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Clinicopathological Analysis of Patients with Breast Cancer and Their Families

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ABSTRACT

Background: Breast cancer is one of the most common malignancies among Iranian women; however, its clinicopathological feature is uncertain. We pioneered a genetic counseling program among patients with breast cancer and their families in Isfahan. This is the first report of this program.
Methods: This was a descriptive cross-sectional study on women with breast cancer registered in Ala Cancer Control and Prevention Center (ACCPC)during 2014. The women and/or their first/second relatives were enrolled for genetic counseling, then their demographic and clinicopathological data were analyzed using SPSSsoftware.
Results: The records of 258 patients with breast cancer and their families were studied. The mean age of the patients at diagnosis was 44.2 years (range: 25-71 years). Of these, 88 (34.1%) patients had ≤40 years at diagnosis. Only 2 (0.8%) patients were men. Also, 21 (8.1%) out of the 258 patients had died at the time of genetic counseling. Distant metastasis was found in 40 (15.5%) patients at diagnosis. The most common pathological feature of breast tumor was invasive ductal carcinoma (68.2%) and the rarest were sarcoma (0.4%) and papillary carcinoma (0.4%). Triple-negative molecular phenotype breast cancer was reported in 25 (9.7%) patients. Estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) were negative in 32.2%, 27.1%, and 44.2% of the patients' tumors, respectively. P53 had been checked in 41.5% of the patients of which about 70.1% were mutant. Overall, 895 cases of cancer were reported among the patients and their families (3.5 patients per family: range=1-9) of which breast, gastric, and colorectal cancers with an incidence of 43.9%, 8.3% and 5.5%, were the most common malignancies, respectively.
Conclusion: Early-onset breast cancer and positive family history for cancer were seen in a significant proportion of the patients in our center, indicating the importance of genetic counseling among the patients and their families.

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Introduction

Cancer is the third cause of death after ischemic heart disease and accidents among the Iranian population.[1] Breast cancer (BC) is the most common cancer in women throughout the world.[2-4] In our country, BC is the most common cancer and the fifth most common cause of death among women.[5]

The number of women affected by BC has been reported to be 1.7 million in 2012, with 6.3 million affected women within the previous five years.[6] Moreover, BC has been

reported as the most common cancer among women in countries in the Eastern Mediterranean Region.[7] More than one million cases of BC occur worldwide every year, of which about 580,000 cases occur in developed countries (>300/100 000 population per year) and the remainder in developing countries (usually <1500/100,000 population per year), despite their much higher overall population and younger age. In 2000, the year for which global data exists, some 400,000 women died from BC, representing 1.6% of all female deaths. The proportion of deaths due to BC was far higher in developed countries (2% of all female deaths) than in developing countries (0.5%).[7] BC is a disease with high cost and expensive treatments which imposes a significant burden on health system of the world-wide countries.[8]

Treatment of BC in Iran is very expensive because the age of patients in Iran is about one decade less than Western countries, so the burden of the disease in Iran is likely to be considerably high.[8] Meanwhile, no comprehensive systematic screening and surveillance program has been set up to promote early detection and diminish the occurrence of BC among Iranian women. There are some dispersed local programs throughout the country, one of which is running in Ala Cancer Control and Prevention Center (ACCPC), Isfahan, Iran. In this study, we assessed some clinicopathological aspects of the registered patients in this center.

Methods

This was a descriptive, cross-sectional study carried out at ACCPC, a health promotion and palliative care clinic in Isfahan, central Iran, in which all specialities including psychology, palliative care, genetics, nutritional counseling and social workers are voluntarily serving cancer patients and their family members. Inclusion criteria were age at diagnosis of ≤50 years and/or a positive family history for any type of cancer regardless of the age at diagnosis. During the counseling, the familial pedigree was drawn. The clinicopathological features of patients with BC were analyzed using SPSS 19 software.

