (Statistical Package for the Social Sciences, IBM, USA) was used for investigation of two by two associations. Dendrogram with ward linkage was used to categorize most prevalent ethnicities using Stata 14 Software (StataCorp LLC, USA).

RESULTS

In this one year census period, 62 patients were evaluated. Type of cancer in 60 patients was invasive ductal carcinoma (96.77%) and in two patients was invasive lobular carcinoma (3.22%). Growth pattern for each cancer has not been commonly reported; however there was one report for mucinous growth pattern and two reports for medullary growth pattern (one of them belonged to a triple negative patient). Ethnicity wise, 27 patients were Fars, 16 patients were Turk/Azeri, 8 patients were Lur/Lak, 7 patients were Mazani, and there were 1 Gilak, 1 Sistanei, 1 Arab and 1 Afghan patient.

The frequency of positive cases for each investigated item is shown in Table 1. Briefly, percentage of positive cases in familial history was 27.42% (16.31-38.52%), lymph node involvement was 55.93% (43.26-68.60%), HER2 was 38.60% (25.96-51.23%), triple positive was 17.54% (7.67-27.42%) and triple negative was 7.02% (0.39-13.65%). The most common stage at the time of diagnosis was stage 3 comprising 43.33% (30.79-55.87%) (Figure 1).

Cluster analysis of ethnicities based on IHC results showed that Fars and Turk/Azeri patients had similar response. Lur/Lak patients had the highest frequency of HER2 positive cases (6 out of 7, with one missing data) whereas Mazani patients had the lowest (1 out of 7) (Figure 2). This difference in the frequency of HER2 positive cases between Lur/Lak and Mazani patients was statistically significant according to Fisher's exact test ($p=0.0291$).

DISCUSSION

Summary of evidence

This study was aimed to report clinical and pathological characteristics of Iranian patients with invasive breast cancer. According to the results, the most common type of breast cancer in Iran was invasive ductal carcinoma, but reporting of its growth pattern has not been a common practice. The most frequently positive IHC marker was ER (it was positive in about 75% of cases). These findings suggest hormone therapy as a default therapy for breast cancer in Iran. Positivity of HER2 was high (at about 38%); however all of these patients were not candidates for trastuzumab (Herceptin®) therapy because some of them were 1+ or 2+ positive with negative result for fluorescence in situ hybridization (FISH) test. The most common stage at the time of diagnosis was stage 3, indicating that majority of patients refer to a physician when they have significant clinical manifestations. Significant number of patients was diagnosed with stage 1 which could indicate positive impact of education on early detection. Frequency of treatment challenging triple negative breast cancer was about 7%. Cluster analysis showed differences in IHC results among different ethnicities (Figure 3). But, presented frequencies for ethnicities were not representative due to referral relationships between Firoozgar Clinical Research Development Center (FCRDC) and some cities in Iran.

Harirchi et al. (2000) reported 903 breast cancer cases for 1985 to 1995 period (13). About 71% of patients were stage 3 at the time of diagnosis and lymph node positivity was higher (69%) than in our study (about 55%). In another report for 1996 to 2000 period the most common stage was 2 and about 96% of the patients had stage 2 or 3 (14). Lower percentage of stage 3 patients in our study (about 43%) could indicate positive impact of education for early detection.

A population-based study for 1996-2000 period by Iranian national registry reported that age specific incidence rate for breast cancer was higher

	ER	PR	Her2	FMHx[1]	Bilateral	Metastasis	Lymph node	Stage 1	Stage 2	Stage 3	Stage 4	Triple negative	Triple positive
Positive	43	36	22	17	5	5	33	21	8	26	5	4	10
Negative	14	21	35	45	55	55	26	39	52	34	55	53	47
Missing	5	5	5	0	2	2	3	2	2	2	2	5	5
% Positive[2]	75.44	63.16	38.60	27.42	8.33	8.33	55.93	35.00	13.33	43.33	8.33	7.02	17.54
Lower limit	64.26	50.64	25.96	16.31	1.34	1.34	43.26	22.93	4.73	30.79	1.34	0.39	7.67
Upper limit	86.61	75.68	51.23	38.52	15.33	15.33	68.60	47.07	21.93	55.87	15.33	13.65	27.42

[1]FMHx: family history, [2] Without considering missing data

Table 1. Clinical and pathologic characteristics of the patients with frequencies of positive response and 95% confidence intervals