Results

The records of 258 patients with breast cancer and their families were studied. The mean age of the patients at diagnosis was 44.2 years (range: 25-71 years). 88 (34.1%) patients had ≤40 years of age at diagnosis. Only 2 (0.8 patients %) were men. 21(8.1%) patients out of 258 had died at the time of genetic counseling. 50.4% of breast tumors were located on the left side, 46.1% of the right, and 3.5% on both sides. The most common pathological feature of BC was invasive ductal carcinoma (68.2%) and the rarest were sarcoma (0.4%) and papillary carcinoma (0.4%) (table 1). 96.5% of tumors were unifocal and 3.5% were multifocal. Radical mastectomy, total mastectomy and partial mastectomy were performed for 38.0%, 25.6%, and 36.0% of the patients, respectively. Averagely, 5.9 lymph nodes per case had been resected during surgery of which 2.7 were involved. Metastasis was seen in 40 (15.5%) patients at diagnosis of whom 12 cases were ≤40 years of age and 28 cases were >40 years of age at diagnosis. Bone, liver, lung and brain were the most frequent metastatic sites with an incidence of 57.5%, 35.0%, 32.5%, and 17.5%, respectively. Triple-negative molecular phenotype was detected in 25 (9.7%) of the 258 patients. ER, PR and HER2 were positive in 67.8%, 48.8%, and 31.8 % of the tumors, respectively.

Table 1: Frequency of Pathologic features of breast tumors according to their diagnostic reports

Pathology	Frequency	Percent
Carcinoma in situ	26	10.1
Infiltrative Ductal Carcinoma	176	68.2
Infiltrative Lobular Carcinoma	26	10.1
Mucinous	3	1.2
Medulary	2	0.8
Sarcoma	1	0.4
Papillary	1	0.4
Otther	8	3.1
Mixed	13	5
Unknown	2	0.8
Total	258	100

P53 was evaluated in 41.5% of the patients, of which 29.9% were mutant. The mean age at diagnosis in patients with mutant and wild-type P53 tumors was 45.8 and 44.2 years, respectively. Moreover, 2 (6.3%) out of 32 patients with BC with mutant P53 versus 14 (18.7%) out of 75 patients with wild-type P53 had metastasis at diagnosis (table 2).

We also found a positive family history of cancer among 86.7% and 62.5% of the patients with wild-type P53 tumors and those with mutant P53, respectively. Altogether, 895 cases of cancer (range: 1-9 per family) were found including the patients and their families, of whom 589 (65.8%) cases were found in women. In the women, breast, uterus and colorectal cancer with an incidence of 65.2%, 5.1%, and 3.9% were the most common observed malignancies, respectively. The corresponding figures for men was gastric, prostate, and lung cancer with an incidence of 18.0%, 11.8%, and 10.5%, respectively (table 3).

Table 2: Frequency of hormone receptors and biomarkers in breast tumors according to their immunohistochemical staining

Biomarker	Positive		Negative		Unchecked	
	Frequency	Percent	Frequency	Percent	Frequency	Percent
ER	175	67.8	83	32.2	0	0
PR	126	48.8	70	27.1	62	24.0
HER2	82	31.8	114	44.2	62	24.0
P53	32	12.4	75	29.1	151	58.5

Table 3: Frequency of cancer sites among family members of breast cancer patients.

Cancer site	Gender		Total
	Male	Female	
Breast	9	384	393
Stomach	55	19	74
Colorectal	26	23	49
Brain	29	17	46
Lung	32	14	46
Leukemia	22	19	41
Prostate	36	1	37
Uterus	1	30	31
Liver	15	10	25
Bone	14	6	20
Larynx	13	3	16
Lymphoma	8	7	15
Bone marrow	5	9	14
Ovarian	0	11	11
Skin	5	1	6
Thyroid	1	4	5
Pancreas	2	3	5
Gall-bladder	0	5	5
Bladder	3	2	5
Small bowell	4	0	4
Testis	2	1	3
Kidney	0	2	2
Nasopharynx	1	1	2
Retinoblastoma	2	0	2
Sarcoma	0	1	1
Unknown	19	16	35
Total	306	589	895

Discussion

Incidence rate of BC is estimated to be 22–24 per 100,000 among Iranian female population which is about one fourth of that in developed countries.[5,9] Iranian women are afflicted by BC at least one decade earlier compared with western countries.[10] Mean age of BC in western countries has been estimated to be about 63 years of age.[11] Some recent studies show that BC has a lower incidence among Iranian women than other developing countries. These studies also show a general growing trend in the 45–49 year-old age group with a decreasing trend for women older than 49 years.[12] We found 44.2 years of age to be the mean age of diagnosis in our population. The peak occurrence of BC was among 40-50 year-old age group. In 32.2% of our patients, the age was less than 40 years at diagnosis. Given the inclusion criteria to select high risk patients with BC including early-onset disease and/or a positive family history for cancer, we expected a lower age at diagnosis in the patients. Comparing our findings with similar Iranian studies, we could not find a distinct gap in this matter. Harirchi and coworkers also found a mean age of about 47 years in 903 patients with BC.[13] This shows a significant proportion of the Iranian patients with BC belong to the early-onset group indicating the importance of screening programs among Iranian young women (figure 1).

We found that 50.4%, 46.1% and 3.5% of the breast tumors to be on the left, right and both sides, respectively. This finding is consistent with previous epidemiological findings reported in the Iranian population. In a large study on 2343 BC patients from five hospitals in Tehran, during 1996-2000, 51.7% and 47.1% of e thtumors were located in the left and right breast, respectively. Also 1.5% of tumors were bilateral.[14] BC was more common in the left breast according to other studies.[15,16] Although the nature of this difference is not clear, the left breast is somewhat larger than the right, and this may explain the higher incidence of BC on left side.[17]

We found invasive ductal carcinoma was the most common pathology among our patients with an incidence

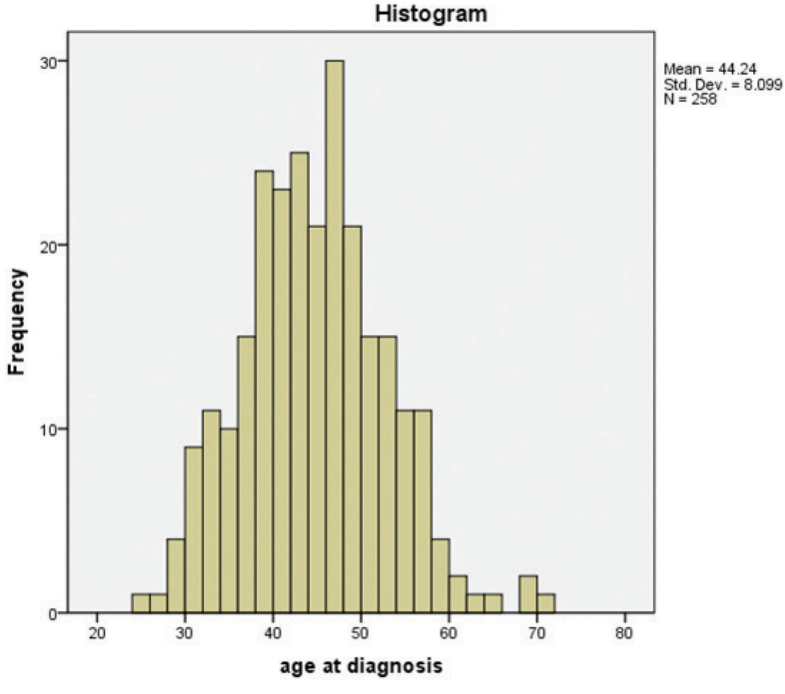

Figure 1: Distribution of breast cancer patients according to mean age at diagnosis.

of 68.2% of 68.2%. It is slightly lower than what is reported in other Iranian studies. According to an epidemiological review among Iranian studies throughout the country, 77% of BC tumor types were reported to be invasive ductal carcinoma.[9] More than 10% of the studied patients in our study were reported as lobular carcinoma, while in similar studies from Iran, different frequencies ranging from 1.9% to 11.6% have been reported for this pathological feature.[9] Moreover, we also found some rare types of breast pathologies such as sarcoma and papillary carcinoma.

Radical and total mastectomy was performed for 38.0% and 25.6% of the patients, respectively; while 36% of the patients underwent partial mastectomy. In a recent study from Isfahan on 119 patients with BC, partial mastectomy was performed in 32.5% of the cases. The patients who had endured partial mastectomy showed more satisfaction and fewer complications than those who had underwent total mastectomy.[18] A cross-sectional study from Iran evaluated the preference of general surgeons toward breast-conserving surgery versus total mastectomy. Breast-conserving surgery techniques were preferred by 19% of the surgeons in their routine practice.[19] In fact, most of the surgeons have more desire to do total mastectomy in order to avoid recurrence of the disease. Some studies have shown an equal incidence rate for recurrence in both techniques. Accordingly, some of the mastectomy surgeries must be changed to breast-conserving methods to prevent psychococial and physical complications.[20,21] It suggests the importance of an exact recurrence risk assessment among patients with BC and hence consider the best option.