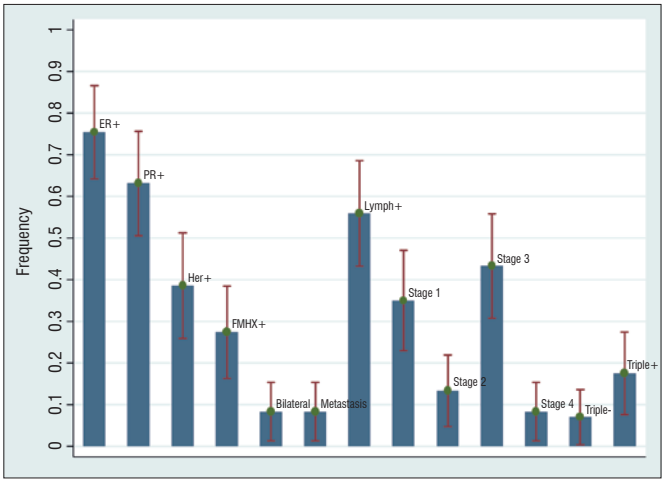

Figure 1. Frequencies (point estimation) of the investigated characteristics with 95% CI

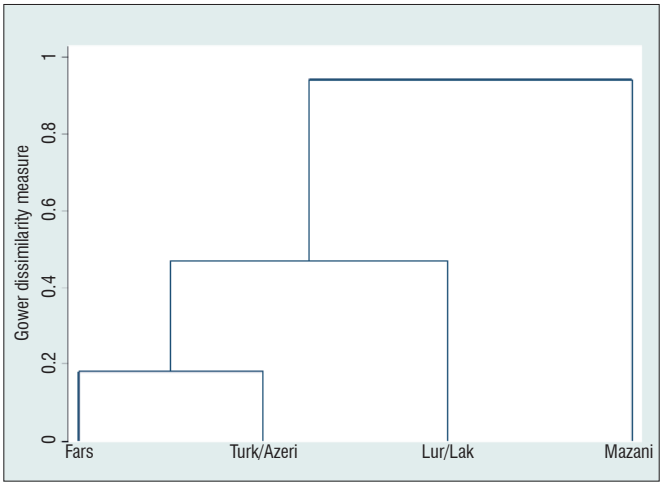

Figure 2. Cluster analysis of ethnicities using ward linkage based on immunohistochemistry (IHC) results

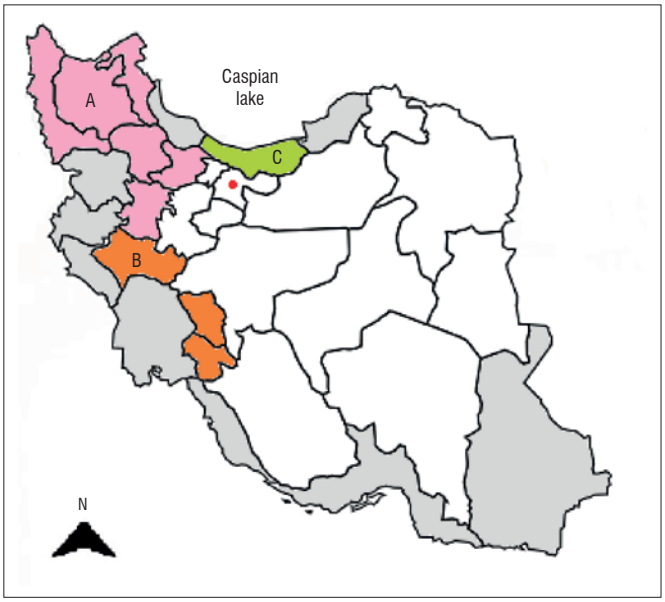

Figure 3. Geographical locations covering investigated ethnicities. A) Locations with predominantlyTurk/Azeri ethnicities (pink); B) Locations with predominantly Lur/Lack ethnicities (orange); C) Locations with predominantly Mazani ethnicities (green). Other ethnicities that were not investigated in cluster analysis were shown in light gray. Locations with predominantly Fars ethnicities (White). The arrowed point is the place of study in Tehran

for Mazani ethnicity (15). Although in our study majority of participants were Mazani, frequencies of ethnicities were not representative. Spatial analysis of Mahdavifar et al. using data from 2009 showed that Tehran had the highest breast cancer incidence rate in Iran. However, it should be regarded that Tehran has a large number of referral hospitals and therefore higher detection rate compared to other Iranian cities (16).

Abdollahi and Etemadi (2016), reported 14% frequency of triple negative breast cancer in Iran, according to FISH test (17). In our study HER2 positivity was based on IHC (1+, 2+ or 3+), and not based on patients who were candidates for Herceptin® therapy (according to FISH).

CONCLUSION

These results could contribute to understanding of breast cancer patterns among different ethnicities. In order to draw clear conclusion future investigations have to be done in several health centers, for longer time periods and with larger number of patients.

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Declaration of Interests

Authors declare no conflicts of interest.

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