The metastatic rate of BC at diagnosis was 15.5% in our study. According to review of the literature, 6% of BCs are averagely metastatic at diagnosis.[22,23] Meanwhile, some larger Iranian studies have shown more frequent advanced BC among Iranian women than developed countries. The exact rate of metastasis at diagnosis.[9,24] It seems that the incidence of advanced BC among Iranian women is more than developed countries. It indicates the necessity of screening for early detection of BC, particularly among the high risk families. We found that the bone with 53.3% was the most frequent metastatic site. Our statistics in this regard was similar to other studies from Iran and other countries,[25,26] indicating the importance of performing bone scan in thestaging of the patients. In total, about 70% of patients with metastatic breast cancer develop bone metastasis. Bone is the most common site of metastasis in BC and the most common site of recurrence in 30%–40% of the cases.[27] Meanwhile, the patients with only bone metastasis have a better prognosis than those with visceral metastasis to the liver, lungs, or brain.[28-30]

In our study 10.2% of the BC patients showed triple-negative BC (TNBC) molecular phenotype in which ER, PR and HER2 were negative. Given the epidemiology of TNBC, our results were similar to other studies.[31,32] Reportedly, 10-15% of all patients with BC show the TNBC phenotype.[33] However, there are some limited evidences of higher frequency of TNBC than other subtypes of BC among Iranian women.[34] Since the prognosis among TNBC cases is poorer than other BC subtypes[32,35], this group of patients needs more attention during post-surgical period in terms of recurrence.

P53 was mutant in 30% of the BC tumors in our study. This findig is consistent with most of the other studies, that have reported P53 mutation in about 20-40% of aggressive breast cancers.[36,37] In a recent study on 104 Iranian patients with BC, 28.8% showed P53 mutant phenotype.[38] In another Iranian study, 29 (40.3%) of the 43 BC samples showed P53 mutations.[39] Although in some studies, patients with BC with mutant P53 tumors have had more age at diagnosis in comparison to patients with wild-type P53.[38,39], we find no significant difference between them. The proportion of high histologic grade in P53 mutant tumors to P53 wild-type tumors in our study was more than two fold. According to many studies, the BC tumors with mutant P53 are usually more aggressive than those with wild-type P53 and are identified as high histopathological grades at diagnosis.[39-41] Positive cancer family history was more frequent among our BC patients with wild-type P53 tumors than those with mutant P53 (86.7% versus 62.5%). There are some discrepancies in this regard according to different studies.[38,42] The fact around which there are yet some active research area.

We found 895 cancer patients in pedigrees related to 258 BC patients. In the other words, about 3.5 cancer patients was registered for each BC patient. As was expected, nearly two-thirds of all cancer patients were female. If we subtract 258 BC patients from 895 cancer patients, we obtain 637 including both male and female affected members among our BC patients' families. Accordingly, the proportion of male to female in cancer patients would be 304/333. Meanwhile, this proportion in Iranian general population has been estimated about 1.12 according to recent studies.[5,43] It means that in families of BC patients, females are likely at more risk to develop cancer. Breast, uterus and colorectal cancer among women and gastric, prostate and lung cancer among men were the most frequent cancers, respectively. According to the last report of Iranian health ministry, breast and gastric cancer are the most common cancers among Iranian women and men, respectively.[5] Similar pattern of cancer frequency between our patients and general population emphasizes the essential role of environmental factors in cancer development compared to hereditary predisposing factors for cancer.

Conclusion

Given the high frequency of early onset BC among Iranian women, necessity for a comprehensive, early-onset genetic counseling and screening program is undeniable. Exploring molecular and clinicopathologic features of breast cancer among Iranian populations could lead to promote all the preventive health-related interventions in this disease.

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Conflict of Interest: None declared.

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